

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 208891

Name: Wixela Inhub (Fluticasone Propionate and Salmeterol Inhalation Powder, USP), 100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg

Sponsor: Mylan Pharmaceuticals Inc

Approval Date: January 30, 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA208891Orig1s000
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 208891

APPROVAL LETTER



ANDA 208891

ANDA APPROVAL

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Wayne Talton
Head of Global Regulatory Affairs

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2015, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Wixela Inhub (Fluticasone Propionate and Salmeterol Inhalation Powder, USP), 100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg.

Reference is also made to the complete response letter issued by this office on June 27, 2018, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your Wixela Inhub (Fluticasone Propionate and Salmeterol Inhalation Powder, USP), 100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Advair Diskus, 100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg, of GlaxoSmithKline.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions¹ with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, Pharm.D.
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

¹ Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).



Sarah
Kurtz

Digitally signed by Sarah Kurtz

Date: 1/30/2019 02:12:55PM

GUID: 54078879000a1b9e15dd31ed6f0343ca

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 208891

LABELING

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Wixela™ Inhub™
(fluticasone propionate and salmeterol inhalation powder, USP)

100/50

Remember:

- Dose counter will be set at 60 when you receive your INHUB.
- A red indicator will be present when there are 9 doses or fewer remaining.
- The dose counter will read 0 when there are no doses remaining.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. Do not swallow the water.
- Do not take an extra dose, even if you did not taste or feel the powder.
- Do not take the INHUB apart.
- Do not wash the INHUB.
- Always keep the INHUB in a dry place.
- Do not use the INHUB with a spacer device.

NDC 0378-9320-32 Rx only

Wixela™ Inhub™
(fluticasone propionate and salmeterol inhalation powder, USP)

100/50

FOR ORAL INHALATION ONLY

Each dose of inhalation powder contains 100 mcg of fluticasone propionate, USP and 72.5 mcg of salmeterol xinafoate, USP equivalent to 50 mcg of salmeterol base, with lactose.

One Inhub™ Inhalation Device
Containing 60 Doses of Inhalation Powder



Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Store in a dry place away from direct heat and sunlight.

Discard the INHUB 1 month after removal from the foil pouch or after all inhalation powder has been used (when the dose counter reads "0"), whichever comes first.

Dosage: Use only as directed by your doctor.

IMPORTANT: Read the accompanying Patient Information and Instructions for Use carefully for further information.

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Made in Ireland



MDR:9320:1C:R10



50070005

VARNISH FREE AREA
for Lot number/Expiration date

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Patented. See wixelainhub.com/patents, Pfizer Limited, exclusively licensed to Mylan Pharmaceuticals Inc.

100/50
inhalation powder, USP)



Instructions for using WIXELA INHUB

Read the Patient Information that comes with WIXELA INHUB before you start using it and each time you get a refill. There may be new information.



Step 1. Open your WIXELA INHUB.

- Hold the INHUB in one hand and with your other hand on the grip lower the mouthpiece cover from top to bottom.



Step 2. Push down the lever.

- Hold the INHUB in the vertical position. Push the yellow lever down to the end of the purple arrows (you may hear a click).



Step 3. Inhale your medicine.

- Before you breathe in your dose from the INHUB, breathe out (exhale) as long as you can while you hold the INHUB away from your mouth. Do not breathe into the mouthpiece.
- Put the mouthpiece to your lips. Breathe in quickly and deeply through the INHUB. Do not breathe in through your nose.
- Remove the INHUB from your mouth and hold your breath for about 10 seconds, or for as long as is comfortable for you.
- Breathe out slowly for as long as you can.
- The INHUB delivers your dose of medicine as a very fine powder that you may or may not taste or feel. Do not take an extra dose from the INHUB even if you do not taste or feel the medicine.



Step 4. Close the INHUB.

- Push the mouthpiece cover up to the closed position, this will automatically return the yellow lever to the start position. Make sure the INHUB is shut and you cannot see the mouthpiece.



Step 5. Rinse your mouth.

- Rinse your mouth with water after breathing in the medicine. Spit out the water. Do not swallow it.

VARNISH FREE AREA



Wixela™
(fluticasone
propionate and
salmeterol inhalation powder, USP)

Inhub™

100/50

FOR ORAL INHALATION ONLY

NDC 0378-9320-32

Rx only

Each dose of inhalation powder contains 100 mcg of fluticasone propionate, USP and 72.5 mcg of salmeterol xinafoate, USP equivalent to 50 mcg of salmeterol base, with lactose.

IMPORTANT: Read the accompanying Patient Information and Instructions for Use carefully before use.

Discard 1 month after removal from the foil pouch.

Fill in the dates on the inhaler label appropriately.

Dosage: Use only as directed by your doctor.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Store in a dry place away from direct heat and sunlight.

Varnish free area for
Lot number/Expiration date

One Inhub™ Inhalation Device
Containing 60 Doses of Inhalation Powder

50069595



Manufactured in Ireland for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
MDR:9320:1P:R5

Fonts: Helvetica Neue LT Pro
Condensed / **Bold**
9.38 pts to 4.5 pts / Black

NDC 0378-9320-32

Wixela™ **Inhub™**
(fluticasone
propionate and
salmeterol inhalation powder, USP)

100/50

NDP-9320-500-12-A

Pouch opened: _____

Use by: _____

Discard 1 month after
removal from the foil pouch.

Rx only



50066301

doses

 **Mylan®**

Helvetica Neue LT Pro

Condensed / Medium / Medium Condensed / Bold
6.97 to 4 pts (vertical/horizontal scale from 145-90%)

(b) (4)

(b) (4)

Do not exhale into
the mouthpiece.

Also contains lactose monohydrate. Read
the accompanying Patient Information and
Instructions for Use carefully before use.

Wixela

Inhali

(fluticasone
propionate and
salmeterol inhalation powder, USP)

100/50

Store at 20° to 25°C (68° to 77°F). Store in a dry place away from direct heat and sunlight.

Varnish free area for
Lot number/Expiration date

MDR-9320-9320-96-8



5 0069 489

Manufactured in Ireland for
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U S A



N3 0378-9320-322

Helvetica Neue LT Pro

Condensed / Medium / Medium Condensed / Bold

5 pts to 4 pts (vertical/horizontal scale from 145-78%)

(b) (4)

Wixela™ Inhub™
(fluticasone propionate and salmeterol inhalation powder, USP)

250/50

Remember:

- Dose counter will be set at 60 when you receive your INHUB.
- A red indicator will be present when there are 9 doses or fewer remaining.
- The dose counter will read 0 when there are no doses remaining.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. **Do not** swallow the water.
- **Do not** take an extra dose, even if you did not taste or feel the powder.
- **Do not** take the INHUB apart.
- **Do not** wash the INHUB.
- Always keep the INHUB in a dry place.
- **Do not** use the INHUB with a spacer device.

NDC 0378-9321-32 Rx only

Wixela™ Inhub™
(fluticasone propionate and salmeterol inhalation powder, USP)

250/50

FOR ORAL INHALATION ONLY

Each dose of inhalation powder contains 250 mcg of fluticasone propionate, USP and 72.5 mcg of salmeterol xinafoate, USP equivalent to 50 mcg of salmeterol base, with lactose.

One Inhub™ Inhalation Device
Containing 60 Doses of Inhalation Powder



Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Store in a dry place away from direct heat and sunlight.

Discard the INHUB 1 month after removal from the foil pouch or after all inhalation powder has been used (when the dose counter reads "0"), whichever comes first.

Dosage: Use only as directed by your doctor.

IMPORTANT: Read the accompanying Patient Information and Instructions for Use carefully for further information.

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Made in Ireland



MDR:9321:1C:R10



5007004

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VARNISH FREE AREA
for Lot number/Expiration date



Wixela™ Inhub™
(fluticasone propionate and salmeterol inhalation powder, USP)
250/50

Instructions for using WIXELA INHUB

Read the Patient Information that comes with WIXELA INHUB before you start using it and each time you get a refill. There may be new information.



Step 1. Open your WIXELA INHUB.

- Hold the INHUB in one hand and with your other hand on the grip lower the mouthpiece cover from top to bottom.



Step 2. Push down the lever.

- Hold the INHUB in the vertical position. Push the yellow lever down to the end of the purple arrows (you may hear a click).



Step 3. Inhale your medicine.

- Before you breathe in your dose from the INHUB, breathe out (exhale) as long as you can while you hold the INHUB away from your mouth. Do not breathe into the mouthpiece.
- Put the mouthpiece to your lips. Breathe in quickly and deeply through the INHUB. Do not breathe in through your nose.
- Remove the INHUB from your mouth and hold your breath for about 10 seconds, or for as long as is comfortable for you.
- Breathe out slowly for as long as you can.
- The INHUB delivers your dose of medicine as a very fine powder that you may or may not taste or feel. **Do not** take an extra dose from the INHUB even if you do not taste or feel the medicine.



Step 4. Close the INHUB.

- Push the mouthpiece cover up to the closed position, this will automatically return the yellow lever to the start position. Make sure the INHUB is shut and you cannot see the mouthpiece.



Step 5. Rinse your mouth.

- Rinse your mouth with water after breathing in the medicine. Spit out the water. **Do not** swallow it.

VARNISH FREE AREA

Wixela™

(fluticasone propionate and salmeterol inhalation powder, USP)

250/50



NDC 0378-9321-32

Rx only

Each dose of inhalation powder contains 250 mcg of fluticasone propionate, USP and 72.5 mcg of salmeterol xinafoate, USP equivalent to 50 mcg of salmeterol base, with lactose.

FOR ORAL INHALATION ONLY

IMPORTANT: Read the accompanying Patient Information and Instructions for Use carefully before use.

Discard 1 month after removal from the foil pouch.

Fill in the dates on the inhaler label appropriately.

Dosage: Use only as directed by your doctor.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]



Varnish free area for
Lot number/Expiration date

Store in a dry place away from direct heat and sunlight.



**One Inhub™ Inhalation Device
Containing 60 Doses of Inhalation Powder**

50069596

Manufactured in Ireland for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
MDR:9321:1P:R5

Fonts: Helvetica Neue LT Pro
Condensed / Bold
9.38 pts to 4.5 pts / Black

NDC 0378-9321-32

Wixela™ **Inhub™**
(fluticasone propionate and salmeterol inhalation powder, USP)

250/50

MDR:9321.500:R2-A

Pouch opened: _____
Use by: _____
Discard 1 month after removal from the foil pouch.

Rx only



50066300

doses

 **Mylan®**

Helvetica Neue LT Pro

Condensed / Medium / Medium Condensed / **Bold**

6.97 to 4 pts (vertical/horizontal scale from 145-90%)

(b) (4)

(b) (4)

Do not exhale into
the mouthpiece.

Also contains lactose monohydrate. Read
the accompanying Patient Information and
Instructions for Use carefully before use.

Wixela

(fluticasone
propionate and
salmeterol inhalation powder, USP)



250/50

Store at 20° to 25°C (68° to 77°F). Store in a dry place away from direct heat and sunlight.

Varnish free area for
Lot number/Expiration date

MDR-9321-600-86-B



500-69590

Manufactured in Ireland for
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U S A



Helvetica Neue LT Pro

Condensed / Medium / Medium Condensed / Bold

5 pts to 4 pts (vertical/horizontal scale from 145-78%)

(b) (4)

Wixela™ Inhub™
(fluticasone propionate and salmeterol inhalation powder, USP)

500/50

Remember:

- Dose counter will be set at 60 when you receive your INHUB.
- A red indicator will be present when there are 9 doses or fewer remaining.
- The dose counter will read 0 when there are no doses remaining.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. Do not swallow the water.
- Do not take an extra dose, even if you did not taste or feel the powder.
- Do not take the INHUB apart.
- Do not wash the INHUB.
- Always keep the INHUB in a dry place.
- Do not use the INHUB with a spacer device.

NDC 0378-9322-32 Rx only

Wixela™ Inhub™
(fluticasone propionate and salmeterol inhalation powder, USP)

500/50

FOR ORAL INHALATION ONLY

Each dose of inhalation powder contains 500 mcg of fluticasone propionate, USP and 72.5 mcg of salmeterol xinafoate, USP equivalent to 50 mcg of salmeterol base, with lactose.

One Inhub™ Inhalation Device
Containing 60 Doses of Inhalation Powder



Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Store in a dry place away from direct heat and sunlight.

Discard the INHUB 1 month after removal from the foil pouch or after all inhalation powder has been used (when the dose counter reads "0"), whichever comes first.

Dosage: Use only as directed by your doctor.

IMPORTANT: Read the accompanying Patient Information and Instructions for Use carefully for further information.

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Made in Ireland



MDR:9322:1C:R10



N 3 0378-9322-32 6

50070007

VARNISH FREE AREA
for Lot number/Expiration date

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Wixela™ Inhub™
(fluticasone propionate and salmeterol inhalation powder, USP)
500/50

Instructions for using WIXELA INHUB

Read the Patient Information that comes with WIXELA INHUB before you start using it and each time you get a refill. There may be new information.



Step 1. Open your WIXELA INHUB.

- Hold the INHUB in one hand and with your other hand on the grip lower the mouthpiece cover from top to bottom.



Step 2. Push down the lever.

- Hold the INHUB in the vertical position. Push the yellow lever down to the end of the purple arrows (you may hear a click).



Step 3. Inhale your medicine.

- Before you breathe in your dose from the INHUB, breathe out (exhale) as long as you can while you hold the INHUB away from your mouth. Do not breathe into the mouthpiece.
- Put the mouthpiece to your lips. Breathe in quickly and deeply through the INHUB. Do not breathe in through your nose.
- Remove the INHUB from your mouth and hold your breath for about 10 seconds, or for as long as is comfortable for you.
- Breathe out slowly for as long as you can.
- The INHUB delivers your dose of medicine as a very fine powder that you may or may not taste or feel. Do not take an extra dose from the INHUB even if you do not taste or feel the medicine.



Step 4. Close the INHUB.

- Push the mouthpiece cover up to the closed position, this will automatically return the yellow lever to the start position. Make sure the INHUB is shut and you cannot see the mouthpiece.



Step 5. Rinse your mouth.

- Rinse your mouth with water after breathing in the medicine. Spit out the water. Do not swallow it.

VARNISH FREE AREA

Wixela™ Inhub
(fluticasone propionate and salmeterol inhalation powder, USP)

500/50

FOR ORAL INHALATION ONLY

NDC 0378-9322-32

Rx only

Each dose of inhalation powder contains 500 mcg of fluticasone propionate, USP and 72.5 mcg of salmeterol xinafoate, USP equivalent to 50 mcg of salmeterol base, with lactose.

IMPORTANT: Read the accompanying Patient Information and Instructions for Use carefully before use.

Discard 1 month after removal from the foil pouch.

Fill in the dates on the inhaler label appropriately.

Dosage: Use only as directed by your doctor.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Store in a dry place away from direct heat and sunlight.



Varnish free area for
Lot number/Expiration date



One Inhub™ Inhalation Device
Containing 60 Doses of Inhalation Powder

50069597

Manufactured in Ireland for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
MDR:9322:1P:R5

Fonts: Helvetica Neue LT Pro
Condensed / Bold
9.38 pts to 4.5 pts / Black

NDC 0378-9322-32

Wixela™ **Inhub™**
(fluticasone
propionate and
salmeterol inhalation powder, USP)

500/50

MDR-9322500-12-A

Pouch opened: _____
Use by: _____
Discard 1 month after
removal from the foil pouch.

Rx only



50066099

doses

 **Mylan®**

Helvetica Neue LT Pro

Condensed / Medium / Medium Condensed / Bold

6.97 to 4 pts. (vertical/horizontal scale from 145-90%)

(b) (4)

(b) (4)

Do not exhale into
the mouthpiece.

Also contains lactose monohydrate. Read
the accompanying Patient Information and
Instructions for Use carefully before use.

Wixela[™] **Inhub**[®]
(fluticasone
propionate and
salmeterol inhalation powder, USP)

500/50

Store at 20° to 25°C (68° to 77°F). Store in a dry place away from direct heat and sunlight.

Varnish free area for
Lot number/Expiration date

MOR9322-80DR6-B



500/66691

Manufactured in Ireland for
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U S A



Helvetica Neue LT Pro

Condensed / Medium / Medium Condensed / Bold

5 pts to 4 pts (vertical/horizontal scale from 145-78%)

(b) (4)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use WIXELA™ INHUB™ safely and effectively. See full prescribing information for WIXELA™ INHUB™.

WIXELA™ INHUB™ (fluticasone propionate and salmeterol inhalation powder), for oral inhalation use
Initial U.S. Approval: 2000

RECENT MAJOR CHANGES

Warnings and Precautions, Glaucoma and Cataracts (5.15) 1/2019

INDICATIONS AND USAGE

Wixela™ Inhub™ is a combination product containing a corticosteroid and a long-acting beta₂-adrenergic agonist (LABA) indicated for:

- Twice-daily treatment of asthma in patients aged 4 years and older. (1.1)
- Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). (1.2)

Important limitation of use: Not indicated for relief of acute bronchospasm. (1.1, 1.2)

DOSAGE AND ADMINISTRATION

For oral inhalation only. (2)

- Treatment of asthma in patients aged 12 years and older: 1 inhalation of Wixela™ Inhub™ 100/50, Wixela™ Inhub™ 250/50, or Wixela™ Inhub™ 500/50 twice daily. Starting dosage is based on asthma severity. (2.1)
- Treatment of asthma in patients aged 4 to 11 years: 1 inhalation of Wixela™ Inhub™ 100/50 twice daily. (2.1)
- Maintenance treatment of COPD: 1 inhalation of Wixela™ Inhub™ 250/50 twice daily. (2.2)

DOSAGE FORMS AND STRENGTHS

Inhalation powder: Inhaler containing a combination of fluticasone propionate (100, 250, or 500 mcg) and salmeterol (50 mcg) as a powder formulation for oral inhalation. (3)

CONTRAINDICATIONS

- Primary treatment of status asthmaticus or acute episodes of asthma or COPD requiring intensive measures. (4)
- Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone propionate, salmeterol, or any of the excipients. (4)

WARNINGS AND PRECAUTIONS

- LABA monotherapy increases the risk of serious asthma-related events. (5.1)
- Do not initiate in acutely deteriorating asthma or COPD. Do not use to treat acute symptoms. (5.2)
- Do not use in combination with an additional medicine containing a LABA because of risk of overdose. (5.3)
- *Candida albicans* infection of the mouth and pharynx may occur. Monitor patients periodically. Advise the patient to rinse his/her mouth with water without swallowing after inhalation to help reduce the risk. (5.4)
- Increased risk of pneumonia in patients with COPD. Monitor patients for signs and symptoms of pneumonia. (5.5)
- Potential worsening of infections (e.g., existing tuberculosis; fungal, bacterial, viral, or parasitic infections; ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.6)

- Risk of impaired adrenal function when transferring from systemic corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to Wixela™ Inhub™. (5.7)
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue Wixela™ Inhub™ slowly. (5.8)
- If paradoxical bronchospasm occurs, discontinue Wixela™ Inhub™ and institute alternative therapy. (5.10)
- Use with caution in patients with cardiovascular or central nervous system disorders because of beta-adrenergic stimulation. (5.12)
- Assess for decrease in bone mineral density initially and periodically thereafter. (5.13)
- Monitor growth of pediatric patients. (5.14)
- Glaucoma and cataracts may occur with long-term use of inhaled corticosteroids. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use Wixela™ Inhub™ long term. (5.15)
- Be alert to eosinophilic conditions, hypokalemia, and hyperglycemia. (5.16, 5.18)
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.17)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 3%) include:

- Asthma: Upper respiratory tract infection or inflammation, pharyngitis, dysphonia, oral candidiasis, bronchitis, cough, headaches, nausea and vomiting. (6.1)
- COPD: Pneumonia, oral candidiasis, throat irritation, dysphonia, viral respiratory infections, headaches, musculoskeletal pain. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole): Use not recommended. May increase risk of systemic corticosteroid and cardiovascular effects. (7.1)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of salmeterol on vascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with non-potassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)

USE IN SPECIFIC POPULATIONS

Hepatic impairment: Monitor patients for signs of increased drug exposure. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Asthma

Wixela™ Inhub™ is indicated for the twice-daily treatment of asthma in patients aged 4 years and older. Wixela™ Inhub™ should be used for patients not adequately controlled on a long-term asthma control medication such as an inhaled corticosteroid (ICS) or whose disease warrants initiation of treatment with both an ICS and long-acting beta₂-adrenergic agonist (LABA).

Important Limitation of Use: Wixela™ Inhub™ is NOT indicated for the relief of acute bronchospasm.

1.2 Maintenance Treatment of Chronic Obstructive Pulmonary Disease

Wixela™ Inhub™ 250/50 is indicated for the twice-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. Wixela™ Inhub™ 250/50 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. Wixela™ Inhub™ 250/50 twice daily is the only approved dosage for the treatment of COPD because an efficacy advantage of the higher strength Wixela™ Inhub™ 500/50 over Wixela™ Inhub™ 250/50 has not been demonstrated.

Important Limitation of Use: Wixela™ Inhub™ is NOT indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

Wixela™ Inhub™ should be administered as 1 inhalation twice daily by the orally inhaled route only. After inhalation, the patient should rinse his/her mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis.

More frequent administration or a greater number of inhalations (more than 1 inhalation twice daily) of the prescribed strength of Wixela™ Inhub™ is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. Patients using Wixela™ Inhub™ should not use additional LABA for any reason. [See Warnings and Precautions (5.3, 5.12).]

2.1 Asthma

If asthma symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate relief.

Adult and Adolescent Patients Aged 12 Years and Older: For patients aged 12 years and older, the dosage is 1 inhalation twice daily, approximately 12 hours apart.

When choosing the starting dosage strength of Wixela™ Inhub™, consider the patients' disease severity, based on their previous asthma therapy, including the ICS dosage, as well as the patients' current control of asthma symptoms and risk of future exacerbation.

The maximum recommended dosage is Wixela™ Inhub™ 500/50 twice daily.

Improvement in asthma control following inhaled administration of Wixela™ Inhub™ can occur within 30 minutes of beginning treatment, although maximum benefit may not be achieved for 1 week or longer after starting treatment. Individual patients will experience a variable time to onset and degree of symptom relief.

For patients who do not respond adequately to the starting dosage after 2 weeks of therapy, replacing the current strength of Wixela™ Inhub™ with a higher strength may provide additional improvement in asthma control.

If a previously effective dosage regimen fails to provide adequate improvement in asthma control, the therapeutic regimen should be reevaluated and additional therapeutic options (e.g., replacing the current strength of Wixela™ Inhub™ with a higher strength, adding additional ICS, initiating oral corticosteroids) should be considered.

Pediatric Patients Aged 4 to 11 Years: For patients with asthma aged 4 to 11 years who are not controlled on an ICS, the dosage is 1 inhalation of Wixela™ Inhub™ 100/50 twice daily, approximately 12 hours apart.

2.2 Chronic Obstructive Pulmonary Disease

The recommended dosage for patients with COPD is 1 inhalation of Wixela™ Inhub™ 250/50 twice daily, approximately 12 hours apart.

If shortness of breath occurs in the period between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate relief.

3 DOSAGE FORMS AND STRENGTHS

Inhalation powder: Inhaler containing two foil sealed discs, each containing 30 pre-metered doses of powder formulation for oral inhalation. Each of the 60 doses contains a combination of fluticasone propionate 100, 250, or 500 mcg and salmeterol 50 mcg per dose.

4 CONTRAINDICATIONS

The use of Wixela™ Inhub™ is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required [*see Warnings and Precautions (5.2)*].
- Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone propionate, salmeterol, or any of the excipients [*see Warnings and Precautions (5.11), Adverse Reactions (6.3), Description (11)*].

5 WARNINGS AND PRECAUTIONS

5.1 Serious Asthma-Related Events – Hospitalizations, Intubations, Death

Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death [see *Salmeterol Multicenter Asthma Research Trial (SMART)*]. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone (see *Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta₂-adrenergic Agonists*).

Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta₂-adrenergic Agonists: Four (4) large, 26-week, randomized, double-blind, active-controlled clinical safety trials were conducted to evaluate the risk of serious asthma-related events when LABA were used in fixed-dose combination with ICS compared with ICS alone in subjects with asthma. Three (3) trials included adult and adolescent subjects aged 12 years and older: 1 trial compared fluticasone propionate/salmeterol inhalation powder with fluticasone propionate inhalation powder, 1 trial compared mometasone furoate/formoterol with mometasone furoate, and 1 trial compared budesonide/formoterol with budesonide. The fourth trial included pediatric subjects aged 4 to 11 years and compared fluticasone propionate/salmeterol inhalation powder with fluticasone propionate inhalation powder. The primary safety endpoint for all 4 trials was serious asthma-related events (hospitalizations, intubations, death). A blinded adjudication committee determined whether events were asthma related.

The 3 adult and adolescent trials were designed to rule out a risk margin of 2.0, and the pediatric trial was designed to rule out a risk margin of 2.7. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the 3 adult and adolescent trials did not show a significant increase in risk of a serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone (Table 1). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS.

Table 1. Meta-analysis of Serious Asthma-Related Events in Subjects with Asthma Aged 12 Years and Older

	ICS/LABA (n = 17,537) ^a	ICS (n = 17,552) ^a	ICS/LABA vs. ICS Hazard Ratio (95% CI) ^b
Serious asthma-related event ^c	116	105	1.10 (0.85, 1.44)
Asthma-related death	2	0	
Asthma-related intubation (endotracheal)	1	2	
Asthma-related hospitalization (≥ 24-hour stay)	115	105	

ICS = Inhaled Corticosteroid, LABA = Long-acting Beta₂-adrenergic Agonist.

^a Randomized subjects who had taken at least 1 dose of study drug. Planned treatment used for analysis.

^b Estimated using a Cox proportional hazards model for time to first event with baseline hazards stratified by each of the 3 trials.

^c Number of subjects with event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Subjects can have one or more events, but only the first event was counted for analysis. A single, blinded, independent adjudication committee determined whether events were asthma related.

The pediatric safety trial included 6,208 pediatric subjects aged 4 to 11 years who received ICS/LABA (fluticasone propionate/salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial, 27/3,107 (0.9%) subjects randomized to ICS/LABA and 21/3,101 (0.7%) subjects randomized to ICS experienced a serious asthma-related event. There were no asthma-related deaths or intubations. ICS/LABA did not show a significantly increased risk of a serious asthma-related event compared with ICS based on the pre-specified risk margin (2.7), with an estimated hazard ratio of time to first event of 1.29 (95% CI: 0.73, 2.27).

Salmeterol Multicenter Asthma Research Trial (SMART): A 28-week, placebo-controlled, U.S. trial that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol versus 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). Use of background ICS was not required in SMART. The increased risk of asthma-related death is considered a class effect of LABA monotherapy.

5.2 Deterioration of Disease and Acute Episodes

Wixela™ Inhub™ should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. Wixela™ Inhub™ has not been studied in subjects with acutely deteriorating asthma or COPD. The initiation of Wixela™ Inhub™ in this setting is not appropriate.

Serious acute respiratory events, including fatalities, have been reported when salmeterol, a component of Wixela™ Inhub™, has been initiated in patients with significantly worsening or acutely deteriorating asthma. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, previous life-threatening acute asthma exacerbations) and in some patients with acutely deteriorating asthma (e.g., patients with significantly increasing symptoms; increasing need for inhaled, short-acting beta₂-agonists; decreasing response to usual medications; increasing need for systemic corticosteroids; recent emergency room visits; deteriorating lung function). However, these events have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether salmeterol contributed to these events.

Increasing use of inhaled, short-acting beta₂-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of Wixela™ Inhub™ with a higher strength, adding additional ICS, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation twice daily of Wixela™ Inhub™.

Wixela™ Inhub™ should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Wixela™ Inhub™ has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist.

When beginning treatment with Wixela™ Inhub™, patients who have been taking oral or inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

5.3 Excessive Use of Wixela™ Inhub™ and Use with Other Long-acting Beta₂-agonists

Wixela™ Inhub™ should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using Wixela™ Inhub™ should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Local Effects of Inhaled Corticosteroids

In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in subjects treated with fluticasone propionate and salmeterol inhalation powder. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with Wixela™ Inhub™ continues, but at times therapy with Wixela™ Inhub™ may need to be

interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

5.5 Pneumonia

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap.

Lower respiratory tract infections, including pneumonia, have been reported in patients with COPD following the inhaled administration of corticosteroids, including fluticasone propionate and fluticasone propionate and salmeterol inhalation powder. In 2 replicate 1-year trials in 1,579 subjects with COPD, there was a higher incidence of pneumonia reported in subjects receiving fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg (7%) than in those receiving salmeterol 50 mcg (3%). The incidence of pneumonia in the subjects treated with fluticasone propionate and salmeterol inhalation powder was higher in subjects older than 65 years (9%) compared with the incidence in subjects younger than 65 years (4%). [*See Adverse Reactions (6.2), Use in Specific Populations (8.5).*]

In a 3-year trial in 6,184 subjects with COPD, there was a higher incidence of pneumonia reported in subjects receiving fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg compared with placebo (16% with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg, 14% with fluticasone propionate 500 mcg, 11% with salmeterol 50 mcg, and 9% with placebo). Similar to what was seen in the 1-year trials with fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg, the incidence of pneumonia was higher in subjects older than 65 years (18% with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg versus 10% with placebo) compared with subjects younger than 65 years (14% with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg versus 8% with placebo). [*See Adverse Reactions (6.2), Use in Specific Populations (8.5).*]

5.6 Immunosuppression

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

ICS should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.7 Transferring Patients from Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available ICS. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During

this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although Wixela™ Inhub™ may control asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to Wixela™ Inhub™. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with Wixela™ Inhub™. Lung function (mean forced expiratory volume in 1 second [FEV₁] or morning peak expiratory flow [AM PEF]), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to Wixela™ Inhub™ may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

5.8 Hypercorticism and Adrenal Suppression

Fluticasone propionate, a component of Wixela™ Inhub™, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of Wixela™ Inhub™ in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing Wixela™ Inhub™.

Because of the possibility of significant systemic absorption of ICS in sensitive patients, patients treated with Wixela™ Inhub™ should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, Wixela™ Inhub™ should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of asthma symptoms should be considered.

5.9 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with Wixela™ Inhub™ is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur [*see Drug Interactions (7.1), Clinical Pharmacology (12.3)*].

5.10 Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medicines, Wixela™ Inhub™ can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with Wixela™ Inhub™, it should be treated immediately with an inhaled, short-acting bronchodilator; Wixela™ Inhub™ should be discontinued immediately; and alternative therapy should be instituted. Upper airway symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported in patients receiving fluticasone propionate and salmeterol inhalation powder.

5.11 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension), including anaphylaxis, may occur after administration of Wixela™ Inhub™. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of powder products containing lactose; therefore, patients with severe milk protein allergy should not use Wixela™ Inhub™ [*see Contraindications (4)*].

5.12 Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia [*see Overdosage (10.2)*]. Therefore, Wixela™ Inhub™, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Salmeterol, a component of Wixela™ Inhub™, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of salmeterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

5.13 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids), should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating Wixela™ Inhub™ and periodically thereafter. If significant reductions in BMD are seen and Wixela™ Inhub™ is still considered medically important for that patient's COPD therapy, use of medicine to treat or prevent osteoporosis should be strongly considered.

2-Year Fluticasone Propionate Trial: A 2-year trial in 160 subjects (females aged 18 to 40 years, males 18 to 50) with asthma receiving chlorofluorocarbon (CFC)-propelled fluticasone propionate inhalation aerosol 88 or 440 mcg twice daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar regions L1 through L4.

3-Year Bone Mineral Density Trial: Effects of treatment with fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg or salmeterol 50 mcg on BMD at the L1-L4 lumbar spine and total hip were evaluated in 186 subjects with COPD (aged 43 to 87 years) in a 3-year double-blind trial. Of those enrolled, 108 subjects (72 males and 36 females) were followed for the entire 3 years. BMD evaluations were conducted at baseline and at 6-month intervals. Conclusions cannot be drawn from this trial regarding BMD decline in subjects treated with fluticasone propionate and salmeterol inhalation powder versus salmeterol due to the inconsistency of treatment differences across gender and between lumbar spine and total hip.

In this trial there were 7 non-traumatic fractures reported in 5 subjects treated with fluticasone propionate and salmeterol inhalation powder and 1 non-traumatic fracture in 1 subject treated with salmeterol. None of the non-traumatic fractures occurred in the vertebrae, hip, or long bones.

3-Year Survival Trial: Effects of treatment with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg, fluticasone propionate 500 mcg, salmeterol 50 mcg, or placebo on BMD was evaluated in a subset of 658 subjects (females and males aged 40 to 80 years) with COPD in the 3-year survival trial. BMD evaluations were conducted at baseline and at 48, 108, and 158 weeks. Conclusions cannot be drawn from this trial because of the large number of dropouts (> 50%) before the end of the follow-up and the maldistribution of covariates among the treatment groups that can affect BMD.

Fracture risk was estimated for the entire population of subjects with COPD in the survival trial (N = 6,184). The probability of a fracture over 3 years was 6.3% for fluticasone propionate and salmeterol inhalation powder, 5.4% for fluticasone propionate, 5.1% for salmeterol, and 5.1% for placebo.

5.14 Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving Wixela™ Inhub™ routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including Wixela™ Inhub™, titrate each patient's dosage to the lowest dosage that effectively controls his/her symptoms [*see Dosage and Administration (2.1), Use in Specific Populations (8.4)*].

5.15 Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of ICS, including fluticasone propionate, a component of Wixela™ Inhub™. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use Wixela™ Inhub™ long term.

Effects of treatment with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg, fluticasone propionate 500 mcg, salmeterol 50 mcg, or placebo on development of cataracts or glaucoma was evaluated in a subset of 658 subjects with COPD in the 3-year survival trial. Ophthalmic examinations were conducted at baseline and at 48, 108, and 158 weeks. Conclusions about cataracts cannot be drawn from this trial because the high incidence of cataracts at baseline (61% to 71%) resulted in an inadequate number of subjects treated with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg who were eligible and available for evaluation of cataracts at the end of the trial (n = 53). The incidence of newly diagnosed glaucoma was 2% with

fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg, 5% with fluticasone propionate, 0% with salmeterol, and 2% with placebo.

5.16 Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled fluticasone propionate, a component of Wixela™ Inhub™, may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other ICS in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established.

5.17 Coexisting Conditions

Wixela™ Inhub™, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta₂-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.18 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [see *Clinical Pharmacology* (12.2)]. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical trials with fluticasone propionate and salmeterol inhalation powder at recommended doses.

6 ADVERSE REACTIONS

Use of LABA may result in the following:

- Serious asthma-related events – hospitalizations, intubations, death [see *Warnings and Precautions* (5.1)]
- Cardiovascular and central nervous system effects [see *Warnings and Precautions* (5.12)]

Systemic and local corticosteroid use may result in the following:

- *Candida albicans* infection [see *Warnings and Precautions* (5.4)]
- Pneumonia in patients with COPD [see *Warnings and Precautions* (5.5)]
- Immunosuppression [see *Warnings and Precautions* (5.6)]
- Hypercorticism and adrenal suppression [see *Warnings and Precautions* (5.8)]
- Reduction in bone mineral density [see *Warnings and Precautions* (5.13)]
- Growth effects [see *Warnings and Precautions* (5.14)]
- Glaucoma and cataracts [see *Warnings and Precautions* (5.15)]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience in Asthma

Adult and Adolescent Subjects Aged 12 Years and Older: The incidence of adverse reactions associated with fluticasone propionate and salmeterol inhalation powder in Table 2 is based upon two 12-week, placebo-controlled, U.S. clinical trials (Trials 1 and 2). A total of 705 adult and adolescent subjects (349 females and 356 males) previously treated with salmeterol or ICS were treated twice daily with fluticasone propionate and salmeterol inhalation powder (100 mcg/50 mcg or 250 mcg/50 mcg doses), fluticasone propionate inhalation

powder (100 or 250 mcg doses), salmeterol inhalation powder 50 mcg, or placebo. The average duration of exposure was 60 to 79 days in the active treatment groups compared with 42 days in the placebo group.

Table 2. Adverse Reactions with Fluticasone Propionate and Salmeterol Inhalation Powder with $\geq 3\%$ Incidence and More Common than Placebo in Adult and Adolescent Subjects with Asthma

Adverse Event	Fluticasone Propionate and Salmeterol Inhalation Powder 100 mcg/50 mcg (n = 92) %	Fluticasone Propionate and Salmeterol Inhalation Powder 250 mcg/50 mcg (n = 84) %	Fluticasone Propionate 100 mcg (n = 90) %	Fluticasone Propionate 250 mcg (n = 84) %	Salmeterol 50 mcg (n = 180) %	Placebo (n = 175) %
Ear, nose, and throat						
Upper respiratory tract infection	27	21	29	25	19	14
Pharyngitis	13	10	7	12	8	6
Upper respiratory inflammation	7	6	7	8	8	5
Sinusitis	4	5	6	1	3	4
Hoarseness/dysphonia	5	2	2	4	< 1	< 1
Oral candidiasis	1	4	2	2	0	0
Lower respiratory						
Viral respiratory infections	4	4	4	10	6	3
Bronchitis	2	8	1	2	2	2
Cough	3	6	0	0	3	2
Neurology						
Headaches	12	13	14	8	10	7
Gastrointestinal						
Nausea and vomiting	4	6	3	4	1	1
Gastrointestinal discomfort and pain	4	1	0	2	1	1
Diarrhea	4	2	2	2	1	1
Viral gastrointestinal infections	3	0	3	1	2	2
Non-site specific						
Candidiasis unspecified site	3	0	1	4	0	1
Musculoskeletal						
Musculoskeletal pain	4	2	1	5	3	3

The types of adverse reactions and events reported in Trial 3, a 28-week non-U.S. clinical trial in 503 subjects previously treated with ICS who were treated twice daily with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg, fluticasone propionate inhalation powder 500 mcg and salmeterol inhalation powder 50 mcg used concurrently, or fluticasone propionate inhalation powder 500 mcg, were similar to those reported in Table 2.

Additional Adverse Reactions: Other adverse reactions not previously listed, whether considered drug-related or not by the investigators, that were reported more frequently by subjects with asthma treated with fluticasone propionate and salmeterol inhalation powder compared with subjects treated with placebo include the following: lymphatic signs and symptoms; muscle injuries; fractures; wounds and lacerations; contusions and hematomas; ear signs and symptoms; nasal signs and symptoms; nasal sinus disorders; keratitis and conjunctivitis; dental discomfort and pain; gastrointestinal signs and symptoms; oral ulcerations; oral discomfort and pain; lower respiratory signs and symptoms; pneumonia; muscle stiffness, tightness, and rigidity; bone and cartilage disorders; sleep disorders; compressed nerve syndromes; viral infections; pain; chest symptoms; fluid retention; bacterial infections; unusual taste; viral skin infections; skin flakiness and acquired ichthyosis; disorders of sweat and sebum.

Pediatric Subjects Aged 4 to 11 Years: The safety data for pediatric subjects aged 4 to 11 years is based upon 1 U.S. trial of 12 weeks' treatment duration. A total of 203 subjects (74 females and 129 males) who were receiving ICS at trial entry were randomized to either fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg or fluticasone propionate inhalation powder 100 mcg twice daily. Common adverse reactions ($\geq 3\%$ and greater than placebo) seen in the pediatric subjects but not reported in the adult and adolescent clinical trials include: throat irritation and ear, nose, and throat infections.

Laboratory Test Abnormalities: Elevation of hepatic enzymes was reported in $\geq 1\%$ of subjects in clinical trials. The elevations were transient and did not lead to discontinuation from the trials. In addition, there were no clinically relevant changes noted in glucose or potassium.

6.2 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

Short-Term (6 Months to 1 Year) Trials: The short-term safety data are based on exposure to fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg twice daily in one 6-month and two 1-year clinical trials. In the 6-month trial, a total of 723 adult subjects (266 females and 457 males) were treated twice daily with fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg, fluticasone propionate inhalation powder 250 mcg, salmeterol inhalation powder, or placebo. The mean age of the subjects was 64, and the majority (93%) was Caucasian. In this trial, 70% of the subjects treated with fluticasone propionate and salmeterol inhalation powder reported an adverse reaction compared with 64% on placebo. The average duration of exposure to fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg was 141.3 days compared with 131.6 days for placebo. The incidence of adverse reactions in the 6-month trial is shown in Table 3.

Table 3. Overall Adverse Reactions with Fluticasone Propionate and Salmeterol Inhalation Powder 250 mcg/50 mcg with $\geq 3\%$ Incidence in Subjects with Chronic Obstructive Pulmonary Disease Associated with Chronic Bronchitis

Adverse Event		Fluticasone Propionate	Salmeterol	

	Fluticasone Propionate and Salmeterol Inhalation Powder 250 mcg/50 mcg (n = 178) %	250 mcg (n = 183) %	50 mcg (n = 177) %	Placebo (n = 185) %
Ear, nose, and throat				
Candidiasis mouth/throat	10	6	3	1
Throat irritation	8	5	4	7
Hoarseness/dysphonia	5	3	< 1	0
Sinusitis	3	8	5	3
Lower respiratory				
Viral respiratory infections	6	4	3	3
Neurology				
Headaches	16	11	10	12
Dizziness	4	< 1	3	2
Non-site specific				
Fever	4	3	0	3
Malaise and fatigue	3	2	2	3
Musculoskeletal				
Musculoskeletal pain	9	8	12	9
Muscle cramps and spasms	3	3	1	1

In the two 1-year trials, fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg was compared with salmeterol in 1,579 subjects (863 males and 716 females). The mean age of the subjects was 65 years, and the majority (94%) was Caucasian. To be enrolled, all of the subjects had to have had a COPD exacerbation in the previous 12 months. In this trial, 88% of the subjects treated with fluticasone propionate and salmeterol inhalation powder and 86% of the subjects treated with salmeterol reported an adverse event. The most common events that occurred with a frequency of > 5% and more frequently in the subjects treated with fluticasone propionate and salmeterol inhalation powder were nasopharyngitis, upper respiratory tract infection, nasal congestion, back pain, sinusitis, dizziness, nausea, pneumonia, candidiasis, and dysphonia. Overall, 55 (7%) of the subjects treated with fluticasone propionate and salmeterol inhalation powder and 25 (3%) of the subjects treated with salmeterol developed pneumonia.

The incidence of pneumonia was higher in subjects older than 65 years, 9% in the subjects treated with fluticasone propionate and salmeterol inhalation powder compared with 4% in the subjects treated with fluticasone propionate and salmeterol inhalation powder younger than 65 years. In the subjects treated with salmeterol, the incidence of pneumonia was the same (3%) in both age groups. [See *Warnings and Precautions* (5.5), *Use in Specific Populations* (8.5).]

Long-Term (3 Years) Trial: The safety of fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg was evaluated in a randomized, double-blind, placebo-controlled, multicenter, international, 3-year trial in 6,184 adult subjects with COPD (4,684 males and 1,500 females). The mean age of the subjects was 65 years, and the majority (82%) was Caucasian. The distribution of adverse events was similar to that seen in the 1-year trials with fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg. In addition, pneumonia was reported in a significantly increased number of subjects treated with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg and fluticasone propionate 500 mcg (16% and 14%, respectively) compared with subjects treated with salmeterol 50 mcg or placebo (11% and 9%, respectively). When adjusted for time on treatment, the rates of pneumonia were 84 and 88 events per 1,000 treatment-years in the groups treated with

fluticasone propionate 500 mcg and with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg, respectively, compared with 52 events per 1,000 treatment-years in the salmeterol and placebo groups. Similar to what was seen in the 1-year trials with fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg, the incidence of pneumonia was higher in subjects older than 65 years (18% with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg versus 10% with placebo) compared with subjects younger than 65 years (14% with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg versus 8% with placebo). [See *Warnings and Precautions (5.5)*, *Use in Specific Populations (8.5)*.]

Additional Adverse Reactions: Other adverse reactions not previously listed, whether considered drug-related or not by the investigators, that were reported more frequently by subjects with COPD treated with fluticasone propionate and salmeterol inhalation powder compared with subjects treated with placebo include the following: syncope; ear, nose, and throat infections; ear signs and symptoms; laryngitis; nasal congestion/blockage; nasal sinus disorders; pharyngitis/throat infection; hypothyroidism; dry eyes; eye infections; gastrointestinal signs and symptoms; oral lesions; abnormal liver function tests; bacterial infections; edema and swelling; viral infections.

Laboratory Abnormalities: There were no clinically relevant changes in these trials. Specifically, no increased reporting of neutrophilia or changes in glucose or potassium was noted.

6.3 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of any formulation of fluticasone propionate and salmeterol, fluticasone propionate, and/or salmeterol regardless of indication. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to fluticasone propionate and salmeterol inhalation powder, fluticasone propionate, and/or salmeterol or a combination of these factors.

Cardiac Disorders: Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular tachycardia), ventricular tachycardia.

Endocrine Disorders: Cushing's syndrome, Cushingoid features, growth velocity reduction in children/adolescents, hypercorticism.

Eye Disorders: Glaucoma.

Gastrointestinal Disorders: Abdominal pain, dyspepsia, xerostomia.

Immune System Disorders: Immediate and delayed hypersensitivity reaction (including very rare anaphylactic reaction). Very rare anaphylactic reaction in patients with severe milk protein allergy.

Infections and Infestations: Esophageal candidiasis.

Metabolic and Nutrition Disorders: Hyperglycemia, weight gain.

Musculoskeletal, Connective Tissue, and Bone Disorders: Arthralgia, cramps, myositis, osteoporosis.

Nervous System Disorders: Paresthesia, restlessness.

Psychiatric Disorders: Agitation, aggression, depression. Behavioral changes, including hyperactivity and irritability, have been reported very rarely and primarily in children.

Reproductive System and Breast Disorders: Dysmenorrhea.

Respiratory, Thoracic, and Mediastinal Disorders: Chest congestion; chest tightness; dyspnea; facial and oropharyngeal edema, immediate bronchospasm; paradoxical bronchospasm; tracheitis; wheezing; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.

Skin and Subcutaneous Tissue Disorders: Ecchymoses, photodermatitis.

Vascular Disorders: Pallor.

7 DRUG INTERACTIONS

Fluticasone propionate and salmeterol inhalation powder has been used concomitantly with other drugs, including short-acting beta₂-agonists, methylxanthines, and intranasal corticosteroids, commonly used in patients with asthma or COPD without adverse drug reactions [see *Clinical Pharmacology (12.2)*]. No formal drug interaction trials have been performed with fluticasone propionate and salmeterol inhalation powder.

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone propionate and salmeterol, the individual components of Wixela™ Inhub™, are substrates of CYP3A4. The use of strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with Wixela™ Inhub™ is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur.

Ritonavir: Fluticasone Propionate: A drug interaction trial with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong CYP3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations [see *Clinical Pharmacology (12.3)*]. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.

Ketoconazole: Fluticasone Propionate: Coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in a 1.9-fold increase in plasma fluticasone propionate exposure and a 45% decrease in plasma cortisol area under the curve (AUC), but had no effect on urinary excretion of cortisol.

Salmeterol: In a drug interaction trial in 20 healthy subjects, coadministration of inhaled salmeterol (50 mcg twice daily) and oral ketoconazole (400 mg once daily) for 7 days resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and C_{max} increased 1.4-fold). Three (3) subjects were withdrawn due to beta₂-agonist side effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Wixela™ Inhub™ should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol, a component of Wixela™ Inhub™, on the vascular system may be potentiated by these agents.

7.3 Beta-adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as salmeterol, a component of Wixela™ Inhub™, but may also produce severe bronchospasm in patients with asthma or COPD. Therefore, patients with asthma or COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non-Potassium-Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, such as salmeterol, a component of Wixela™ Inhub™, especially when the recommended dose of the beta-agonist is exceeded.

Although the clinical significance of these effects is not known, caution is advised in the coadministration of Wixela™ Inhub™ with non-potassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary: There are insufficient data on the use of fluticasone propionate and salmeterol inhalation powder or individual monoproducts, fluticasone propionate and salmeterol xinafoate, in pregnant women. There are clinical considerations with the use of fluticasone propionate and salmeterol inhalation powder in pregnant women (see Clinical Considerations). In animals, teratogenicity characteristic of corticosteroids, decreased fetal body weight and/or skeletal variations, in rats, mice, and rabbits were observed with subcutaneously administered maternal toxic doses of fluticasone propionate less than the maximum recommended human daily inhaled dose (MRHDID) on a mcg/m² basis (see Data). However, fluticasone propionate administered via inhalation to rats decreased fetal body weight, but did not induce teratogenicity at a maternal toxic dose less than the MRHDID on a mcg/m² basis (see Data). Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. Oral administration of salmeterol to pregnant rabbits caused teratogenicity characteristic of beta-adrenoceptor stimulation at maternal doses approximately 50 times the MRHDID on an AUC basis. These adverse effects generally occurred at large multiples of the MRHDID when salmeterol was administered by the oral route to achieve high systemic exposures. No such effects occurred at an oral salmeterol dose approximately 20 times the MRHDID (see Data).

The estimated risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations: Disease-Associated Maternal and/or Embryofetal Risk: In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal outcomes such as pre-eclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women should be closely monitored and medication adjusted as necessary to maintain optimal control of asthma.

Labor and Delivery: There are no human studies evaluating the effects of fluticasone propionate and salmeterol inhalation powder during labor and delivery. Because of the potential for beta-agonist interference with uterine contractility, use of Wixela™ Inhub™ during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Data: Human Data: Fluticasone Propionate: Following inhaled administration, fluticasone propionate was detected in the neonatal cord blood after delivery.

Animal Data: Fluticasone Propionate and Salmeterol: In an embryofetal development study with pregnant rats that received the combination of subcutaneous administration of fluticasone propionate and oral administration of salmeterol at doses of 0/1,000; 30/0; 10/100; 30/1,000; and 100/10,000 mcg/kg/day (as fluticasone propionate/salmeterol) during the period of organogenesis, findings were generally consistent with the individual monoproducts and there was no exacerbation of expected fetal effects. Omphalocele, increased embryofetal deaths, decreased body weight, and skeletal variations were observed in rat fetuses in the presence of maternal toxicity when combining fluticasone propionate at a dose approximately equivalent to the MRHDID (on a mcg/m² basis at a maternal subcutaneous dose of 100 mcg/kg/day) and salmeterol at a dose approximately 970 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 10,000 mcg/kg/day). The rat no observed adverse effect level (NOAEL) was observed when combining fluticasone propionate at a dose approximately 0.3 times the MRHDID (on a mcg/m² basis at a maternal subcutaneous dose of 30 mcg/kg/day) and salmeterol at a dose approximately 100 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 1,000 mcg/kg/day).

In an embryofetal development study with pregnant mice that received the combination of subcutaneous administration of fluticasone propionate and oral administration of salmeterol at doses of 0/1,400; 40/0; 10/200; 40/1,400; or 150/10,000 mcg/kg/day (as fluticasone propionate/salmeterol) during the period of organogenesis, findings were generally consistent with the individual monoproducts and there was no exacerbation of expected fetal effects. Cleft palate, fetal death, increased implantation loss, and delayed ossification were observed in mouse fetuses when combining fluticasone propionate at a dose approximately 0.7 times the MRHDID (on a mcg/m² basis at a maternal subcutaneous dose of 150 mcg/kg/day) and salmeterol at a dose approximately 490 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 10,000 mcg/kg/day). No developmental toxicity was observed at combination doses of fluticasone propionate up to approximately 0.2 times the MRHDID (on a mcg/m² basis at a maternal subcutaneous dose of 40 mcg/kg) and doses of salmeterol up to approximately 70 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 1,400 mcg/kg).

Fluticasone Propionate: In embryofetal development studies with pregnant rats and mice dosed by the subcutaneous route throughout the period of organogenesis, fluticasone propionate was teratogenic in both species. Omphalocele, decreased body weight, and skeletal variations were observed in rat fetuses, in the presence of maternal toxicity, at a dose approximately equivalent to the MRHDID (on a mcg/m² basis with a maternal subcutaneous dose of 100 mcg/kg/day). The rat NOAEL was observed at approximately 0.3 times the MRHDID (on a mcg/m² basis with a maternal subcutaneous dose of 30 mcg/kg/day). Cleft palate and fetal skeletal variations were observed in mouse fetuses at a dose approximately 0.2 times the MRHDID (on a mcg/m² basis with a maternal subcutaneous dose of 45 mcg/kg/day). The mouse NOAEL was observed with a dose approximately 0.07 times the MRHDID (on a mcg/m² basis with a maternal subcutaneous dose of 15 mcg/kg/day).

In an embryofetal development study with pregnant rats dosed by the inhalation route throughout the period of organogenesis, fluticasone propionate produced decreased fetal body weights and skeletal variations, in the presence of maternal toxicity, at a dose approximately 0.25 times the MRHDID (on a mcg/m² basis with a maternal inhalation dose of 25.7 mcg/kg/day); however, there was no evidence of teratogenicity. The NOAEL was observed with a dose approximately 0.05 times the MRHDID (on a mcg/m² basis with a maternal inhalation dose of 5.5 mcg/kg/day).

In an embryofetal development study in pregnant rabbits that were dosed by the subcutaneous route throughout organogenesis, fluticasone propionate produced reductions of fetal body weights, in the presence of maternal toxicity, at doses approximately 0.012 times the MRHDID and higher (on a mcg/m² basis with a maternal subcutaneous dose of 0.57 mcg/kg/day). Teratogenicity was evident based upon a finding of cleft palate for 1 fetus at a dose approximately 0.08 times the MRHDID (on a mcg/m² basis with a maternal subcutaneous dose of 4 mcg/kg/day). The NOAEL was observed in rabbit fetuses with a dose approximately 0.002 times the MRHDID (on a mcg/m² basis with a maternal subcutaneous dose of 0.08 mcg/kg/day).

Fluticasone propionate crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits.

In a pre- and post-natal development study in pregnant rats dosed by the subcutaneous route from late gestation through delivery and lactation (Gestation Day 17 to Postpartum Day 22), fluticasone propionate was not associated with decreases in pup body weight, and had no effects on developmental landmarks, learning, memory, reflexes, or fertility at doses up to 0.5 times the MRHDID (on a mcg/m² basis with maternal subcutaneous doses up to 50 mcg/kg/day).

Salmeterol: In 3 embryofetal development studies, pregnant rabbits received oral administration of salmeterol at doses ranging from 100 to 10,000 mcg/kg/day during the period of organogenesis. In pregnant Dutch rabbits

administered salmeterol doses approximately 50 times the MRHDID (on an AUC basis at maternal oral doses of 1,000 mcg/kg/day and higher), fetal toxic effects were observed characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No such effects occurred at a salmeterol dose approximately 20 times the MRHDID (on an AUC basis at a maternal oral dose of 600 mcg/kg/day). New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at a salmeterol dose approximately 2,000 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 10,000 mcg/kg/day).

In 2 embryofetal development studies, pregnant rats received salmeterol by oral administration at doses ranging from 100 to 10,000 mcg/kg/day during the period of organogenesis. Salmeterol produced no maternal toxicity or embryofetal effects at doses up to 973 times the MRHDID (on a mcg/m² basis at maternal oral doses up to 10,000 mcg/kg/day).

In a peri- and post-natal development study in pregnant rats dosed by the oral route from late gestation through delivery and lactation, salmeterol at a dose 973 times the MRHDID (on a mcg/m² basis with a maternal oral dose of 10,000 mcg/kg/day) was fetotoxic and decreased the fertility of survivors.

Salmeterol xinafoate crossed the placenta following oral administration to mice and rats.

8.2 Lactation

Risk Summary: There are no available data on the presence of fluticasone propionate or salmeterol in human milk, the effects on the breastfed child, or the effects on milk production. Other corticosteroids have been detected in human milk. However, fluticasone propionate and salmeterol concentrations in plasma after inhaled therapeutic doses are low and therefore concentrations in human breast milk are likely to be correspondingly low [see *Clinical Pharmacology (12.3)*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Wixela™ Inhub™ and any potential adverse effects on the breastfed child from Wixela™ Inhub™ or from the underlying maternal condition.

Data: Animal Data: Subcutaneous administration of tritiated fluticasone propionate at a dose of 10 mcg/kg/day to lactating rats resulted in measurable levels in milk. Oral administration of salmeterol at a dose of 10,000 mcg/kg/day to lactating rats resulted in measurable levels in milk.

8.4 Pediatric Use

Use of fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg in patients aged 4 to 11 years is supported by extrapolation of efficacy data from older subjects and by safety and efficacy data from a trial of fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg in children with asthma aged 4 to 11 years [see *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*, *Clinical Studies (14.1)*]. The safety and effectiveness of fluticasone propionate and salmeterol inhalation powder in children with asthma younger than 4 years have not been established.

ICS, including fluticasone propionate, a component of Wixela™ Inhub™, may cause a reduction in growth velocity in children and adolescents [see *Warnings and Precautions (5.14)*]. The growth of pediatric patients receiving orally inhaled corticosteroids, including Wixela™ Inhub™, should be monitored.

A 52-week placebo-controlled trial to assess the potential growth effects of fluticasone propionate inhalation powder (FLOVENT® ROTADISK®) at 50 and 100 mcg twice daily was conducted in the U.S. in 325 prepubescent children (244 males and 81 females) aged 4 to 11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the placebo group (n = 76), 6.07 cm/year in the 50 mcg group (n = 98), and 5.66 cm/year in the 100 mcg group (n = 89). An imbalance in the proportion of

children entering puberty between groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be confounding factors in interpreting these data. A separate subset analysis of children who remained prepubertal during the trial revealed growth rates at 52 weeks of 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and 5.67 cm/year in the 100-mcg group (n = 79). In children aged 8.5 years, the mean age of children in this trial, the range for expected growth velocity is: boys – 3rd percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; girls – 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year. The clinical relevance of these growth data is not certain.

If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect of corticosteroids should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including Wixela™ Inhub™, each patient should be titrated to the lowest strength that effectively controls his/her asthma [see *Dosage and Administration (2.1)*].

8.5 Geriatric Use

Clinical trials of fluticasone propionate and salmeterol inhalation powder for asthma did not include sufficient numbers of subjects aged 65 years and older to determine whether older subjects with asthma respond differently than younger subjects.

Of the total number of subjects in clinical trials receiving fluticasone propionate and salmeterol inhalation powder for COPD, 1,621 were aged 65 years and older and 379 were aged 75 years and older. Subjects with COPD aged 65 years and older had a higher incidence of serious adverse events compared with subjects younger than 65 years. Although the distribution of adverse events was similar in the 2 age groups, subjects older than 65 years experienced more severe events. In two 1-year trials, the excess risk of pneumonia that was seen in subjects treated with fluticasone propionate and salmeterol inhalation powder compared with those treated with salmeterol was greater in subjects older than 65 years than in subjects younger than 65 years [see *Adverse Reactions (6.2)*]. As with other products containing beta₂-agonists, special caution should be observed when using Wixela™ Inhub™ in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta₂-agonists. Based on available data for fluticasone propionate and salmeterol inhalation powder or its active components, no adjustment of dosage of Wixela™ Inhub™ in geriatric patients is warranted.

No relationship between fluticasone propionate systemic exposure and age was observed in 57 subjects with COPD (aged 40 to 82 years) given 250 or 500 mcg twice daily.

8.6 Hepatic Impairment

Formal pharmacokinetic studies using fluticasone propionate and salmeterol inhalation powder have not been conducted in patients with hepatic impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

8.7 Renal Impairment

Formal pharmacokinetic studies using fluticasone propionate and salmeterol inhalation powder have not been conducted in patients with renal impairment.

10 OVERDOSAGE

No human overdose data has been reported for fluticasone propionate and salmeterol inhalation powder.

Wixela™ Inhub™ contains both fluticasone propionate and salmeterol; therefore, the risks associated with overdosage for the individual components described below apply to Wixela™ Inhub™. Treatment of overdosage consists of discontinuation of Wixela™ Inhub™ together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

10.1 Fluticasone Propionate

Chronic overdosage of fluticasone propionate may result in signs/symptoms of hypercorticism [see *Warnings and Precautions* (5.8)]. Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate CFC inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at dosages of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in subjects were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups.

10.2 Salmeterol

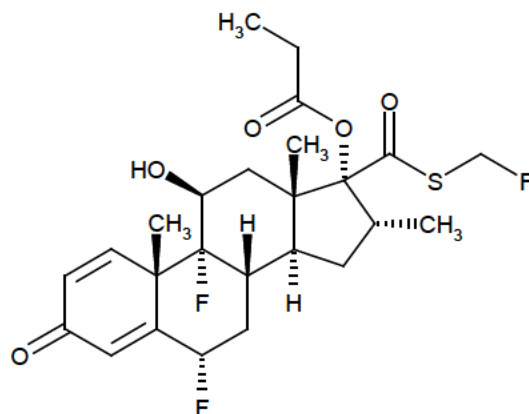
The expected signs and symptoms with overdosage of salmeterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). Overdosage with salmeterol can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias.

As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of salmeterol.

11 DESCRIPTION

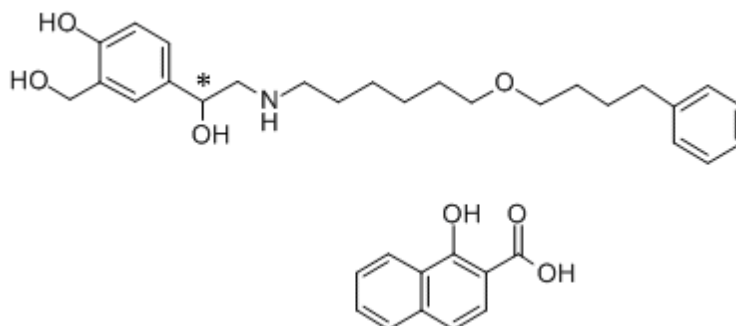
Wixela™ Inhub™ 100/50, Wixela™ Inhub™ 250/50, and Wixela™ Inhub™ 500/50 are combinations of fluticasone propionate and salmeterol xinafoate.

One active component of Wixela™ Inhub™ is fluticasone propionate, a corticosteroid having the chemical name *S*-Fluoromethyl 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate and the following chemical structure:



Fluticasone propionate, USP is a white to almost white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

The other active component of Wixela™ Inhub™ is salmeterol xinafoate, a beta₂-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. It has the chemical name (±)-4-Hydroxy-α'-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-*m*-xylene-α,α'-diol 1-hydroxy-2-naphthoate (salt) and the following chemical structure:



Salmeterol xinafoate, USP is a white to almost white powder with a molecular weight of 603.8, and the empirical formula is $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

Wixela™ Inhub™ is a grey colored plastic inhaler containing two foil sealed discs, each disc containing 30 pre-metered doses. Each of the 60 doses contains a white to off white powder mix of micronized fluticasone propionate (100, 250, or 500 mcg) and micronized salmeterol xinafoate salt (72.5 mcg, equivalent to 50 mcg of salmeterol base) in 12.5 mg of formulation containing lactose monohydrate (which contains milk proteins). After the inhaler is activated, the powder is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized *in vitro* test conditions, Wixela™ Inhub™ delivers 93, 233, and 465 mcg of fluticasone propionate and 45 mcg of salmeterol base per dose from Wixela™ Inhub™ 100/50, Wixela™ Inhub™ 250/50, and Wixela™ Inhub™ 500/50, respectively, when tested at a flow rate of 60 L/min for 2 seconds.

In adult subjects with obstructive lung disease and severely compromised lung function (mean FEV₁ 20% to 30% of predicted), mean peak inspiratory flow (PIF) through another dry powder inhaler was 82.4 L/min (range: 46.1 to 115.3 L/min).

Inhalation profiles for adolescent (N = 13, aged 12 to 17 years) and adult (N = 17, aged 18 to 50 years) subjects with asthma inhaling maximally through another dry powder inhaler show mean PIF of 122.2 L/min (range: 81.6 to 152.1 L/min). Inhalation profiles for pediatric subjects with asthma inhaling maximally through another dry powder inhaler show a mean PIF of 75.5 L/min (range: 49.0 to 104.8 L/min) for the 4-year-old subject set (N = 20) and 107.3 L/min (range: 82.8 to 125.6 L/min) for the 8-year-old subject set (N = 20).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

Meets USP Aerodynamic Particle Size Distribution Test 2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

WIXELA™ INHUB™: Wixela™ Inhub™ contains both fluticasone propionate and salmeterol. The mechanisms of action described below for the individual components apply to Wixela™ Inhub™. These drugs represent 2 different classes of medications (a synthetic corticosteroid and a LABA) that have different effects on clinical, physiologic, and inflammatory indices.

Fluticasone Propionate: Fluticasone propionate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone propionate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor that is 18 times that of dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results. The clinical significance of these findings is unknown.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Inflammation is also a component in the pathogenesis of COPD. In contrast to asthma, however, the predominant inflammatory cells in COPD include neutrophils, CD8+ T-lymphocytes, and macrophages. The effects of corticosteroids in the treatment of COPD are not well defined and ICS and fluticasone propionate when used apart from Wixela™ Inhub™ are not indicated for the treatment of COPD.

Salmeterol Xinafoate: Salmeterol is a selective LABA. *In vitro* studies show salmeterol to be at least 50 times more selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-adrenoceptors are the predominant receptors in the heart, there are also beta₂-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but their presence raises the possibility that even selective beta₂-agonists may have cardiac effects.

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D₂, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

12.2 Pharmacodynamics

Fluticasone Propionate and Salmeterol Inhalation Powder: Healthy Subjects: Cardiovascular Effects: Since systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher doses were used to produce measurable effects. Four (4) trials were conducted with healthy adult subjects: (1) a single-dose crossover trial using 2 inhalations of fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg, fluticasone propionate inhalation powder 500 mcg and salmeterol inhalation powder 50 mcg given concurrently, or fluticasone propionate inhalation powder 500 mcg given alone, (2) a cumulative dose trial using 50 to 400 mcg of salmeterol inhalation powder given alone or as fluticasone propionate and salmeterol

inhalation powder 500 mcg/50 mcg, (3) a repeat-dose trial for 11 days using 2 inhalations twice daily of fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg, fluticasone propionate inhalation powder 250 mcg, or salmeterol inhalation powder 50 mcg, and (4) a single-dose trial using 5 inhalations of fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg, fluticasone propionate inhalation powder 100 mcg alone, or placebo. In these trials no significant differences were observed in the pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given as fluticasone propionate and salmeterol inhalation powder, concurrently with fluticasone propionate from separate inhalers, or as salmeterol alone. The systemic pharmacodynamic effects of salmeterol were not altered by the presence of fluticasone propionate in fluticasone propionate and salmeterol inhalation powder. The potential effect of salmeterol on the effects of fluticasone propionate on the HPA axis was also evaluated in these trials.

Hypothalamic-Pituitary-Adrenal Axis Effects: No significant differences across treatments were observed in 24-hour urinary cortisol excretion and, where measured, 24-hour plasma cortisol AUC. The systemic pharmacodynamic effects of fluticasone propionate were not altered by the presence of salmeterol in fluticasone propionate and salmeterol inhalation powder in healthy subjects.

Subjects with Asthma: Adult and Adolescent Subjects: Cardiovascular Effects: In clinical trials with fluticasone propionate and salmeterol inhalation powder in adult and adolescent subjects aged 12 years and older with asthma, no significant differences were observed in the systemic pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given alone or as fluticasone propionate and salmeterol inhalation powder. In 72 adult and adolescent subjects with asthma given either fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg or fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg, continuous 24-hour electrocardiographic monitoring was performed after the first dose and after 12 weeks of therapy, and no clinically significant dysrhythmias were noted.

Hypothalamic-Pituitary-Adrenal Axis Effects: In a 28-week trial in adult and adolescent subjects with asthma, fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg twice daily was compared with the concurrent use of salmeterol inhalation powder 50 mcg plus fluticasone propionate inhalation powder 500 mcg from separate inhalers or fluticasone propionate inhalation powder 500 mcg alone. No significant differences across treatments were observed in serum cortisol AUC after 12 weeks of dosing or in 24-hour urinary cortisol excretion after 12 and 28 weeks.

In a 12-week trial in adult and adolescent subjects with asthma, fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg twice daily was compared with fluticasone propionate inhalation powder 250 mcg alone, salmeterol inhalation powder 50 mcg alone, and placebo. For most subjects, the ability to increase cortisol production in response to stress, as assessed by 30-minute cosyntropin stimulation, remained intact with fluticasone propionate and salmeterol inhalation powder. One subject (3%) who received fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg had an abnormal response (peak serum cortisol less than 18 mcg/dL) after dosing, compared with 2 subjects (6%) who received placebo, 2 subjects (6%) who received fluticasone propionate 250 mcg, and no subjects who received salmeterol.

In a repeat-dose, 3-way crossover trial, 1 inhalation twice daily of fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg, FLOVENT® DISKUS® 100 mcg (fluticasone propionate inhalation powder 100 mcg), or placebo was administered to 20 adult and adolescent subjects with asthma. After 28 days of treatment, geometric mean serum cortisol AUC over 12 hours showed no significant difference between fluticasone propionate and salmeterol inhalation powder and FLOVENT DISKUS or between either active treatment and placebo.

Pediatric Subjects: Hypothalamic-Pituitary-Adrenal Axis Effects: In a 12-week trial in subjects with asthma aged 4 to 11 years who were receiving ICS at trial entry, fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg twice daily was compared with fluticasone propionate inhalation powder 100 mcg administered twice daily via a dry powder inhaler. The values for 24-hour urinary cortisol excretion at trial entry and after 12 weeks of treatment were similar within each treatment group. After 12 weeks, 24-hour urinary cortisol excretion was also similar between the 2 groups.

Subjects with Chronic Obstructive Pulmonary Disease: Cardiovascular Effects: In clinical trials with fluticasone propionate and salmeterol inhalation powder in subjects with COPD, no significant differences were seen in pulse rate, blood pressure, potassium, and glucose between fluticasone propionate and salmeterol inhalation powder, the individual components of fluticasone propionate and salmeterol inhalation powder, and placebo. In a trial of fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg, 8 subjects (2 [1.1%] in the group given fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg, 1 [0.5%] in the fluticasone propionate 250 mcg group, 3 [1.7%] in the salmeterol group, and 2 [1.1%] in the placebo group) had QTc intervals > 470 msec at least 1 time during the treatment period. Five (5) of these 8 subjects had a prolonged QTc interval at baseline.

In a 24-week trial, 130 subjects with COPD received continuous 24-hour electrocardiographic monitoring prior to the first dose and after 4 weeks of twice-daily treatment with either fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg, fluticasone propionate inhalation powder 500 mcg, salmeterol inhalation powder 50 mcg, or placebo. No significant differences in ventricular or supraventricular arrhythmias and heart rate were observed among the groups treated with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg, the individual components, or placebo. One (1) subject in the fluticasone propionate group experienced atrial flutter/atrial fibrillation, and 1 subject in the group given fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg experienced heart block. There were 3 cases of nonsustained ventricular tachycardia (1 each in the placebo, salmeterol, and fluticasone propionate 500 mcg treatment groups).

In 24-week clinical trials in subjects with COPD, the incidence of clinically significant ECG abnormalities (myocardial ischemia, ventricular hypertrophy, clinically significant conduction abnormalities, clinically significant arrhythmias) was lower for subjects who received salmeterol (1%, 9 of 688 subjects who received either salmeterol 50 mcg or fluticasone propionate and salmeterol inhalation powder) compared with placebo (3%, 10 of 370 subjects).

No significant differences with salmeterol 50 mcg alone or in combination with fluticasone propionate as fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg were observed on pulse rate and systolic and diastolic blood pressure in a subset of subjects with COPD who underwent 12-hour serial vital sign measurements after the first dose (n = 183) and after 12 weeks of therapy (n = 149). Median changes from baseline in pulse rate and systolic and diastolic blood pressure were similar to those seen with placebo.

Hypothalamic-Pituitary-Adrenal Axis Effects: Short-cosyntropin stimulation testing was performed both at Day 1 and Endpoint in 101 subjects with COPD receiving twice-daily fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg, fluticasone propionate inhalation powder 250 mcg, salmeterol inhalation powder 50 mcg, or placebo. For most subjects, the ability to increase cortisol production in response to stress, as assessed by short cosyntropin stimulation, remained intact with fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg. One (1) subject (3%) who received fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg had an abnormal stimulated cortisol response (peak cortisol < 14.5 mcg/dL assessed by high-performance liquid chromatography) after dosing, compared with 2 subjects (9%) who received fluticasone propionate 250 mcg, 2 subjects (7%) who received salmeterol 50 mcg, and 1 subject (4%) who received placebo following 24 weeks of treatment or early discontinuation from trial.

After 36 weeks of dosing, serum cortisol concentrations in a subset of subjects with COPD (n = 83) were 22% lower in subjects receiving fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg and 21% lower in subjects receiving fluticasone propionate 500 mcg than in subjects receiving placebo.

Other Fluticasone Propionate Products: Subjects with Asthma: Hypothalamic-Pituitary-Adrenal Axis Effects: In clinical trials with fluticasone propionate inhalation powder using dosages up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol < 18 mcg/dL assessed by radioimmunoassay) were noted both in subjects receiving fluticasone propionate and in subjects receiving placebo. The incidence of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year trial carried out with a dry powder inhaler in 64 subjects with mild, persistent asthma (mean FEV₁ 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo, no subject receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin infusion (peak serum cortisol < 18 mcg/dL). With a peak cortisol threshold of < 35 mcg/dL, 1 subject receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing at 18 months and 2 years was normal. Another subject receiving fluticasone propionate (5%) had an abnormal response at 2 years. No subject on placebo had an abnormal response at 1 or 2 years.

Subjects with Chronic Obstructive Pulmonary Disease: Hypothalamic-Pituitary-Adrenal Axis Effects: After 4 weeks of dosing, the steady-state fluticasone propionate pharmacokinetics and serum cortisol levels were described in a subset of subjects with COPD (n = 86) randomized to twice-daily fluticasone propionate inhalation powder via a dry powder inhaler 500 mcg, fluticasone propionate inhalation powder 250 mcg, or placebo. Serial serum cortisol concentrations were measured across a 12-hour dosing interval. Serum cortisol concentrations following 250 mcg and 500 mcg twice-daily dosing were 10% and 21% lower than placebo, respectively, indicating a dose-dependent increase in systemic exposure to fluticasone propionate.

Other Salmeterol Xinafoate Products: Subjects with Asthma: Cardiovascular Effects: Inhaled salmeterol, like other beta-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium [see *Warnings and Precautions (5.12, 5.18)*]. The cardiovascular effects (heart rate, blood pressure) associated with salmeterol inhalation aerosol occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

The effects of rising inhaled doses of salmeterol and standard inhaled doses of albuterol were studied in volunteers and in subjects with asthma. Salmeterol doses up to 84 mcg administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adult and adolescent subjects receiving 50 mcg doses of salmeterol inhalation powder (N = 60) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 1 month of therapy, and no clinically significant dysrhythmias were noted.

Concomitant Use of Wixela™ Inhub™ with Other Respiratory Medicines: Short-acting Beta₂-agonists: In clinical trials in subjects with asthma, the mean daily need for albuterol by 166 adult and adolescent subjects aged 12 years and older using fluticasone propionate and salmeterol inhalation powder was approximately 1.3 inhalations/day and ranged from 0 to 9 inhalations/day. Five percent (5%) of subjects using fluticasone propionate and salmeterol inhalation powder in these trials averaged 6 or more inhalations per day over the course of the 12-week trials. No increase in frequency of cardiovascular adverse events was observed among subjects who averaged 6 or more inhalations per day.

In a clinical trial in subjects with COPD, the mean daily need for albuterol for subjects using fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg was 4.1 inhalations/day. Twenty-six percent (26%) of subjects using fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg averaged 6

or more inhalations of albuterol per day over the course of the 24-week trial. No increase in frequency of cardiovascular adverse reactions was observed among subjects who averaged 6 or more inhalations per day.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by adult and adolescent subjects aged 12 years and older receiving fluticasone propionate and salmeterol inhalation powder has not been completely evaluated. In clinical trials in subjects with asthma, 39 subjects receiving fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg, fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg, or fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg twice daily concurrently with a theophylline product had adverse event rates similar to those in 304 subjects receiving fluticasone propionate and salmeterol inhalation powder without theophylline. Similar results were observed in subjects receiving salmeterol 50 mcg plus fluticasone propionate 500 mcg twice daily concurrently with a theophylline product (n = 39) or without theophylline (n = 132).

In a clinical trial in subjects with COPD, 17 subjects receiving fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg twice daily concurrently with a theophylline product had adverse event rates similar to those in 161 subjects receiving fluticasone propionate and salmeterol inhalation powder without theophylline. Based on the available data, the concomitant administration of methylxanthines with fluticasone propionate and salmeterol inhalation powder did not alter the observed adverse event profile.

Fluticasone Propionate Nasal Spray: In adult and adolescent subjects aged 12 years and older receiving fluticasone propionate and salmeterol inhalation powder in clinical trials, no difference in the profile of adverse events or HPA axis effects was noted between subjects who were receiving FLONASE[®] (fluticasone propionate) Nasal Spray, 50 mcg concurrently (n = 46) and those who were not (n = 130).

12.3 Pharmacokinetics

Absorption: *Fluticasone Propionate:* Healthy Subjects: Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Trials using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (< 1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed.

Following administration of fluticasone propionate and salmeterol inhalation powder to healthy adult subjects, peak plasma concentrations of fluticasone propionate were achieved in 1 to 2 hours. In a single-dose crossover trial, a higher-than-recommended dose of fluticasone propionate and salmeterol inhalation powder was administered to 14 healthy adult subjects. Two (2) inhalations of the following treatments were administered: fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg, fluticasone propionate inhalation powder 500 mcg and salmeterol inhalation powder 50 mcg given concurrently, and fluticasone propionate inhalation powder 500 mcg alone. Mean peak plasma concentrations of fluticasone propionate averaged 107, 94, and 120 pg/mL, respectively, indicating no significant changes in systemic exposures of fluticasone propionate.

In 15 healthy subjects, systemic exposure to fluticasone propionate from 4 inhalations of ADVAIR[®] HFA 230/21 (fluticasone propionate 230 mcg and salmeterol 21 mcg) Inhalation Aerosol (920/84 mcg) and 2 inhalations of fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg (1,000 mcg/100 mcg) was similar between the 2 inhalers (i.e., 799 versus 832 pg•h/mL, respectively), but approximately half the systemic exposure from 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg (880 mcg, AUC = 1,543 pg•h/mL). Similar results were observed for peak fluticasone propionate plasma concentrations (186 and 182 pg/mL from ADVAIR HFA and fluticasone propionate and salmeterol inhalation powder, respectively, and 307 pg/mL from the fluticasone propionate CFC inhalation aerosol). Absolute bioavailability

of fluticasone propionate was 5.3% and 5.5% following administration of ADVAIR HFA and fluticasone propionate and salmeterol inhalation powder, respectively.

Subjects with Asthma and COPD: Peak steady-state fluticasone propionate plasma concentrations in adult subjects with asthma (N = 11) ranged from undetectable to 266 pg/mL after a 500 mcg twice-daily dose of fluticasone propionate inhalation powder using a dry powder inhaler. The mean fluticasone propionate plasma concentration was 110 pg/mL.

Full pharmacokinetic profiles were obtained from 9 female and 16 male subjects with asthma given fluticasone propionate inhalation powder 500 mcg twice daily using a dry powder inhaler and from 14 female and 43 male subjects with COPD given 250 or 500 mcg twice daily. No overall differences in fluticasone propionate pharmacokinetics were observed.

Peak steady-state fluticasone propionate plasma concentrations in subjects with COPD averaged 53 pg/mL (range: 19.3 to 159.3 pg/mL) after treatment with 250 mcg twice daily (n = 30) and 84 pg/mL (range: 24.3 to 197.1 pg/mL) after treatment with 500 mcg twice daily (n = 27) via a fluticasone propionate dry powder inhaler. In another trial in subjects with COPD, peak steady-state fluticasone propionate plasma concentrations averaged 115 pg/mL (range: 52.6 to 366.0 pg/mL) after treatment with 500 mcg twice daily via a fluticasone propionate dry powder inhaler (n = 15) and 105 pg/mL (range: 22.5 to 299.0 pg/mL) via fluticasone propionate and salmeterol inhalation powder (n = 24).

Salmeterol Xinafoate: Healthy Subjects: Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and eliminated independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

Following administration of fluticasone propionate and salmeterol inhalation powder to healthy adult subjects, peak plasma concentrations of salmeterol were achieved in about 5 minutes.

In 15 healthy subjects receiving ADVAIR HFA 230/21 Inhalation Aerosol (920/84 mcg) and fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg (1,000 mcg/100 mcg), systemic exposure to salmeterol was higher (317 versus 169 pg•h/mL) and peak salmeterol concentrations were lower (196 versus 223 pg/mL) following ADVAIR HFA compared with fluticasone propionate and salmeterol inhalation powder, although pharmacodynamic results were comparable.

Subjects with Asthma: Because of the small therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended dosages (50 mcg of salmeterol inhalation powder twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7 subjects with asthma; plasma concentrations were very low, with mean peak concentrations of 167 pg/mL at 20 minutes and no accumulation with repeated doses.

Distribution: Fluticasone Propionate: Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averages 99%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

Salmeterol: The percentage of salmeterol bound to human plasma proteins averages 96% *in vitro* over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

Metabolism: Fluticasone Propionate: The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for < 0.02% of the total. The only circulating metabolite detected in man is the 17 β -carboxylic acid derivative of fluticasone propionate, which is formed through the CYP3A4 pathway. This metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol *in vitro* and negligible pharmacological activity in animal studies. Other metabolites detected *in vitro* using cultured human hepatoma cells have not been detected in man.

Salmeterol: Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominantly in the feces. No significant amount of unchanged salmeterol base was detected in either urine or feces.

An *in vitro* study using human liver microsomes showed that salmeterol is extensively metabolized to α -hydroxysalmeterol (aliphatic oxidation) by CYP3A4. Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of α -hydroxysalmeterol *in vitro*.

Elimination: Fluticasone Propionate: Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites. Terminal half-life estimates of fluticasone propionate for ADVAIR HFA, fluticasone propionate and salmeterol inhalation powder, and fluticasone propionate CFC inhalation aerosol were similar and averaged 5.6 hours.

Salmeterol: In 2 healthy adult subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only).

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (> 99%) and has a long elimination half-life of 11 days. No terminal half-life estimates were calculated for salmeterol following administration of fluticasone propionate and salmeterol inhalation powder.

Specific Populations: A population pharmacokinetic analysis was performed for fluticasone propionate and salmeterol utilizing data from 9 controlled clinical trials that included 350 subjects with asthma aged 4 to 77 years who received treatment with fluticasone propionate and salmeterol inhalation powder, the combination of HFA-propelled fluticasone propionate and salmeterol inhalation aerosol (ADVAIR HFA), fluticasone propionate inhalation powder (FLOVENT DISKUS), HFA-propelled fluticasone propionate inhalation aerosol (FLOVENT[®] HFA), or CFC-propelled fluticasone propionate inhalation aerosol. The population pharmacokinetic analyses for fluticasone propionate and salmeterol showed no clinically relevant effects of age, gender, race, body weight, body mass index, or percent of predicted FEV₁ on apparent clearance and apparent volume of distribution.

Age: When the population pharmacokinetic analysis for fluticasone propionate was divided into subgroups based on fluticasone propionate strength, formulation, and age (adolescents/adults and children), there were some differences in fluticasone propionate exposure. Higher fluticasone propionate exposure from fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg compared with FLOVENT DISKUS 100 mcg was observed in adolescents and adults (ratio 1.52 [90% CI: 1.08, 2.13]). However, in clinical trials of up to 12 weeks' duration comparing fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg and

FLOVENT DISKUS 100 mcg in adolescents and adults, no differences in systemic effects of corticosteroid treatment (e.g., HPA axis effects) were observed. Similar fluticasone propionate exposure was observed from fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg and FLOVENT DISKUS 500 mcg (ratio 0.83 [90% CI: 0.65, 1.07]) in adolescents and adults.

Steady-state systemic exposure to salmeterol when delivered as fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg, fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg, or ADVAIR HFA 115/21 (fluticasone propionate 115 mcg and salmeterol 21 mcg) Inhalation Aerosol was evaluated in 127 subjects aged 4 to 57 years. The geometric mean AUC was 325 pg•h/mL (90% CI: 309, 341) in adolescents and adults.

The population pharmacokinetic analysis included 160 subjects with asthma aged 4 to 11 years who received fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg or FLOVENT DISKUS 100 mcg. Higher fluticasone propionate exposure (AUC) was observed in children from fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg compared with FLOVENT DISKUS 100 mcg (ratio 1.20 [90% CI: 1.06, 1.37]). Higher fluticasone propionate exposure (AUC) from fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg was observed in children compared with adolescents and adults (ratio 1.63 [90% CI: 1.35, 1.96]). However, in clinical trials of up to 12 weeks' duration comparing fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg and FLOVENT DISKUS 100 mcg in both adolescents and adults and in children, no differences in systemic effects of corticosteroid treatment (e.g., HPA axis effects) were observed.

Exposure to salmeterol was higher in children compared with adolescents and adults who received fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg (ratio 1.23 [90% CI: 1.10, 1.38]). However, in clinical trials of up to 12 weeks' duration with fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg in both adolescents and adults and in children, no differences in systemic effects of beta₂-agonist treatment (e.g., cardiovascular effects, tremor) were observed.

Male and Female Patients: The population pharmacokinetic analysis involved 202 males and 148 females with asthma who received fluticasone propionate alone or in combination with salmeterol and showed no gender differences for fluticasone propionate pharmacokinetics.

The population pharmacokinetic analysis involved 76 males and 51 females with asthma who received salmeterol in combination with fluticasone propionate and showed no gender differences for salmeterol pharmacokinetics.

Patients with Hepatic and Renal Impairment: Formal pharmacokinetic studies using fluticasone propionate and salmeterol inhalation powder have not been conducted in patients with hepatic or renal impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Drug Interaction Studies: In the repeat- and single-dose trials, there was no evidence of significant drug interaction in systemic exposure between fluticasone propionate and salmeterol when given alone or in combination via a dry powder inhaler. The population pharmacokinetic analysis from 9 controlled clinical trials in 350 subjects with asthma showed no significant effects on fluticasone propionate or salmeterol pharmacokinetics following co-administration with beta₂-agonists, corticosteroids, antihistamines, or theophyllines.

Inhibitors of Cytochrome P450 3A4: Ritonavir; Fluticasone Propionate: Fluticasone propionate is a substrate of CYP3A4. Coadministration of fluticasone propionate and the strong CYP3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction trial in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (< 10 pg/mL) in most subjects, and when concentrations were detectable peak levels (C_{max}) averaged 11.9 pg/mL (range: 10.8 to 14.1 pg/mL) and $AUC_{(0-\tau)}$ averaged 8.43 pg•h/mL (range: 4.2 to 18.8 pg•h/mL). Fluticasone propionate C_{max} and $AUC_{(0-\tau)}$ increased to 318 pg/mL (range: 110 to 648 pg/mL) and 3,102.6 pg•h/mL (range: 1,207.1 to 5,662.0 pg•h/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in serum cortisol AUC.

Ketoconazole; Fluticasone Propionate: In a placebo-controlled crossover trial in 8 healthy adult volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

Salmeterol: In a placebo-controlled, crossover drug interaction trial in 20 healthy male and female subjects, coadministration of salmeterol (50 mcg twice daily) and the strong CYP3A4 inhibitor ketoconazole (400 mg once daily) for 7 days resulted in a significant increase in plasma salmeterol exposure as determined by a 16-fold increase in AUC (ratio with and without ketoconazole 15.76 [90% CI: 10.66, 23.31]) mainly due to increased bioavailability of the swallowed portion of the dose. Peak plasma salmeterol concentrations were increased by 1.4-fold (90% CI: 1.23, 1.68). Three (3) out of 20 subjects (15%) were withdrawn from salmeterol and ketoconazole coadministration due to beta-agonist-mediated systemic effects (2 with QTc prolongation and 1 with palpitations and sinus tachycardia). Coadministration of salmeterol and ketoconazole did not result in a clinically significant effect on mean heart rate, mean blood potassium, or mean blood glucose. Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration.

Erythromycin; Fluticasone Propionate: In a multiple-dose drug interaction trial, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Salmeterol: In a repeat-dose trial in 13 healthy subjects, concomitant administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol resulted in a 40% increase in salmeterol C_{max} at steady state (ratio with and without erythromycin 1.4 [90% CI: 0.96, 2.03], $P = 0.12$), a 3.6-beat/min increase in heart rate ([95% CI: 0.19, 7.03], $P < 0.04$), a 5.8-msec increase in QTc interval ([95% CI: -6.14, 17.77], $P = 0.34$), and no change in plasma potassium.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone Propionate: Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 5 and 10 times the MRHDID for adults and children, respectively, on a mcg/m² basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than and approximately equivalent to the MRHDID for adults and children, respectively, on a mcg/m² basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells *in vitro*. No significant clastogenic effect was seen in cultured human peripheral lymphocytes *in vitro* or in the *in vivo* mouse micronucleus test.

Fertility and reproductive performance were unaffected in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 0.5 times the MRHDID for adults on a mcg/m² basis).

Salmeterol: In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1,400 mcg/kg and above (approximately 20 times the MRHDID for adults and children based on comparison of the plasma AUCs) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumors were seen at 200 mcg/kg (approximately 3 times the MRHDID for adults and children based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 680 mcg/kg and above (approximately 66 and 35 times the MRHDID for adults and children, respectively, on a mcg/m² basis). No tumors were seen at 210 mcg/kg (approximately 20 and 10 times the MRHDID for adults and children, respectively, on a mcg/m² basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation *in vitro*. No clastogenic activity occurred *in vitro* in human lymphocytes or *in vivo* in a rat micronucleus test.

Fertility and reproductive performance were unaffected in male and female rats at oral doses up to 2,000 mcg/kg (approximately 195 times the MRHDID for adults on a mcg/m² basis).

13.2 Animal Toxicology and/or Pharmacology

Preclinical: Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical relevance of these findings is unknown.

14 CLINICAL STUDIES

14.1 Asthma

Adult and Adolescent Subjects Aged 12 Years and Older: In clinical trials comparing fluticasone propionate and salmeterol inhalation powder with its individual components, improvements in most efficacy endpoints were greater with fluticasone propionate and salmeterol inhalation powder than with the use of either fluticasone propionate or salmeterol alone. In addition, clinical trials showed similar results between fluticasone propionate and salmeterol inhalation powder and the concurrent use of fluticasone propionate plus salmeterol at corresponding doses from separate inhalers.

Trials Comparing Fluticasone Propionate and Salmeterol Inhalation Powder with Fluticasone Propionate Alone or Salmeterol Alone: Three (3) double-blind, parallel-group clinical trials were conducted with fluticasone propionate and salmeterol inhalation powder in 1,208 adult and adolescent subjects (aged 12 years and older, baseline FEV₁ 63% to 72% of predicted normal) with asthma that was not optimally controlled on their current therapy. All treatments were inhalation powders given as 1 inhalation from a dry powder inhaler twice daily, and other maintenance therapies were discontinued.

Trial 1: Clinical Trial with Fluticasone Propionate and Salmeterol Inhalation Powder 100 mcg/50 mcg: This placebo-controlled, 12-week, U.S. trial compared fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg with its individual components, fluticasone propionate 100 mcg and salmeterol 50 mcg. The trial was stratified according to baseline asthma maintenance therapy; subjects were using either ICS (n = 250) (daily doses of beclomethasone dipropionate 252 to 420 mcg; flunisolide 1,000 mcg; fluticasone propionate inhalation aerosol 176 mcg; or triamcinolone acetonide 600 to 1,000 mcg) or salmeterol (n = 106). Baseline FEV₁

measurements were similar across treatments: fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg, 2.17 L; fluticasone propionate 100 mcg, 2.11 L; salmeterol, 2.13 L; and placebo, 2.15 L.

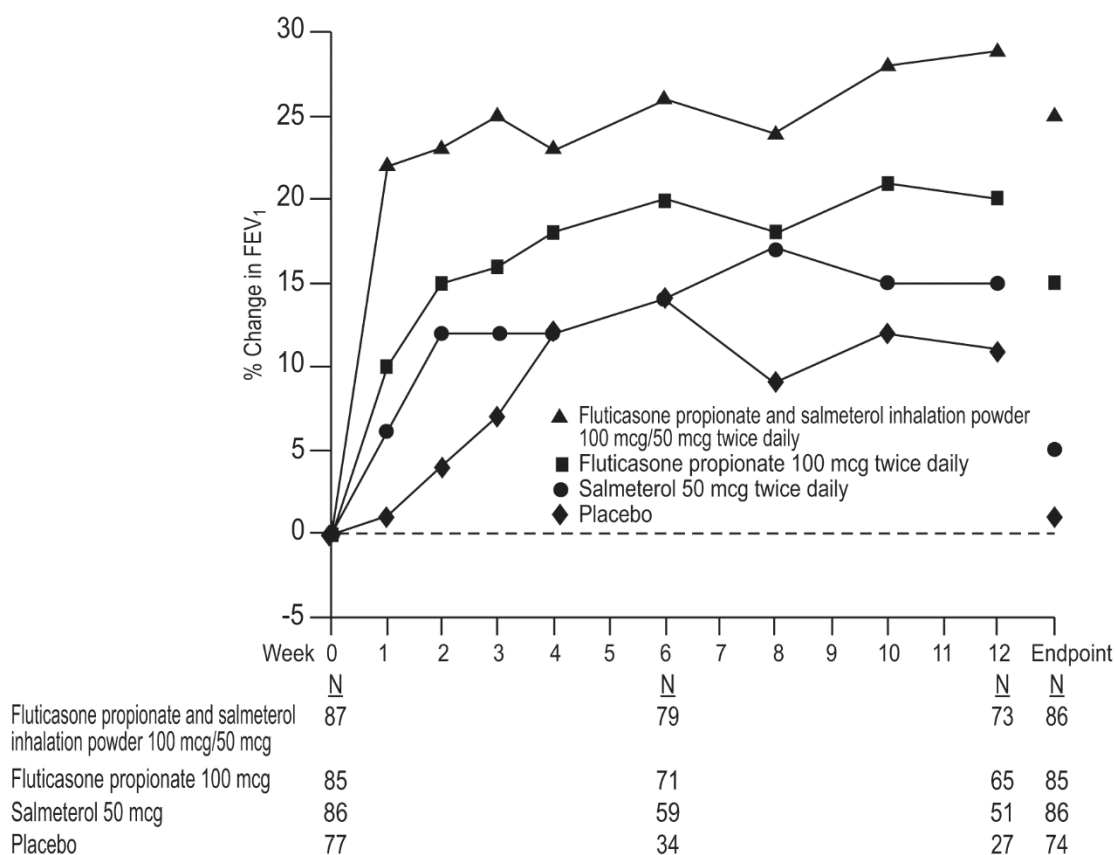
Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were utilized for this placebo-controlled trial. Worsening asthma was defined as a clinically important decrease in FEV₁ or PEF, increase in use of VENTOLIN[®] (albuterol, USP) Inhalation Aerosol, increase in night awakenings due to asthma, emergency intervention or hospitalization due to asthma, or requirement for asthma medication not allowed by the protocol. As shown in Table 4, statistically significantly fewer subjects receiving fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg were withdrawn due to worsening asthma compared with fluticasone propionate, salmeterol, and placebo.

Table 4. Percent of Subjects Withdrawn due to Worsening Asthma in Subjects Previously Treated with Either Inhaled Corticosteroids or Salmeterol (Trial 1)

Fluticasone Propionate and Salmeterol Inhalation Powder 100 mcg/50 mcg (n = 87)	Fluticasone Propionate 100 mcg (n = 85)	Salmeterol 50 mcg (n = 86)	Placebo (n = 77)
3%	11%	35%	49%

The FEV₁ results are displayed in Figure 1. Because this trial used predetermined criteria for worsening asthma, which caused more subjects in the placebo group to be withdrawn, FEV₁ results at Endpoint (last available FEV₁ result) are also provided. Subjects receiving fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg had significantly greater improvements in FEV₁ (0.51 L, 25%) compared with fluticasone propionate 100 mcg (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L, 1%). These improvements in FEV₁ with fluticasone propionate and salmeterol inhalation powder were achieved regardless of baseline asthma maintenance therapy (ICS or salmeterol).

Figure 1. Mean Percent Change from Baseline in FEV₁ in Subjects with Asthma Previously Treated with Either Inhaled Corticosteroids or Salmeterol (Trial 1)



The effect of fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg on morning and evening PEF endpoints is shown in Table 5.

Table 5. Peak Expiratory Flow Results for Subjects with Asthma Previously Treated with Either Inhaled Corticosteroids or Salmeterol (Trial 1)

Efficacy Variable ^a	Fluticasone Propionate and Salmeterol Inhalation Powder 100 mcg/50 mcg (n = 87)	Fluticasone Propionate 100 mcg (n = 85)	Salmeterol 50 mcg (n = 86)	Placebo (n = 77)
AM PEF (L/min)				
Baseline	393	374	369	382
Change from baseline	53	17	-2	-24
PM PEF (L/min)				
Baseline	418	390	396	398
Change from baseline	35	18	-7	-13

^a Change from baseline = change from baseline at Endpoint (last available data).

The subjective impact of asthma on subjects' perception of health was evaluated through use of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7 point scale where 1 = maximum impairment and 7 = none). Subjects receiving fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg had clinically meaningful improvements in overall asthma-specific quality of life as defined by a difference between groups of ≥ 0.5 points in change from baseline AQLQ scores (difference in AQLQ score of 1.25 compared with placebo).

Trial 2: Clinical Trial with Fluticasone Propionate and Salmeterol Inhalation Powder 250 mcg/50 mcg: This placebo-controlled, 12-week, U.S. trial compared fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg with its individual components, fluticasone propionate 250 mcg and salmeterol 50 mcg, in 349 subjects with asthma using ICS (daily doses of beclomethasone dipropionate 462 to 672 mcg; flunisolide 1,250 to 2,000 mcg; fluticasone propionate inhalation aerosol 440 mcg; or triamcinolone acetonide 1,100 to 1,600 mcg). Baseline FEV₁ measurements were similar across treatments: fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg, 2.23 L; fluticasone propionate 250 mcg, 2.12 L; salmeterol, 2.20 L; and placebo, 2.19 L.

Efficacy results in this trial were similar to those observed in Trial 1. Subjects receiving fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg had significantly greater improvements in FEV₁ (0.48 L, 23%) compared with fluticasone propionate 250 mcg (0.25 L, 13%), salmeterol (0.05 L, 4%), and placebo (decrease of 0.11 L, decrease of 5%). Statistically significantly fewer subjects receiving fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg were withdrawn from this trial for worsening asthma (4%) compared with fluticasone propionate (22%), salmeterol (38%), and placebo (62%). In addition, fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg was superior to fluticasone propionate, salmeterol, and placebo for improvements in morning and evening PEF. Subjects receiving fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg also had clinically meaningful improvements in overall asthma-specific quality of life as described in Trial 1 (difference in AQLQ score of 1.29 compared with placebo).

Trial 3: Clinical Trial with Fluticasone Propionate and Salmeterol Inhalation Powder 500 mcg/50 mcg: This 28-week, non-U.S. trial compared fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg with fluticasone propionate 500 mcg alone and concurrent therapy (salmeterol 50 mcg plus fluticasone propionate 500 mcg administered from separate inhalers) twice daily in 503 subjects with asthma using ICS (daily doses of beclomethasone dipropionate 1,260 to 1,680 mcg; budesonide 1,500 to 2,000 mcg; flunisolide 1,500 to 2,000 mcg; or fluticasone propionate inhalation aerosol 660 to 880 mcg [750 to 1,000 mcg inhalation powder]). The primary efficacy parameter, morning PEF, was collected daily for the first 12 weeks of the trial. The primary purpose of weeks 13 to 28 was to collect safety data.

Baseline PEF measurements were similar across treatments: fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg, 359 L/min; fluticasone propionate 500 mcg, 351 L/min; and concurrent therapy, 345 L/min. Morning PEF improved significantly with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg compared with fluticasone propionate 500 mcg over the 12-week treatment period. Improvements in morning PEF observed with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg were similar to improvements observed with concurrent therapy.

Onset of Action and Progression of Improvement in Asthma Control: The onset of action and progression of improvement in asthma control were evaluated in the 2 placebo-controlled U.S. trials. Following the first dose, the median time to onset of clinically significant bronchodilatation ($\geq 15\%$ improvement in FEV₁) in most subjects was seen within 30 to 60 minutes. Maximum improvement in FEV₁ generally occurred within 3 hours,

and clinically significant improvement was maintained for 12 hours (Figure 2). Following the initial dose, predose FEV₁ relative to Day 1 baseline improved markedly over the first week of treatment and continued to improve over the 12 weeks of treatment in both trials. No diminution in the 12-hour bronchodilator effect was observed with either fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg (Figures 2 and 3) or fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg as assessed by FEV₁ following 12 weeks of therapy.

Figure 2. Percent Change in Serial 12-Hour FEV₁ in Subjects with Asthma Previously Using Either Inhaled Corticosteroids or Salmeterol (Trial 1)

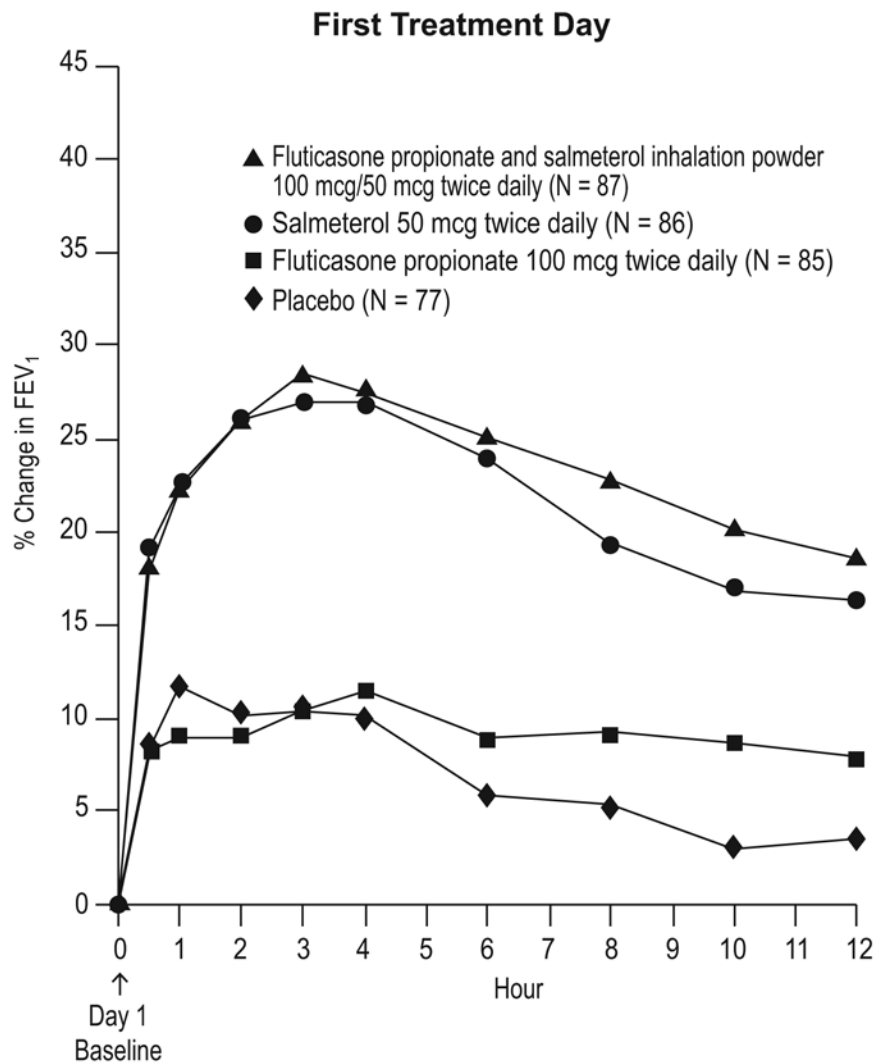
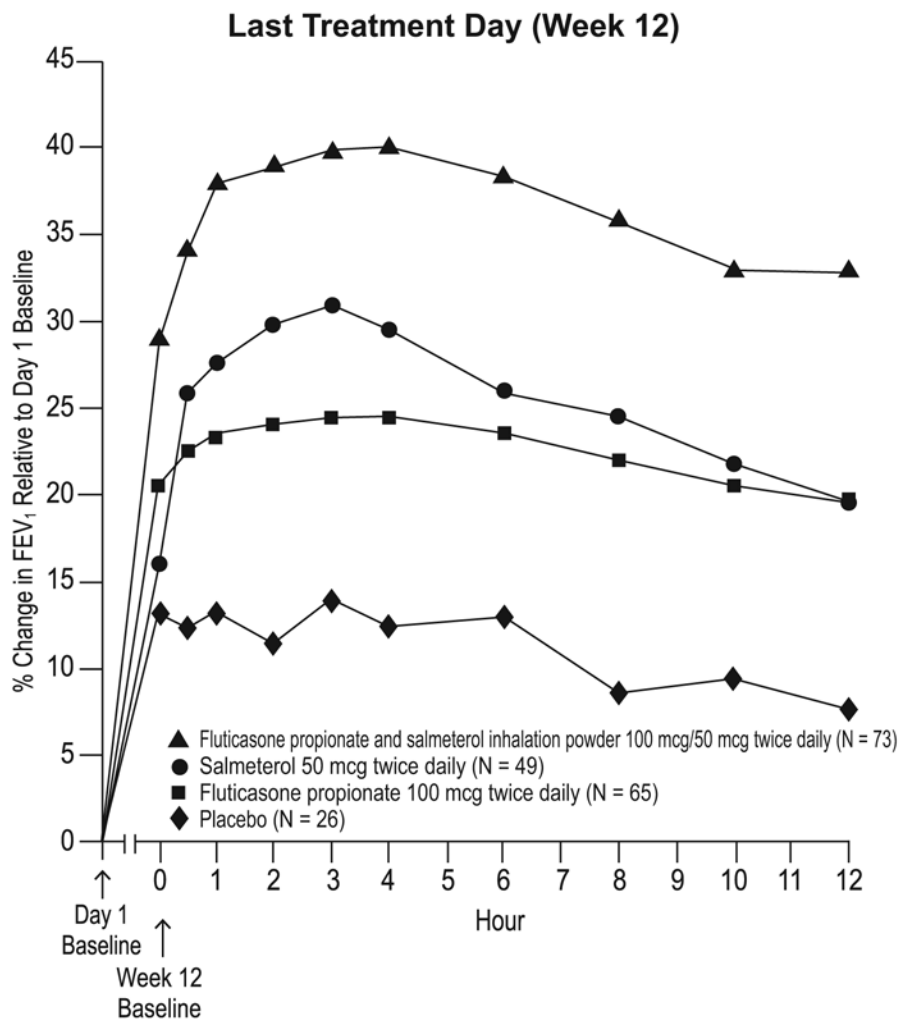


Figure 3. Percent Change in Serial 12-Hour FEV₁ in Subjects with Asthma Previously Using Either Inhaled Corticosteroids or Salmeterol (Trial 1)



Reduction in asthma symptoms and use of rescue VENTOLIN Inhalation Aerosol and improvement in morning and evening PEF also occurred within the first day of treatment with fluticasone propionate and salmeterol inhalation powder, and continued to improve over the 12 weeks of therapy in both trials.

Pediatric Subjects: In a 12-week U.S. trial, fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg twice daily was compared with fluticasone propionate inhalation powder 100 mcg twice daily in 203 children with asthma aged 4 to 11 years. At trial entry, the children were symptomatic on low doses of ICS (beclomethasone dipropionate 252 to 336 mcg/day; budesonide 200 to 400 mcg/day; flunisolide 1,000 mcg/day; triamcinolone acetonide 600 to 1,000 mcg/day; or fluticasone propionate 88 to 250 mcg/day). The primary objective of this trial was to determine the safety of fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg compared with fluticasone propionate inhalation powder 100 mcg in this age group; however, the trial also included secondary efficacy measures of pulmonary function. Morning predose FEV₁ was obtained at baseline and Endpoint (last available FEV₁ result) in children aged 6 to 11 years. In subjects receiving fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg, FEV₁ increased from 1.70 L at baseline (n = 79) to 1.88 L at Endpoint (n = 69) compared with an increase from 1.65 L at baseline (n = 83) to 1.77 L at Endpoint (n = 75) in subjects receiving fluticasone propionate 100 mcg.

The findings of this trial, along with extrapolation of efficacy data from subjects aged 12 years and older, support the overall conclusion that fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg is efficacious in the treatment of asthma in subjects aged 4 to 11 years.

14.2 Chronic Obstructive Pulmonary Disease

The efficacy of fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg and fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg in the treatment of subjects with COPD was evaluated in 6 randomized, double-blind, parallel-group clinical trials in adult subjects aged 40 years and older. These trials were primarily designed to evaluate the efficacy of fluticasone propionate and salmeterol inhalation powder on lung function (3 trials), exacerbations (2 trials), and survival (1 trial).

Lung Function: Two (2) of the 3 clinical trials primarily designed to evaluate the efficacy of fluticasone propionate and salmeterol inhalation powder on lung function were conducted in 1,414 subjects with COPD associated with chronic bronchitis. In these 2 trials, all the subjects had a history of cough productive of sputum that was not attributable to another disease process on most days for at least 3 months of the year for at least 2 years. The trials were randomized, double-blind, parallel-group, 24-week treatment duration. One (1) trial evaluated the efficacy of fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg compared with its components fluticasone propionate 250 mcg and salmeterol 50 mcg and with placebo, and the other trial evaluated the efficacy of fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg compared with its components fluticasone propionate 500 mcg and salmeterol 50 mcg and with placebo. Trial treatments were inhalation powders given as 1 inhalation from the dry powder inhaler twice daily. Maintenance COPD therapies were discontinued, with the exception of theophylline. The subjects had a mean pre-bronchodilator FEV₁ of 41% and 20% reversibility at trial entry. Percent reversibility was calculated as 100 times (FEV₁ post-albuterol minus FEV₁ pre-albuterol)/FEV₁ pre-albuterol.

Improvements in lung function (as defined by predose and postdose FEV₁) were significantly greater with fluticasone propionate and salmeterol inhalation powder than with fluticasone propionate, salmeterol, or placebo. The improvement in lung function with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg was similar to the improvement seen with fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg.

Figures 4 and 5 display predose and 2-hour postdose, respectively, FEV₁ results for the trial with fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg. To account for subject withdrawals during the trial, FEV₁ at Endpoint (last evaluable FEV₁) was evaluated. Subjects receiving fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg had significantly greater improvements in predose FEV₁ at Endpoint (165 mL, 17%) compared with salmeterol 50 mcg (91 mL, 9%) and placebo (1 mL, 1%), demonstrating the contribution of fluticasone propionate to the improvement in lung function with fluticasone propionate and salmeterol inhalation powder (Figure 4). Subjects receiving fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg had significantly greater improvements in postdose FEV₁ at Endpoint (281 mL, 27%) compared with fluticasone propionate 250 mcg (147 mL, 14%) and placebo (58 mL, 6%), demonstrating the contribution of salmeterol to the improvement in lung function with fluticasone propionate and salmeterol inhalation powder (Figure 5).

Figure 4. Predose FEV₁: Mean Percent Change from Baseline in Subjects with Chronic Obstructive Pulmonary Disease

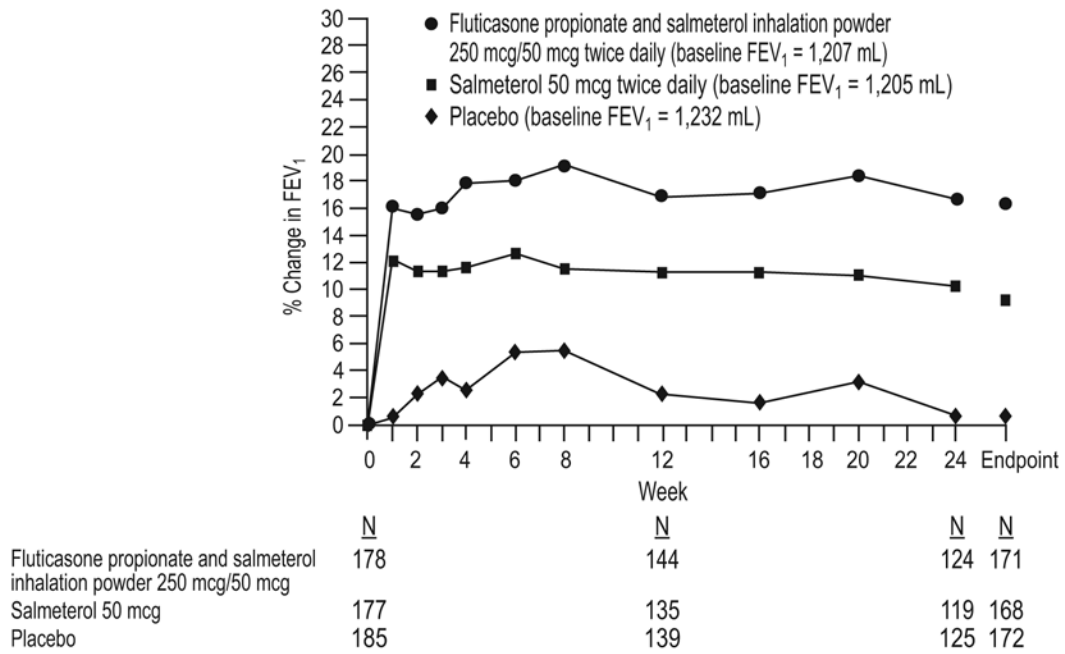
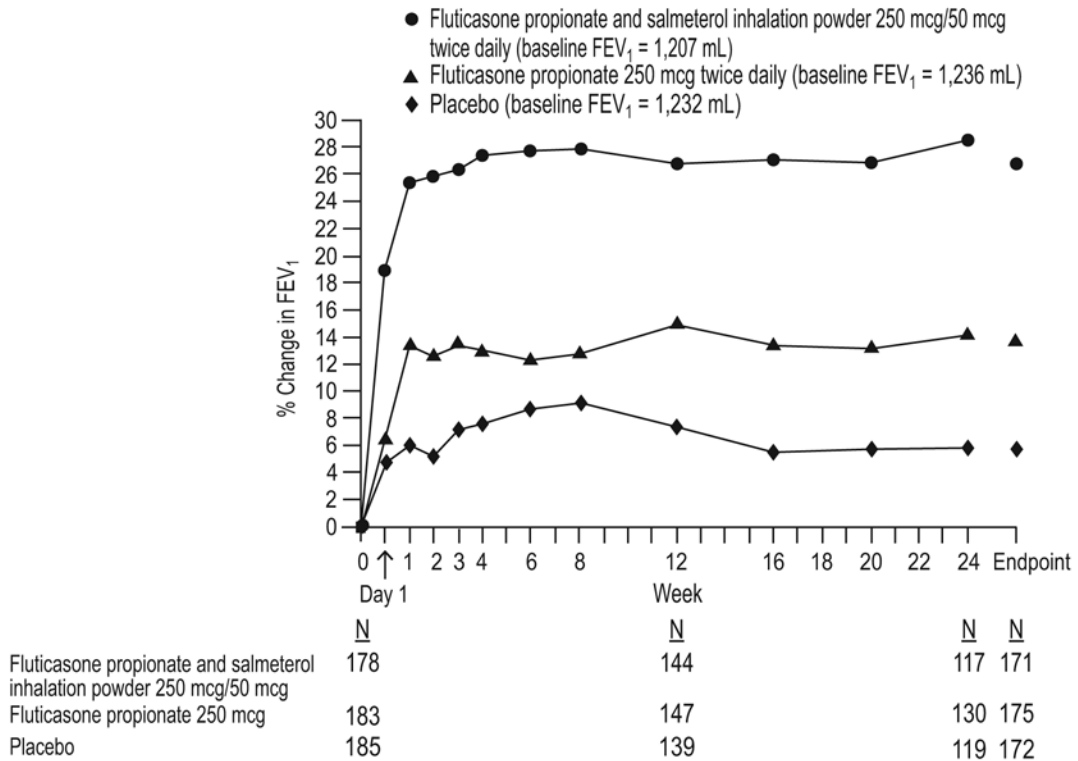


Figure 5. Two-Hour Postdose FEV₁: Mean Percent Changes from Baseline over Time in Subjects with Chronic Obstructive Pulmonary Disease



The third trial was a 1-year trial that evaluated fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg, fluticasone propionate 500 mcg, salmeterol 50 mcg, and placebo in 1,465 subjects. The subjects had an established history of COPD and exacerbations, a pre-bronchodilator FEV₁ < 70% of predicted at trial entry, and 8.3% reversibility. The primary endpoint was the comparison of pre-bronchodilator FEV₁ in the groups receiving fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg or placebo. Subjects treated with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg had greater improvements in FEV₁ (113 mL, 10%) compared with fluticasone propionate 500 mcg (7 mL, 2%), salmeterol (15 mL, 2%), and placebo (-60 mL, -3%).

Exacerbations: Two (2) trials were primarily designed to evaluate the effect of fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg on exacerbations. In these 2 trials, exacerbations were defined as worsening of 2 or more major symptoms (dyspnea, sputum volume, and sputum purulence) or worsening of any 1 major symptom together with any 1 of the following minor symptoms: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, and increased cough or wheeze for at least 2 consecutive days. COPD exacerbations were considered of moderate severity if treatment with systemic corticosteroids and/or antibiotics was required and were considered severe if hospitalization was required.

Exacerbations were also evaluated as a secondary outcome in the 1- and 3-year trials with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg. There was not a symptomatic definition of exacerbation in these 2 trials. Exacerbations were defined in terms of severity requiring treatment with antibiotics and/or systemic corticosteroids (moderately severe) or requiring hospitalization (severe).

The 2 exacerbation trials with fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg were identical trials designed to evaluate the effect of fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg and salmeterol 50 mcg, each given twice daily, on exacerbations of COPD over a 12-month period. A total of 1,579 subjects had an established history of COPD (but no other significant respiratory disorders). Subjects had a pre-bronchodilator FEV₁ of 33% of predicted, a mean reversibility of 23% at baseline, and a history of ≥ 1 COPD exacerbation in the previous year that was moderate or severe. All subjects were treated with fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg twice daily during a 4-week run-in period prior to being assigned trial treatment with twice-daily fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg or salmeterol 50 mcg. In both trials, treatment with fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg resulted in a significantly lower annual rate of moderate/severe COPD exacerbations compared with salmeterol (30.5% reduction [95% CI: 17.0, 41.8], $P < 0.001$) in the first trial and (30.4% reduction [95% CI: 16.9, 41.7], $P < 0.001$) in the second trial. Subjects treated with fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg also had a significantly lower annual rate of exacerbations requiring treatment with oral corticosteroids compared with subjects treated with salmeterol (39.7% reduction [95% CI: 22.8, 52.9], $P < 0.001$) in the first trial and (34.3% reduction [95% CI: 18.6, 47.0], $P < 0.001$) in the second trial. Secondary endpoints including pulmonary function and symptom scores improved more in subjects treated with fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg than with salmeterol 50 mcg in both trials.

Exacerbations were evaluated in the 1- and the 3-year trials with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg as 1 of the secondary efficacy endpoints. In the 1-year trial, the group receiving fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg had a significantly lower rate of moderate and severe exacerbations compared with placebo (25.4% reduction compared with placebo [95% CI: 13.5, 35.7]) but not when compared with its components (7.5% reduction compared with fluticasone propionate [95% CI: -7.3, 20.3] and 7% reduction compared with salmeterol [95% CI: -8.0, 19.9]). In the 3-year trial, the group receiving fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg had a significantly lower rate of moderate and severe exacerbations compared with each of the other treatment groups

(25.1% reduction compared with placebo [95% CI: 18.6, 31.1], 9.0% reduction compared with fluticasone propionate [95% CI: 1.2, 16.2], and 12.2% reduction compared with salmeterol [95% CI: 4.6, 19.2]).

There were no trials conducted to directly compare the efficacy of fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg on exacerbations. Across trials, the reduction in exacerbations seen with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg was not greater than the reduction in exacerbations seen with fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg.

Survival: A 3-year multicenter, international trial evaluated the efficacy of fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg compared with fluticasone propionate 500 mcg, salmeterol 50 mcg, and placebo on survival in 6,112 subjects with COPD. During the trial subjects were permitted usual COPD therapy with the exception of other ICS and long-acting bronchodilators. The subjects were aged 40 to 80 years with an established history of COPD, a pre-bronchodilator FEV₁ < 60% of predicted at trial entry, and < 10% of predicted reversibility. Each subject who withdrew from double-blind treatment for any reason was followed for the full 3-year trial period to determine survival status. The primary efficacy endpoint was all-cause mortality. Survival with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg was not significantly improved compared with placebo or the individual components (all-cause mortality rate 12.6% fluticasone propionate and salmeterol inhalation powder versus 15.2% placebo). The rates for all-cause mortality were 13.5% and 16.0% in the groups treated with salmeterol 50 mcg and fluticasone propionate 500 mcg, respectively. Secondary outcomes, including pulmonary function (post-bronchodilator FEV₁), improved with fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg, salmeterol 50 mcg, and fluticasone propionate 500 mcg compared with placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

Wixela™ Inhub™ 100/50 is supplied as a disposable grey colored plastic dry powder inhaler containing two foil sealed discs, providing a total of 60 pre-metered doses. The inhaler is packaged in a moisture-protective foil pouch.

NDC 0378-9320-32

carton containing one dry powder inhaler

Wixela™ Inhub™ 250/50 is supplied as a disposable grey colored plastic dry powder inhaler containing two foil sealed discs, providing a total of 60 pre-metered doses. The inhaler is packaged in a moisture-protective foil pouch.

NDC 0378-9321-32

carton containing one dry powder inhaler

Wixela™ Inhub™ 500/50 is supplied as a disposable grey colored plastic dry powder inhaler containing two foil sealed discs, providing a total of 60 pre-metered doses. The inhaler is packaged in a moisture-protective foil pouch.

NDC 0378-9322-32

carton containing one dry powder inhaler

Store at 20° to 25° C (68° to 77°F). [See USP Controlled Room Temperature.]

Store in a dry place away from direct heat and sunlight.

Keep this and all medication out of the reach of children.

Wixela™ Inhub™ should be stored inside the unopened moisture-protective foil pouch and only removed from the pouch immediately before initial use. Discard Wixela™ Inhub™ 1 month after opening the foil pouch or when the counter reads “0” (after all doses have been used), whichever comes first. The inhaler is not reusable. Do not attempt to take the inhaler apart.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Serious Asthma-Related Events: Inform patients with asthma that LABA when used alone increases the risk of asthma-related hospitalization or asthma-related death. Available data show that when ICS and LABA are used together, such as with Wixela™ Inhub™, there is not a significant increase in the risk of these events.

Not for Acute Symptoms: Inform patients that Wixela™ Inhub™ is not meant to relieve acute asthma symptoms or exacerbations of COPD and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta₂-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta₂-agonists
- Need for more inhalations than usual of inhaled, short-acting beta₂-agonists
- Significant decrease in lung function as outlined by the physician

Tell patients they should not stop therapy with Wixela™ Inhub™ without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-acting Beta₂-agonists: Instruct patients not to use other LABA for asthma and COPD.

Local Effects: Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, treat it with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with Wixela™ Inhub™, but at times therapy with Wixela™ Inhub™ may need to be temporarily interrupted under close medical supervision. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush.

Pneumonia: Patients with COPD have a higher risk of pneumonia; instruct them to contact their healthcare providers if they develop symptoms of pneumonia.

Immunosuppression: Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Hypercorticism and Adrenal Suppression: Advise patients that Wixela™ Inhub™ may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to Wixela™ Inhub™.

Immediate Hypersensitivity Reactions: Advise patients that immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension), including anaphylaxis, may occur after administration of Wixela™ Inhub™. Patients should discontinue Wixela™ Inhub™ if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of powder products containing lactose; therefore, patients with severe milk protein allergy should not take Wixela™ Inhub™.

Reduction in Bone Mineral Density: Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.

Reduced Growth Velocity: Inform patients that orally inhaled corticosteroids, including fluticasone propionate, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route.

Glaucoma and Cataracts: Advise patients that long-term use of ICS may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations.

Risks Associated with Beta-agonist Therapy: Inform patients of adverse effects associated with beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

PATIENT INFORMATION
Wixela™ Inhub™ (wicks-EL-uh IN-hub)
(fluticasone propionate and
salmeterol inhalation powder, USP)
for oral inhalation use

What is Wixela™ Inhub™?

- Wixela™ Inhub™ combines the inhaled corticosteroid (ICS) medicine fluticasone propionate and the long-acting beta₂-adrenergic agonist (LABA) medicine salmeterol.
 - ICS medicines such as fluticasone propionate help to decrease inflammation in the lungs. Inflammation in the lungs can lead to breathing problems.
 - LABA medicines such as salmeterol help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing, cough, chest tightness, and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe.
- **Wixela™ Inhub™ is not used to relieve sudden breathing problems** and will not replace a rescue inhaler.
- It is not known if Wixela™ Inhub™ is safe and effective in children younger than 4 years.
- Wixela™ Inhub™ is used for asthma and COPD as follows:

Asthma:

- Wixela™ Inhub™ is a prescription medicine used to control symptoms of asthma and to prevent symptoms such as wheezing in adults and children aged 4 years and older.
- Wixela™ Inhub™ contains salmeterol, the same medicine found in SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder). LABA medicines such as salmeterol when used alone increase the risk of hospitalizations and death from asthma problems. Wixela™ Inhub™ contains an ICS and a LABA. When an ICS and LABA are used together there is not a significant increased risk in hospitalizations and death from asthma problems.
- Wixela™ Inhub™ is not for adults and children with asthma who are well controlled with an asthma control medicine, such as a low to medium dose of an ICS medicine. Wixela™ Inhub™ is for adults and children with asthma who need both an ICS and LABA medicine.

COPD:

Wixela™ Inhub™ 250/50 is a prescription medicine used to treat COPD. COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both. Wixela™ Inhub™ 250/50 is used long term as 1 inhalation 2 times each day to improve symptoms of COPD for better breathing and to reduce the number of flare-ups (the worsening of your COPD symptoms for several days).

Do not use Wixela™ Inhub™:

- to relieve sudden breathing problems.
- as a rescue inhaler.
- if you have a severe allergy to milk proteins. Ask your healthcare provider if you are not sure.
- if you are allergic to fluticasone propionate, salmeterol, or any of the ingredients in Wixela™ Inhub™. See the end of this Patient Information for a complete list of ingredients in Wixela™ Inhub™.

Before using Wixela™ Inhub™, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems.
- have high blood pressure.
- have seizures.
- have thyroid problems.
- have diabetes.
- have liver problems.
- have weak bones (osteoporosis).
- have an immune system problem.
- have or have had eye problems such as glaucoma, increased pressure in your eye, cataracts, or other changes in vision.
- are allergic to milk proteins.
- have any type of viral, bacterial, or fungal infection.
- are exposed to chickenpox or measles.

- are pregnant or plan to become pregnant. It is not known if Wixela™ Inhub™ may harm your unborn baby.
- are breastfeeding. It is not known if the medicines in Wixela™ Inhub™ pass into your milk and if they can harm your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Wixela™ Inhub™ and certain other medicines may interact with each other. This may cause serious side effects. Especially tell your healthcare provider if you take antifungal or anti-HIV medicines. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use Wixela™ Inhub™?

Read the step-by-step instructions for using Wixela™ Inhub™ at the end of this Patient Information.

- **Do not** use Wixela™ Inhub™ unless your healthcare provider has taught you how to use the inhaler and you understand how to use it correctly.
- Children should use Wixela™ Inhub™ with an adult's help, as instructed by the child's healthcare provider.
- Wixela™ Inhub™ comes in 3 different strengths. Your healthcare provider prescribed the strength that is best for you.
- Use Wixela™ Inhub™ exactly as your healthcare provider tells you to use it. **Do not** use Wixela™ Inhub™ more often than prescribed.
- Use 1 inhalation of Wixela™ Inhub™ 2 times each day. Use Wixela™ Inhub™ at the same time each day, about 12 hours apart.
- If you miss a dose of Wixela™ Inhub™, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at 1 time.
- If you take too much Wixela™ Inhub™, call your healthcare provider or go to the nearest hospital emergency room right away if you have any unusual symptoms, such as worsening shortness of breath, chest pain, increased heart rate, or shakiness.
- **Do not use other medicines that contain a LABA for any reason.** Ask your healthcare provider or pharmacist if any of your other medicines are LABA medicines.
- **Do not** stop using Wixela™ Inhub™, even if you are feeling better, unless your healthcare provider tells you to.
- **Wixela™ Inhub™ does not relieve sudden breathing problems.** Always have a rescue inhaler with you to treat sudden symptoms. If you do not have a rescue inhaler, call your healthcare provider to have one prescribed for you.
- Rinse your mouth with water **without swallowing** after each dose of Wixela™ Inhub™. This will help lessen the chance of getting a yeast infection (thrush) in your mouth and throat.
- Call your healthcare provider or get medical care right away if:
 - your breathing problems get worse.
 - you need to use your rescue inhaler more often than usual.
 - your rescue inhaler does not work as well to relieve your symptoms.
 - you need to use 4 or more inhalations of your rescue inhaler in 24 hours for 2 or more days in a row.
 - you use 1 whole canister of your rescue inhaler in 8 weeks.
 - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
 - you have asthma and your symptoms do not improve after using Wixela™ Inhub™ regularly for 1 week.

What are the possible side effects of Wixela™ Inhub™?

Wixela™ Inhub™ can cause serious side effects, including:

- **fungal infection in your mouth or throat (thrush).** Rinse your mouth with water **without swallowing** after using Wixela™ Inhub™ to help reduce your chance of getting thrush.
- **pneumonia.** People with COPD have a higher chance of getting pneumonia. Wixela™ Inhub™ may increase the chance of you getting pneumonia. Call your healthcare provider right away if you have any of the following symptoms:
 - increase in mucus (sputum) production
 - change in mucus color
 - fever
 - chills
 - increased cough
 - increased breathing problems
- **weakened immune system and increased chance of getting infections (immunosuppression)**
- **reduced adrenal function (adrenal insufficiency).** Adrenal insufficiency is a condition where the adrenal glands do not make enough steroid hormones. This can happen when you stop taking oral corticosteroid medicines (such as prednisone) and start taking a medicine containing an inhaled steroid (such as Wixela™ Inhub™). During this transition period when your body is under stress such as from fever, trauma (such as a car accident), infection, surgery, or worse COPD symptoms, adrenal insufficiency can get worse and may cause death. Symptoms of adrenal insufficiency include:
 - feeling tired
 - lack of energy
 - weakness
 - nausea and vomiting
 - low blood pressure (hypotension)
- **sudden breathing problems immediately after inhaling your medicine.** If you have sudden breathing problems immediately after inhaling your medicine stop using Wixela™ Inhub™ and call your healthcare provider right away.
- **serious allergic reactions.** Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction:
 - rash
 - hives
 - swelling of your face, mouth, and tongue
 - breathing problems
- **effects on heart**
 - increased blood pressure
 - a fast or irregular heartbeat
 - chest pain
- **effects on nervous system**
 - tremor
 - nervousness
- **bone thinning or weakness (osteoporosis)**
- **slowed growth in children.** Your child's growth should be checked regularly by the healthcare provider while using Wixela™ Inhub™.
- **eye problems** including glaucoma, increased pressure in your eye, cataracts, or other changes in vision. You should have regular eye exams while using Wixela™ Inhub™.
- **changes in laboratory blood levels (sugar, potassium, certain types of white blood cells).**

Common side effects of Wixela™ Inhub™ include:

Asthma:

- upper respiratory tract infection
- throat irritation
- hoarseness and voice changes
- thrush in your mouth or throat. Rinse your mouth with water without swallowing after use to help prevent this
- bronchitis
- cough
- headache
- nausea and vomiting

In children with asthma, infections in the ear, nose, and throat are common.

COPD:

- thrush in your mouth or throat. Rinse your mouth with water without swallowing after use to help prevent this
- throat irritation
- hoarseness and voice changes
- viral respiratory infections
- headache
- muscle and bone pain

These are not all the possible side effects of Wixela™ Inhub™.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Wixela™ Inhub™?

- Store Wixela™ Inhub™ at room temperature between 20° to 25°C (68° to 77°F). Keep in a dry place away from direct heat and sunlight.
- Store Wixela™ Inhub™ in the unopened foil pouch and only open when ready for use.
- Safely throw away Wixela™ Inhub™ in the trash 1 month after you open the foil pouch or when the counter reads **0**, whichever comes first.
- **Keep Wixela™ Inhub™ and all medicines out of the reach of children.**

General information about the safe and effective use of Wixela™ Inhub™.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Wixela™ Inhub™ for a condition for which it was not prescribed. Do not give your Wixela™ Inhub™ to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about Wixela™ Inhub™ that was written for health professionals.

What are the ingredients in Wixela™ Inhub™?

Active ingredients: fluticasone propionate, salmeterol xinafoate

Inactive ingredients: lactose monohydrate (which contains milk proteins)

For more information about Wixela™ Inhub™, call Mylan at 1-877-446-3679 (1-877-4-INFO-RX).

This Patient Information has been approved by the U.S. Food and Drug Administration.

Instructions For Use

WIXELA™ INHUB™ (wicks-EL-uh IN-hub) **(fluticasone propionate and salmeterol inhalation powder, USP)** **for oral inhalation use**

Read this Instructions for Use before you start using WIXELA INHUB and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

Your WIXELA INHUB inhaler

Closed Position

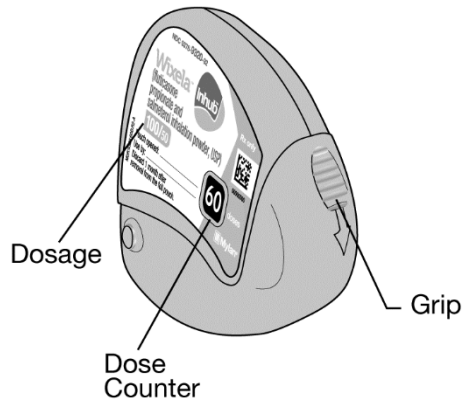


Figure A

Open Position

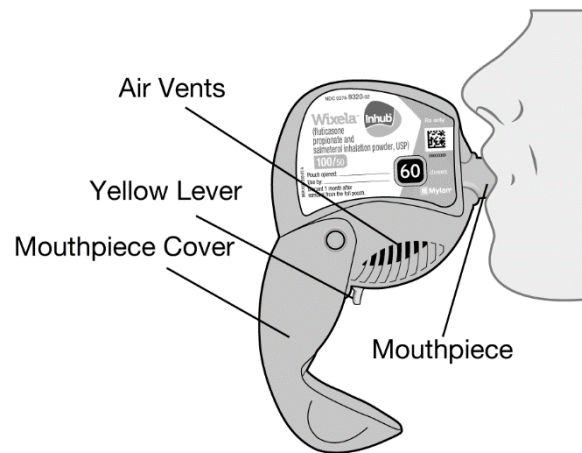


Figure B

Important information about your WIXELA INHUB inhaler:

- **WIXELA INHUB is for oral inhalation use only.**
- Take WIXELA INHUB out of the foil pouch just before you use it for the first time. Safely throw away the pouch. The INHUB will be in the closed position. **See Figure A.**
- Write the date you opened the foil pouch in the first blank line on the label. **See Figure B.**
- Write the “use by” date in the second blank line on the label. **See Figure B.** That date is 1 month after the date you wrote in the first line.
- The counter should read **60**. **See Figure A.**

How to use your WIXELA INHUB inhaler
Follow these steps every time you use WIXELA INHUB.

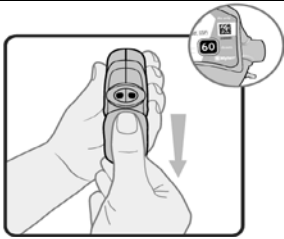


Figure C

Step 1. Open your WIXELA INHUB.

- Hold the INHUB in one hand and with your other hand on the grip **lower** the mouthpiece cover from top to bottom. **See Figure C.**

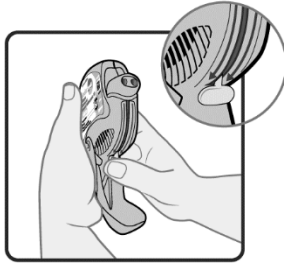


Figure D

Step 2. Push down the lever.

- Hold the INHUB in the **vertical** position. Push the yellow lever down to the end of the purple arrows (you may hear a click). **See Figure D.**
- The INHUB is now ready to use.

Follow the instructions below so you will not accidentally waste a dose:

- **Do not** close the INHUB.
- **Do not** move the lever on the INHUB once pushed down.

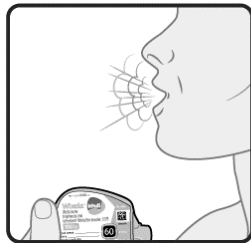


Figure E

Step 3. Inhale your medicine.

- Before you breathe in your dose from the INHUB, breathe out (exhale) as long as you can while you hold the INHUB away from your mouth. **See Figure E.** Do not breathe into the mouthpiece.
- Put the mouthpiece to your lips. **See Figure F.** Breathe in quickly and deeply through the INHUB. Do not breathe in through your nose.
- Remove the INHUB from your mouth **and hold your breath for about 10 seconds**, or for as long as is comfortable for you.
- **Breathe out slowly for as long as you can.** **See Figure E.**
- The INHUB delivers your dose of medicine as a very fine powder that you may or may not taste or feel. **Do not** take an extra dose from the INHUB even if you do not taste or feel the medicine.



Figure F

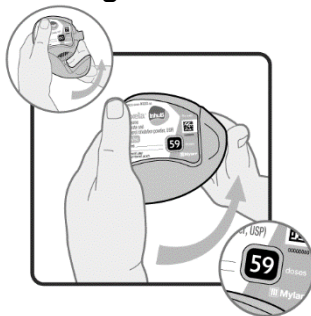


Figure G

Step 4. Close the INHUB.

- Push the mouthpiece cover up to the closed position, this will automatically return the yellow lever to the start position. **See Figure G.** Make sure the INHUB is shut and you cannot see the mouthpiece.
- The dose counter will count down 1 dose as you close the mouthpiece cover. This will now tell you how many doses are left.
- The INHUB is now ready for you to take your next scheduled dose in about 12 hours. **When you are ready to take your next dose, repeat Steps 1 through 4.**

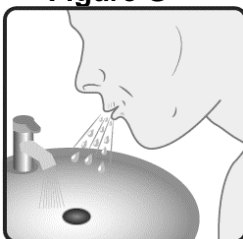


Figure H

Step 5. Rinse your mouth.

- **Rinse your mouth with water after breathing in the medicine.** Spit out the water. **Do not** swallow it. **See Figure H.**

When should you get a refill?

The dose counter on the INHUB shows you how many doses are left.



Your dose counter will be set at **60** when you first receive your INHUB.

After you have taken 51 doses, a red indicator will be present. This indicator warns you there are **9** or fewer doses left and is a reminder to get a refill.

The dose counter will read **0** and the lever will not reach the end of the purple arrows when there are no doses remaining.

For correct use of the INHUB, remember:

- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. **Do not** swallow the water.
- **Do not** take an extra dose, even if you did not taste or feel the powder.
- **Do not** take the INHUB apart.
- **Do not** wash the INHUB.
- Always keep the INHUB in a dry place.
- **Do not** use the INHUB with a spacer device.

For more information about WIXELA INHUB or how to use your inhaler, call Mylan at 1-877-446-3679 (1-877-4-INFO-RX).

The brands listed are trademarks of their respective owners.

Wixela™ and Inhub™ are trademarks of Mylan Pharmaceuticals Inc.

The Inhub™ device is patent protected. U.S. Pat. Nos. 7,401,713, 7,987,985, 8,181,645, 8,256,416, 8,528,549, 8,851,070, 9,056,175, 9,314,578, 9,399,103, D569,967, D560,793.

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This Instructions for Use has been approved by the U.S. Food and Drug Administration.



Manufactured for:

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Manufactured by:
McDermott Laboratories Ltd.
t/a Mylan Dublin Respiratory
Unit 25 Baldoyle Industrial Estate, Grange Road, Baldoyle, Dublin 13, Ireland
Revised: 1/2019
MDR:FPSX:R9/MDR:PI:FPSX:R4/MDR:IFU:FPSX:R5

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 208891

LABELING REVIEW(s)

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	1/11/2019
ANDA Number(s)	208891
Review Number	5
Applicant Name	Mylan Pharmaceuticals Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Fluticasone Propionate and Salmeterol Inhalation Powder USP, 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg/50 mcg
Proposed Proprietary Name	Wixela™ Inhub™ (Proprietary name granted 9/6/2018)
Submission Received Date	January 10, 2019
Primary Labeling Reviewer	JuWon Lee, Pharm. D.
Secondary Labeling Reviewer	Refer to signature page
Review Conclusion	
☒ ACCEPTABLE – No Comments ☐ ACCEPTABLE – Include Post Approval Comments ☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant †Theme - Choose an item. Justification for Major Deficiency - Choose an item.	
*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.	
On Policy Alert List	☒ Yes ☐ No
Combined Insert/Outsert	☐ Yes ☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT-NA

Labeling Deficiencies determined on (add date) based on your submission(s) received (add date):

1. GENERAL COMMENTS
Comment
2. CONTAINER LABEL
 - a. Comment
 - b. Comment
3. CARTON LABELING
4. PRESCRIBING INFORMATION
 - a. Comment
 - b. Subheading
 - i. Comment
 - ii. Comment
5. MEDICATION GUIDE
6. STRUCTURED PRODUCT LABELING (SPL)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with **Choose an item**. all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission received 1/10/2019.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
NA

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

The below comments are from the IR issued January 9, 2019 (via email).

FDA COMMENT

1. CONTAINER/CARTON/FOIL LABELING

Please remove the statement, "(b) (4)" from container, carton and foil labeling.

MYLAN RESPONSE

As requested by the Agency, Mylan has revised the container labels, pouches (foils) and cartons accordingly. Please refer to Section 1.14.2.1. A side-by-side comparison of Mylan's proposed final printed container labels, pouches (foils) and cartons to Mylan's previously submitted final printed container labels, pouches (foils) and cartons is provided in Section 1.14.1.2 (Container).

FDA COMMENT

2. PRESCRIBING INFORMATION

a. Revise your labeling to be in accordance with the labeling for the reference listed drug (RLD), Advair Diskus, NDA 021077/S-061 approved January 7, 2019.

b. Remove "USP" from the product title in the Highlights Section; i.e., WIXELA™ INHUB™ (fluticasone propionate and salmeterol inhalation powder, USP) for oral inhalation

c. The USP Notice of Intent to Revise for Fluticasone Propionate and Salmeterol Inhalation Powder USP, posted December 13, 2018, added, among other things, a Labeling section to support articles that use "(b) (4)". In accordance with the revisions proposed in the Notice of Intent to Revise, revise the statement in the Description section of the prescribing information to read: "Meets USP Aerodynamic Particle Size Distribution Test 2."

MYLAN RESPONSE

As requested by the Agency, Mylan has revised our proposed insert in accordance with comments 2.a., 2.b. and 2.c. above. Mylan's proposed final printed insert labeling (MDR:FPSX:R9; Revised: 1/2019) is provided in Section 1.14.2.2. Mylan's proposed final printed standalone Patient Information/Instructions for Use labeling is provided in Section 1.14.2.2. A copy of the RLD's labeling approved on January 7, 2019 is provided in Section 1.14.3.3. for reference. As requested by the Agency, a side-by-side comparison (Word version) of Mylan's proposed final printed insert/Patient Information/Instructions for Use to the Reference Listed Drug's (RLD) labeling approved on January 7, 2019 is provided in Section 1.14.3.1 (Labeling).

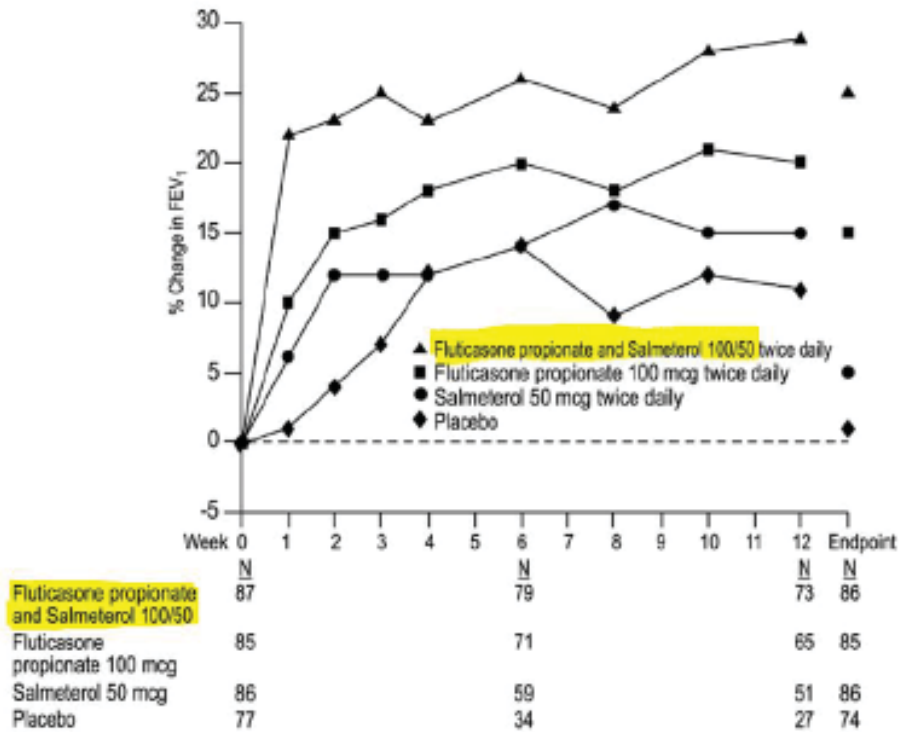
The below comments are from the labeling review C4 (DRL issued on 12/12/2018) based on the submissions dated 10/4/2018 (PI) and 7/13/2018 (Container/carton).

Labeling Deficiencies determined on 12/12/2018 based on your submissions received 7/13/2018 and 10/4/2018:

1. PRESCRIBING INFORMATION

- a. When replacing the RLD proprietary name, Advair Diskus, with your established name, ensure to include the full established name with the dosage form (e.g., inhalation powder). Where the RLD proprietary name is described by strength (e.g., Advair Diskus 100/50), the strength for your established name should include a unit of measurement (e.g., 100 mcg/50 mcg). For example, in the figure below, the full established name should be “Fluticasone propionate and Salmeterol inhalation powder 100 mcg/50 mcg” (see yellow highlighted text). Ensure to revise accordingly throughout the labeling, including all figures.

Figure 1. Mean Percent Change from Baseline in FEV₁ in Subjects with Asthma Previously Treated with Either Inhaled Corticosteroids or Salmeterol (Trial 1)



- b. Revise the highlighted text below to state “fluticasone propionate and salmeterol.” We note that “ADVAIR” in the RLD labeling in this instance references any formulation of ADVAIR, which includes either the inhalation powder or inhalation aerosol.

6.3 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of any formulation of fluticasone propionate and salmeterol inhalation powder, fluticasone propionate, and/or salmeterol regardless of indication. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to fluticasone propionate and salmeterol inhalation powder, fluticasone propionate, and/or salmeterol or a combination of these factors.

- c. Revise **the proposed labeling** to be consistent with the RLD labeling. For example:
- i. Except for the instances covered by deficiency 1a, include the unit of measurement, “mcg,” only in places where the RLD labeling includes it. For example, the highlights section of the proposed labeling currently states:

-----**DOSAGE FORMS AND STRENGTHS**-----
Inhalation powder: Inhaler containing a combination of fluticasone propionate (100 mcg, 250 mcg, or 500 mcg) and salmeterol (50 mcg) as a powder formulation for oral inhalation. (3)

We note, however, that the RLD labeling includes “mcg” only after the last strength of fluticasone propionate, 500 mcg. Therefore, for this example, the instances of “mcg” highlighted in yellow should be deleted so that the proposed labeling for this example states “(100, 250, or 500 mcg).”

- ii. Revise proposed labeling to express numbers in a manner consistent with the RLD (i.e., if the RLD spells out a number, the proposed labeling should also spell out that number; if the RLD labeling expresses a number as a numeral, the proposed labeling should also express the number as a numeral). For example, the Dosage and Administration section of the PI currently states:

2 DOSAGE AND ADMINISTRATION
Wixela™ Inhub™ should be administered as one inhalation twice daily by the orally inhaled route only. After inhalation, the patient should rinse his/her mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis.

More frequent administration or a greater number of inhalations (more than one inhalation twice daily) of the prescribed strength of Wixela™ Inhub™ is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. Patients using Wixela™ Inhub™ should not use additional LABA for any reason. [See Warnings and Precautions (5.3, 5.12).]

We note, however, that the RLD labeling expresses the number highlighted in yellow above as a numeral. Therefore, for this example, “one” should be revised to “1” in the proposed labeling.

- d. Section 11 Description: Revise to state “empirical formula” in place of “molecular formula” to be consistent with the RLD labeling.

- e. Section 12.2 Pharmacodynamics: Revise the highlighted text below to state “a dry powder inhaler.” We note that “the DISKUS” in the RLD labeling in this instance references the ADVAIR DISKUS inhaler (combination of fluticasone propionate and salmeterol inhalation powder) and the FLOVENT DISKUS (fluticasone propionate inhalation powder) inhaler.

Pediatric Subjects: Hypothalamic-Pituitary-Adrenal Axis Effects: In a 12-week trial in subjects with asthma aged 4 to 11 years who were receiving ICS at trial entry, fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg twice daily was compared with fluticasone propionate inhalation powder 100 mcg administered twice daily via another dry powder inhaler. The values for 24-hour urinary cortisol excretion at trial entry and after 12 weeks of treatment were similar within each treatment group. After 12 weeks, 24-hour urinary cortisol excretion was also similar between the 2 groups.

- f. Section 12.2 Pharmacodynamics: Revise the highlighted text below to state “a dry powder inhaler.” We note that “the DISKHALER inhalation device” in the RLD labeling references the Flovent Rotadisk dry powder inhaler.

Other Fluticasone Propionate Products: Subjects with Asthma: Hypothalamic-Pituitary-Adrenal Axis Effects: In clinical trials with fluticasone propionate inhalation powder using dosages up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol < 18 mcg/dL assessed by radioimmunoassay) were noted both in subjects receiving fluticasone propionate and in subjects receiving placebo. The incidence of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year trial carried out with the DISKHALER[®] inhalation device in 64 subjects with mild, persistent asthma (mean FEV₁ 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo, no subject receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin infusion (peak serum cortisol < 18 mcg/dL). With a peak cortisol threshold of < 35 mcg/dL, 1 subject receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing at 18 months and 2 years was normal. Another subject receiving fluticasone propionate (5%) had an abnormal response at 2 years. No subject on placebo had an abnormal response at 1 or 2 years.

- g. Section 12.2 Pharmacodynamics: Revise the highlighted text below to state “a dry powder inhaler.” We note that “the DISKUS” in the RLD labeling in this instance references the FLOVENT DISKUS (fluticasone propionate inhalation powder) inhaler.

Subjects with Chronic Obstructive Pulmonary Disease: Hypothalamic-Pituitary-Adrenal Axis Effects: After 4 weeks of dosing, the steady-state fluticasone propionate pharmacokinetics and serum cortisol levels were described in a subset of subjects with COPD (n = 86) randomized to twice-daily fluticasone propionate inhalation powder via another dry powder inhaler 500 mcg, fluticasone propionate inhalation powder 250 mcg, or placebo. Serial serum cortisol concentrations were measured across a 12-hour dosing interval. Serum cortisol concentrations following 250 mcg and 500 mcg twice-daily dosing were 10% and 21% lower than placebo, respectively, indicating a dose-dependent increase in systemic exposure to fluticasone propionate.

- h. Section 12.3 Pharmacokinetics: Revise the highlighted text below to state “a dry powder inhaler” (first two instances) and “a fluticasone propionate dry powder inhaler (last two instances) respectively.” We note that “the DISKUS inhaler” and “the fluticasone propionate DISKUS inhaler” in the RLD labeling in these instances reference the FLOVENT DISKUS (fluticasone propionate inhalation powder) inhaler.

Subjects with Asthma and COPD: Peak steady-state fluticasone propionate plasma concentrations in adult subjects with asthma (N = 11) ranged from undetectable to 266 pg/mL after a 500 mcg twice-daily dose of fluticasone propionate inhalation powder using another dry powder inhaler. The mean fluticasone propionate plasma concentration was 110 pg/mL.

Full pharmacokinetic profiles were obtained from 9 female and 16 male subjects with asthma given fluticasone propionate inhalation powder 500 mcg twice daily using another dry powder inhaler and from 14 female and 43 male subjects with COPD given 250 or 500 mcg twice daily. No overall differences in fluticasone propionate pharmacokinetics were observed.

Peak steady-state fluticasone propionate plasma concentrations in subjects with COPD averaged 53 pg/mL (range: 19.3 to 159.3 pg/mL) after treatment with 250 mcg twice daily (n = 30) and 84 pg/mL (range: 24.3 to 197.1 pg/mL) after treatment with 500 mcg twice daily (n = 27) via another fluticasone propionate dry powder inhaler. In another trial in subjects with COPD, peak steady-state fluticasone propionate plasma concentrations averaged 115 pg/mL (range: 52.6 to 366.0 pg/mL) after treatment with 500 mcg twice daily via another fluticasone propionate dry powder inhaler (n = 15) and 105 pg/mL (range: 22.5 to 299.0 pg/mL) via fluticasone propionate and salmeterol inhalation powder (n = 24).

- i. 12.3 Pharmacokinetics: Revise the highlighted text below to state “a dry powder inhaler.” We note that “the DISKUS” in the RLD labeling in this instance references the FLOVENT DISKUS (fluticasone propionate inhalation powder) inhaler, the SEREVENT DISKUS (salmeterol inhalation powder) inhaler, or the ADVAIR DISKUS (combination of fluticasone propionate and salmeterol inhalation powder) inhaler.

Drug Interaction Studies: In the repeat- and single-dose trials, there was no evidence of significant drug interaction in systemic exposure between fluticasone propionate and salmeterol when given alone or in combination via another dry powder inhaler. The population pharmacokinetic analysis from nine controlled clinical trials in 350 subjects with asthma showed no significant effects on fluticasone propionate or salmeterol pharmacokinetics following co-administration with beta₂-agonists, corticosteroids, antihistamines, or theophyllines.

- j. 14.1 Asthma: Revise the highlighted text to state “a dry powder inhaler.” We note that “the DISKUS inhaler” in the RLD labeling in this instance references the FLOVENT DISKUS (fluticasone propionate inhalation powder) inhaler, the SERVENT DISKUS (salmeterol inhalation powder) inhaler, or the ADVAIR DISKUS (combination of fluticasone propionate and salmeterol inhalation powder) inhaler.

14.1 Asthma

Adult and Adolescent Subjects Aged 12 Years and Older: In clinical trials comparing fluticasone propionate and salmeterol inhalation powder with its individual components, improvements in most efficacy endpoints were greater with fluticasone propionate and salmeterol inhalation powder than with the use of either fluticasone propionate or salmeterol alone. In addition, clinical trials showed similar results between fluticasone propionate and salmeterol inhalation powder and the concurrent use of fluticasone propionate plus salmeterol at corresponding doses from separate inhalers.

Trials Comparing Fluticasone Propionate and Salmeterol Inhalation Powder with Fluticasone Propionate Alone or Salmeterol Alone: Three (3) double-blind, parallel-group clinical trials were conducted with fluticasone propionate and salmeterol inhalation powder in 1,208 adult and adolescent subjects (aged 12 years and older, baseline FEV₁ 63% to 72% of predicted normal) with asthma that was not optimally controlled on their current therapy. All treatments were inhalation powders given as one inhalation from another dry powder inhaler twice daily, and other maintenance therapies were discontinued.

- k. 14.2 Chronic Obstructive Pulmonary Disease: Revise the highlighted text to state “the dry powder inhaler.” We note that “the DISKUS inhaler” in the RLD labeling in this instance references the ADVAIR DISKUS (combination of fluticasone propionate and salmeterol inhalation powder) inhaler.

14.2 Chronic Obstructive Pulmonary Disease

The efficacy of fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg and fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg in the treatment of subjects with COPD was evaluated in 6 randomized, double-blind, parallel-group clinical trials in adult subjects aged 40 years and older. These trials were primarily designed to evaluate the efficacy of fluticasone propionate and salmeterol inhalation powder on lung function (3 trials), exacerbations (2 trials), and survival (1 trial).

Lung Function: Two of the 3 clinical trials primarily designed to evaluate the efficacy of fluticasone propionate and salmeterol inhalation powder on lung function were conducted in 1,414 subjects with COPD associated with chronic bronchitis. In these 2 trials, all the subjects had a history of cough productive of sputum that was not attributable to another disease process on most days for at least 3 months of the year for at least 2 years. The trials were randomized, double-blind, parallel-group, 24-week treatment duration. One trial evaluated the efficacy of fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg compared with its components fluticasone propionate 250 mcg and salmeterol 50 mcg and with placebo, and the other trial evaluated the efficacy of fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg compared with its components fluticasone propionate 500 mcg and salmeterol 50 mcg and with placebo. Trial treatments were inhalation powders given as one inhalation from another dry powder inhaler twice daily. Maintenance COPD therapies were discontinued, with the exception of theophylline. The subjects had a mean pre-bronchodilator FEV₁ of 41% and 20% reversibility at trial entry. Percent reversibility was calculated as 100 times (FEV₁ post-albuterol minus FEV₁ pre-albuterol)/FEV₁ pre-albuterol.

1. Section 16 How Supplied/Storage and Handling: Remove the following statements to align with the RLD labeling.



2. INSTRUCTIONS FOR USE (IFU)



3. CARTON LABELING

Refer to comments 2.a and 2.b. and revise accordingly.

Reviewer Comments: Revised container/carton/foil labeling, revised PI, and revised IFU are acceptable. Firm addressed all comments from C4 review and IR adequately. DCR found Mylan's IFU acceptable.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: Firm deleted the USP statement per IR dated 1/9/2019. No other changes were made to container/carton/foil labeling.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

NA

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in [DLR's SharePoint Drug Facts](#)? NO
 If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the [Policy Alert Tracker](#) on [OGD's SharePoint](#)? YES
 If Yes, please explain.

CP	FDA-2009-P-0597	Multiple: Serevent Diskus, Flovent Diskus, Flovent HFA, Advair Diskus, and Advair HFA (Metered and powdered inhalation products MDIs and PDIs)	Multiple: aerosol, Metered and Powder Inhalation, Fulvicion propionate and salmeterol xinafoate, aerosol, Metered and Powder, Inhalation	Requests FDA to not approve any ANDA referencing inhalation products containing fulvicosone propionate and/or salmeterol xinafoate unless conforms to the RLD. In patient instructions for use and handling, Q10Q BE, successful clinical testing in pediatric and adults as part of BE, and successfully clinically tested in asthma and COPD patients.	020692 (Serevent Diskus), 020833 (Flovent Diskus), 021433 (Flovent HFA), 021077 (Advair Diskus), and 21254 (Advair HFA)	No Approval Actions (APITA) can be taken prior to contacting Policy Lead	No CRL can be issued prior to contacting Policy Lead; No CC/IR/DR/L for Bioequivalence or Labeling
No CRL can be issued prior to contacting Policy Lead; No CC/IR/DR/L for Bioequivalence or Labeling				Petitioner is specifically referring to metered-dose inhalers (MDIs) and dry-powder inhalers (DPIs) with these active ingredients that treat asthma and chronic obstructive pulmonary disease (COPD). The petitioner provides the following NDAs as their applications that fall within under the category of Inhalation Products: 020692 (Serevent Diskus), 020833 (Flovent Diskus), 021433 (Flovent HFA), 021077 (Advair Diskus), and 21254 (Advair HFA).		12/16/2009	Andrea Bautista

Is the drug product listed on the [Susceptibility Test Interpretive Criteria web page](#)? NO

3.2 MODEL LABELING

Table 1: Review Model Labeling
(Check the box used as the Model Labeling)

MOST RECENTLY APPROVED NDA MODEL LABELING

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)

NDA# /Supplement# (S-000 if original): 021077/S-061

Supplement Approval Date: 1/7/2019

Proprietary Name: Advair Diskus®

Established Name: Fluticasone Propionate and Salmeterol Inhalation Powder

Description of Supplement:

Background and Summary Description:

On June 27, 2018, GSK submitted a prior approval supplement proposing updates to the labeling to add information regarding the development of central serous chorioretinopathy (CSCR). The supplement includes these labeling pieces, package insert (PI), patient information leaflet (PIL) and the instructions for use (IFU). The supplement proposes the following revisions to the labeling:

- Addition of the term central serous chorioretinopathy to Section 5.15.
- Glaucoma and Cataracts heading in Sections 5.15 and 6 was replaced with Eye Disorders.
- Blurred vision was added under Ocular Effects in Section 17.
- Updates to the Highlights as appropriate to reflect changes made in the Full Prescribing Information.
- Updates to PIL to instruct patients to tell their healthcare provider about blurred vision and other changes in vision.
- Addition of language to the PIL that Advair Diskus can cause serious side effects including blurred vision or other changes in vision may be associated with use of Advair Diskus.
- Revisions throughout labeling to be consistent with current labeling for Breo Ellipta and Trelegy Ellipta.
- Addition of a Labor and Delivery sub-section to Section 8.1 to align with the approved labeling of other long-acting beta agonist-containing GSK products.

Annual reportable changes to the IFU were implemented on January 30, 2018; the trademark symbol was removed from the device label in Figures A and H.

Please note the following from the Clinical review:

CSCR was not added to Section 5 and the Division did use this PAS to update the language of the ocular warning to include a referral to an ophthalmologist in patients who develop ocular symptoms, similar to the language that was added to Dulera and Asmanex HFA.

MOST RECENTLY APPROVED ANDA MODEL LABELING

ANDA#/Supplement# (S-000 if original): [Click here to enter text.](#)

Supplement Approval Date: [Click here to enter text.](#)

Proprietary Name: [Click here to enter text.](#)

Established Name: [Click here to enter text.](#)

Description of Supplement:

TEMPLATE (e.g., BPCA, PREA, Carve-out): [Click here to enter text.](#)

OTHER (Describe): [Click here to enter text.](#)

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **YES**
Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#), or [201.66 \(OTC\)](#)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments: Revised PI is acceptable.

Note: In labeling review C4, we stated that it was the Agency's current thinking that the labeling for ANDAs that reference Advair Diskus should include PIF data from the RLD labeling in the Description section of the labeling. We found the applicant's proposed approach acceptable.

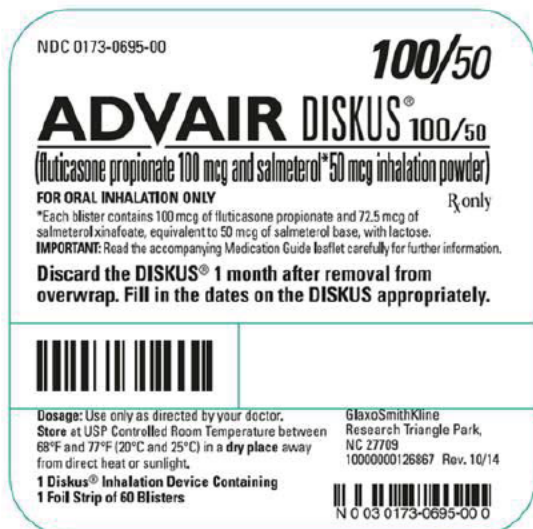
3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: Source: AR-15]

Container:



Foil Overwrap:



Carton:

ADVAIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

Remember:

- Always use the DISKUS in a level, flat position.
- Make sure the lever firmly clicks into place.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. Do not swallow the water.
- Do not take an extra dose, even if you did not taste or feel the powder.
- Do not take the DISKUS apart.
- Do not wash the DISKUS.
- Always keep the DISKUS in a dry place.
- Do not use the DISKUS with a spacer device.

For live assistance with using your ADVAIR DISKUS, call 1-800-884-0593. Visit www.advair.com

NDC 0173-0695-00

ADVAIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

FOR ORAL INHALATION ONLY

*Each blister contains 100 mcg of fluticasone propionate and 72.5 mcg of salmeterol xinafoate, equivalent to 50 mcg of salmeterol base, with lactose.

Rx only



1 DISKUS Inhalation Device
Containing 1 Foil Strip of 60 Blisters

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) (See USP Controlled Room Temperature). Store in a dry place away from direct heat or sunlight. **Keep out of reach of children.** Discard ADVAIR DISKUS 1 month after opening the foil pouch or when the counter reads "0" (after all blisters have been used), whichever comes first. **Dosage:** Use only as directed by your doctor.

IMPORTANT: Read the accompanying Patient Information Leaflet carefully for further information. Trademarks are owned by or licensed to the GSK group of companies or its licensors. ©2018 GSK group of companies or its licensors. GlaxoSmithKline Research Triangle Park, NC 27709

For FREE information, please visit our website at advair.com Or call 888-825-5249



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Rev. 3/18

Continued on side panel.

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in a dry place away from direct heat or sunlight. **Keep out of reach of children.** Discard ADVAIR DISKUS 1 month after opening the foil pouch or when the counter reads "0" (after all blisters have been used), whichever comes first.

Dosage: Use only as directed by your doctor.

IMPORTANT: Read the accompanying Patient Information leaflet carefully for further information.

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GlaxoSmithKline
Research Triangle Park,
NC 27709

For FREE information,
please visit our website at:

advair.com

Or call 888-825-5249



Instructions for using ADVAIR DISKUS

Read the Patient Information that comes with ADVAIR DISKUS before you start using it and each time you get a refill. There may be new information.



Step 1. Open your ADVAIR DISKUS.

Hold the DISKUS in your left hand. Place the thumb of your right hand in the thumb grip and push it away from you as far as it will go until the mouthpiece snaps into place.



Step 2. Slide the lever until you hear it click.

Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the lever away from the mouthpiece as far as it will go until it clicks.



Step 3. Inhale your medicine.

Breathe out (exhale) as long as you can while you hold the DISKUS level and away from your mouth. Do not breathe into the mouthpiece.

Put the mouthpiece to your lips. Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.



Remove the DISKUS from your mouth and hold your breath for about 10 seconds, or for as long as is comfortable for you.

Breathe out slowly as long as you can.

The DISKUS delivers your dose of medicine as a very fine powder that you may or may not taste or feel. Do not take an extra dose from the DISKUS even if you do not taste or feel the medicine.

Step 4. Close the DISKUS. Make sure the DISKUS clicks shut and you cannot see the mouthpiece.

Step 5. Rinse your mouth with water after breathing in the medicine. Spit out the water. Do not swallow it.

Continued on side panel.

Enlarged:

ADVAIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

NDC 0173-0695-00

Remember:

- Always use the DISKUS in a level, flat position.
- Make sure the lever firmly clicks into place.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. Do not swallow the water.
- **Do not** take an extra dose, even if you did not taste or feel the powder.
- **Do not** take the DISKUS apart.
- **Do not** wash the DISKUS.
- Always keep the DISKUS in a dry place.
- **Do not** use the DISKUS with a spacer device.

For live assistance with using your ADVAIR DISKUS, call 1-800-884-0593. Visit www.advair.com

ADVAIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

FOR ORAL INHALATION ONLY

*Each blister contains 100 mcg of fluticasone propionate and 72.5 mcg of salmeterol xinafoate, equivalent to 50 mcg of salmeterol base, with lactose.

Rx only

100/50

**1 DISKUS Inhalation Device
Containing 1 Foil Strip of 60 Blisters**

ADVAIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in a dry place away from direct heat or sunlight. **Keep out of reach of children.** Discard ADVAIR DISKUS 1 month after opening the foil pouch or when the counter reads "0" (after all blisters have been used), whichever comes first.

Dosage: Use only as directed by your doctor.

IMPORTANT: Read the accompanying Patient Information leaflet carefully for further information.

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GlaxoSmithKline
Research Triangle Park,
NC 27709

For FREE information, please visit our website at advair.com Or call 888-825-5249

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Rev. 3/18

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0148880

3.4 UNITED STATES PHARMACOPEIA (USP)

The [USP](#) was searched on 1/11/2019.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	YES		Fluticasone Propionate and Salmeterol Inhalation Powder	Packaging and Storage: Preserve in tight, light-resistant containers. Store at controlled room temperature, in a dry place away from direct heat or sunlight.
Not Yet Official	No	NA	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **YES**

Reviewer Comments:

The description section of the PI includes "Meets USP Aerodynamic Particle Size Distribution Test 2" per IR issued January 9, 2019.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 1/11/2019.

Table 3 provides Orange Book patents for the Model Labeling NDA 021077 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
NA						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

NA

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
M-214	12/20/2020	INFORMATION ADDED TO THE CLINICAL TRIALS SECTION OF THE LABELING REGARDING A POSTMARKETING SAFETY AND EFFICACY STUDY EVALUATING THE RISK OF SERIOUS ASTHMA-RELATED EVENTS	(b) (4)	2/26/2018	Carve-out

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **YES**

Reviewer Comments:

(b) (4)

(b) (4) The Agency has concluded that the applicant's proposed exclusivity carve-out is acceptable.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
 Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **YES**
 Are there changes to the manufacturer/distributor/packer statements? **NO**
 If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	Currently Proposed	Assessment
Wixela™ Inhub™ is a grey colored plastic inhaler containing two foil sealed discs, each disc containing 30 pre-metered doses. Each of the 60 doses contains a white to off white powder mix of micronized fluticasone propionate (100 mcg, 250 mcg, or 500 mcg) and micronized salmeterol xinafoate salt (72.5 mcg, equivalent to 50 mcg of salmeterol base) in 12.5 mg of formulation containing lactose monohydrate (which contains milk proteins). After the inhaler is activated, the powder is dispersed into the airstream created by the patient inhaling through the mouthpiece.	Wixela™ Inhub™ is a grey colored plastic inhaler containing two foil sealed discs, each disc containing 30 pre-metered doses. Each of the 60 doses contains a white to off white powder mix of micronized fluticasone propionate (100, 250, or 500 mcg) and micronized salmeterol xinafoate salt (72.5 mcg, equivalent to 50 mcg of salmeterol base) in 12.5 mg of formulation containing lactose monohydrate (which contains milk proteins). After the inhaler is activated, the powder is dispersed into the airstream created by the patient inhaling through the mouthpiece.	No changes in the inactives. Revision made to be consistent with RLD: Acceptable.

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	Currently Proposed	Assessment
(b) (4)	16 HOW SUPPLIED/STORAGE AND HANDLING Wixela™ Inhub™ 100/50 is supplied as a disposable grey colored plastic dry powder inhaler containing two foil sealed discs, providing a total of 60 pre-metered doses. The inhaler is packaged in a moisture-protective foil pouch. NDC 0378-9320-32 carton containing one dry powder inhaler Wixela™ Inhub™ 250/50 is supplied as a disposable grey colored plastic dry powder inhaler containing two foil sealed discs, providing a total of 60 pre-metered doses. The inhaler is packaged in a moisture-protective foil pouch. NDC 0378-9321-32 carton containing one dry powder inhaler Wixela™ Inhub™ 500/50 is supplied as a disposable grey colored plastic dry powder inhaler containing two foil sealed discs, providing a total of 60 pre-metered doses. The inhaler is packaged in a moisture-protective foil pouch. NDC 0378-9322-32 carton containing one dry powder inhaler Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] Store in a dry place away from direct heat and sunlight. Keep this and all medication out of the reach of children. Wixela™ Inhub™ should be stored inside the unopened moisture-protective foil pouch and only removed from the pouch immediately before initial use. Discard Wixela™ Inhub™ 1 month after opening the foil pouch or when the counter reads "0" (after all doses have been used), whichever comes first. The inhaler is not reusable. Do not attempt to take the inhaler apart.	Highlighted text deleted to be consistent with RLD: Acceptable.

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	Currently Proposed	Assessment
 Manufactured for: Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A. Manufactured by: McDermott Laboratories Ltd. t/a Mylan Dublin Respiratory Unit 25 Baldoyle Industrial Estate, Grange Road, Baldoyle, Dublin 13, Ireland	 Manufactured for: Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A. Manufactured by: McDermott Laboratories Ltd. t/a Mylan Dublin Respiratory Unit 25 Baldoyle Industrial Estate, Grange Road, Baldoyle, Dublin 13, Ireland	No change

5. COMMENTS FOR OTHER DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

An IR was sent to the firm on 1/9/2019 to revise the USP statement in the Description section of the PI to “Meets USP Aerodynamic Particle Size Distribution Test 2.” The USP statement change is consistent with the December 13, 2018 USP Notice of Intent to Revise for Fluticasone Propionate and Salmeterol Inhalation Powder USP.

The following FYI issue was created for Chemistry (1/11/2018) to note the USP statement change.

Ref #	Name	Issue Description	Drug Product
28550757	FYI from Labeling	This is to inform you that the proposed PI (1/10/2019 submission) now includes the USP statement “Meets USP Aerodynamic Particle Size Distribution Test 2” in the Description section of the PI per IR sent on 1/9/2019. Thank you.	FLUTICASONE PROPIONATE AND SALMETEROL

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item “Final, Draft, or “NA”. If you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	One inhaler	1/10/2019	Satisfactory
Blister	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Carton	Final	Containing one inhaler	1/10/2019	Satisfactory
(Other – specify) Foil Pouch label	Final	Containing one inhaler	1/10/2019	Satisfactory

Table 9 Review Summary of Prescribing Information and Patient Labeling				

	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	1/2019	1/10/2019	Satisfactory
Medication Guide	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patient Information	Draft	1/2019	1/10/2019	Satisfactory
Instructions for Use	Draft	1/2019	1/10/2019	Satisfactory
SPL Data Elements		1/2019	1/10/2019	Satisfactory



Juwon
Lee

Digitally signed by Juwon Lee
Date: 1/28/2019 05:44:20PM
GUID: 508da6f700027fdcd32f67dfe9fc22f8



Keisha
Redd

Digitally signed by Keisha Redd
Date: 1/28/2019 08:54:16PM
GUID: 5511c09c0002a85ed531a9e88c322b6e

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	12/12/2018
ANDA Number(s)	208891
Review Number	4
Applicant Name	Mylan Pharmaceuticals Inc.
Established Name & Strength(s)	Fluticasone Propionate and Salmeterol Inhalation Powder USP, 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg/50 mcg
Proposed Proprietary Name	Wixela™ Inhub™ (Proprietary name granted 9/6/2018)
Submission Received Date	10/4/2018 (PI) and 7/13/2018 (Container/carton)
Primary Labeling Reviewer	JuWon Lee, Pharm. D.
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

- ACCEPTABLE – No Comments.
- ACCEPTABLE – Include Post Approval Comments
- Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.
- Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List

Yes No

Combined Insert/Outsert

Yes No (If yes, indicate ANDA number)

1. LABELING COMMENTS

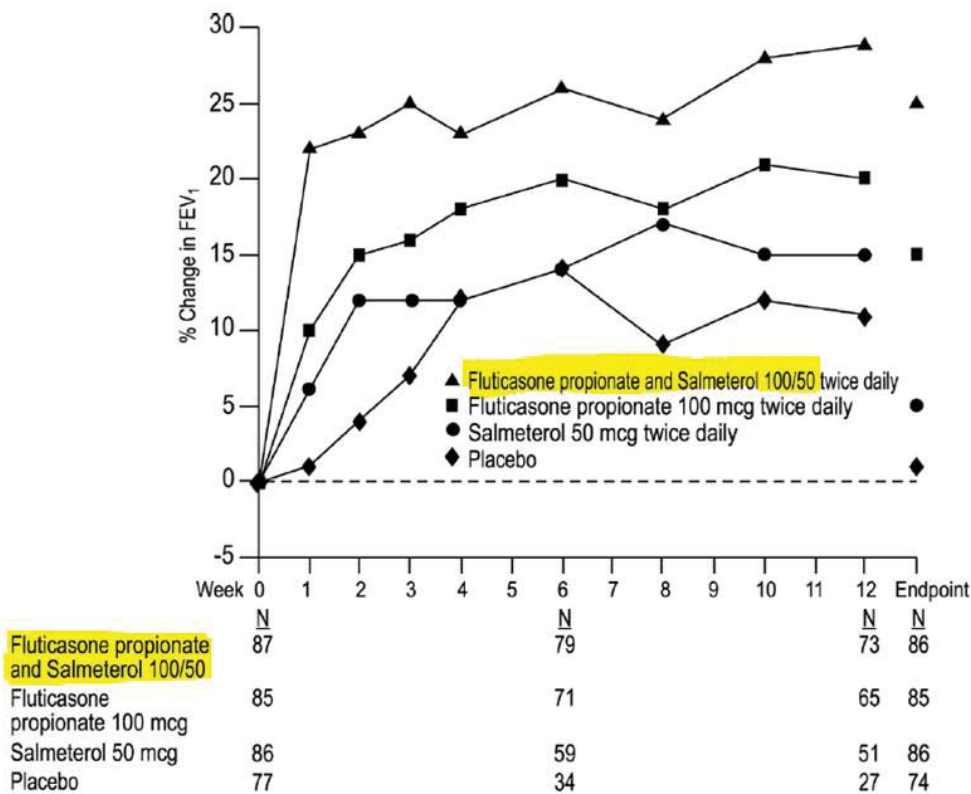
1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on 12/12/2018 based on your submissions received 7/13/2018 and 10/4/2018:

1. PRESCRIBING INFORMATION

- a. When replacing the RLD proprietary name, Advair Diskus, with your established name, ensure to include the full established name with the dosage form (e.g., inhalation powder). Where the RLD proprietary name is described by strength (e.g., Advair Diskus 100/50), the strength for your established name should include a unit of measurement (e.g., 100 mcg/50 mcg). For example, in the figure below, the full established name should be “Fluticasone propionate and Salmeterol inhalation powder 100 mcg/50 mcg” (see yellow highlighted text). Ensure to revise accordingly **throughout the labeling**, including all figures.

Figure 1. Mean Percent Change from Baseline in FEV1 in Subjects with Asthma Previously Treated with Either Inhaled Corticosteroids or Salmeterol (Trial 1)



- b. Revise the highlighted text below to state “fluticasone propionate and salmeterol.” We note that “ADVAIR” in the RLD labeling in this instance references any formulation of ADVAIR, which includes either the inhalation powder or inhalation aerosol.

6.3 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of any formulation of fluticasone propionate and salmeterol inhalation powder, fluticasone propionate, and/or salmeterol regardless of indication. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to fluticasone propionate and salmeterol inhalation powder, fluticasone propionate, and/or salmeterol or a combination of these factors.

- c. Revise **the proposed labeling** to be consistent with the RLD labeling. For example:
 - i. Except for the instances covered by deficiency 1a, include the unit of measurement, “mcg,” only in places where the RLD labeling includes it. For example, the highlights section of the proposed labeling currently states:

-----DOSAGE FORMS AND STRENGTHS -----
Inhalation powder: Inhaler containing a combination of fluticasone propionate (100 mcg, 250 mcg, or 500 mcg) and salmeterol (50 mcg) as a powder formulation for oral inhalation. (3)

We note, however, that the RLD labeling includes “mcg” only after the last strength of fluticasone propionate, 500 mcg. Therefore, for this example, the instances of “mcg” highlighted in yellow should be deleted so that the proposed labeling for this example states “(100, 250, or 500 mcg).”

- ii. Revise proposed labeling to express numbers in a manner consistent with the RLD (i.e., if the RLD spells out a number, the proposed labeling should also spell out that number; if the RLD labeling expresses a number as a numeral, the proposed labeling should also express the number as a numeral). For example, the Dosage and Administration section of the PI currently states:

2 DOSAGE AND ADMINISTRATION

Wixela™ Inhub™ should be administered as one inhalation twice daily by the orally inhaled route only. After inhalation, the patient should rinse his/her mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis.

More frequent administration or a greater number of inhalations (more than one inhalation twice daily) of the prescribed strength of Wixela™ Inhub™ is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. Patients using Wixela™ Inhub™ should not use additional LABA for any reason. [See Warnings and Precautions (5.3, 5.12).]

We note, however, that the RLD labeling expresses the number highlighted in yellow above as a numeral. Therefore, for this example, “one” should be revised to “1” in the proposed labeling.

- d. Section 11 Description: Revise to state “empirical formula” in place of “molecular formula” to be consistent with the RLD labeling.
- e. Section 12.2 Pharmacodynamics: Revise the highlighted text below to state “a dry powder inhaler.” We note that “the DISKUS” in the RLD labeling in this instance references the ADVAIR DISKUS inhaler (combination of fluticasone propionate and salmeterol inhalation powder) and the FLOVENT DISKUS (fluticasone propionate inhalation powder) inhaler.

Pediatric Subjects: Hypothalamic-Pituitary-Adrenal Axis Effects: In a 12-week trial in subjects with asthma aged 4 to 11 years who were receiving ICS at trial entry, fluticasone propionate and salmeterol inhalation powder 100 mcg/50 mcg twice daily was compared with fluticasone propionate inhalation powder 100 mcg administered twice daily via another dry powder inhaler. The values for 24-hour urinary cortisol excretion at trial entry and after 12 weeks of treatment were similar within each treatment group. After 12 weeks, 24-hour urinary cortisol excretion was also similar between the 2 groups.

- f. Section 12.2 Pharmacodynamics: Revise the highlighted text below to state “a dry powder inhaler.” We note that “the DISKHALER inhalation device” in the RLD labeling references the Flovent Rotadisk dry powder inhaler.

Other Fluticasone Propionate Products: Subjects with Asthma: Hypothalamic-Pituitary-Adrenal Axis Effects: In clinical trials with fluticasone propionate inhalation powder using dosages up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol < 18 mcg/dL assessed by radioimmunoassay) were noted both in subjects receiving fluticasone propionate and in subjects receiving placebo. The incidence of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year trial carried out with the DISKHALER® inhalation device in 64 subjects with mild, persistent asthma (mean FEV₁ 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo, no subject receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin infusion (peak serum cortisol < 18 mcg/dL). With a peak cortisol threshold of < 35 mcg/dL, 1 subject receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing at 18 months and 2 years was normal. Another subject receiving fluticasone propionate (5%) had an abnormal response at 2 years. No subject on placebo had an abnormal response at 1 or 2 years.

- g. Section 12.2 Pharmacodynamics: Revise the highlighted text below to state “a dry powder inhaler.” We note that “the DISKUS” in the RLD labeling in this instance references the FLOVENT DISKUS (fluticasone propionate inhalation powder) inhaler.

Subjects with Chronic Obstructive Pulmonary Disease: Hypothalamic-Pituitary-Adrenal Axis Effects: After 4 weeks of dosing, the steady-state fluticasone propionate pharmacokinetics and serum cortisol levels were described in a subset of subjects with COPD (n = 86) randomized to twice-daily fluticasone propionate inhalation powder via another dry powder inhaler 500 mcg, fluticasone propionate inhalation powder 250 mcg, or placebo. Serial serum cortisol concentrations were measured across a 12-hour dosing interval. Serum cortisol concentrations following 250 mcg and 500 mcg twice-daily dosing were 10% and 21% lower than placebo, respectively, indicating a dose-dependent increase in systemic exposure to fluticasone propionate.

- h. Section 12.3 Pharmacokinetics: Revise the highlighted text below to state “a dry powder inhaler” (first two instances) and “a fluticasone propionate dry powder inhaler (last two instances) respectively.” We note that “the DISKUS inhaler” and “the fluticasone propionate DISKUS inhaler” in the RLD labeling in these instances reference the FLOVENT DISKUS (fluticasone propionate inhalation powder) inhaler.

Subjects with Asthma and COPD: Peak steady-state fluticasone propionate plasma concentrations in adult subjects with asthma (N = 11) ranged from undetectable to 266 pg/mL after a 500 mcg twice-daily dose of fluticasone propionate inhalation powder using another dry powder inhaler. The mean fluticasone propionate plasma concentration was 110 pg/mL.

Full pharmacokinetic profiles were obtained from 9 female and 16 male subjects with asthma given fluticasone propionate inhalation powder 500 mcg twice daily using another dry powder inhaler and from 14 female and 43 male subjects with COPD given 250 or 500 mcg twice daily. No overall differences in fluticasone propionate pharmacokinetics were observed.

Peak steady-state fluticasone propionate plasma concentrations in subjects with COPD averaged 53 pg/mL (range: 19.3 to 159.3 pg/mL) after treatment with 250 mcg twice daily (n = 30) and 84 pg/mL (range: 24.3 to 197.1 pg/mL) after treatment with 500 mcg twice daily (n = 27) via another fluticasone propionate dry powder inhaler. In another trial in subjects with COPD, peak steady-state fluticasone propionate plasma concentrations averaged 115 pg/mL (range: 52.6 to 366.0 pg/mL) after treatment with 500 mcg twice daily via another fluticasone propionate dry powder inhaler (n = 15) and 105 pg/mL (range: 22.5 to 299.0 pg/mL) via fluticasone propionate and salmeterol inhalation powder (n = 24).

- i. 12.3 Pharmacokinetics: Revise the highlighted text below to state “a dry powder inhaler.” We note that “the DISKUS” in the RLD labeling in this instance references the FLOVENT DISKUS (fluticasone propionate inhalation powder) inhaler, the SEREVENT DISKUS (salmeterol inhalation powder) inhaler, or the ADVAIR DISKUS (combination of fluticasone propionate and salmeterol inhalation powder) inhaler.

Drug Interaction Studies: In the repeat- and single-dose trials, there was no evidence of significant drug interaction in systemic exposure between fluticasone propionate and salmeterol when given alone or in combination via another dry powder inhaler. The population pharmacokinetic analysis from nine controlled clinical trials in 350 subjects with asthma showed no significant effects on fluticasone propionate or salmeterol pharmacokinetics following co-administration with beta₂-agonists, corticosteroids, antihistamines, or theophyllines.

- j. 14.1 Asthma: Revise the highlighted text to state “a dry powder inhaler.” We note that “the DISKUS inhaler” in the RLD labeling in this instance references the FLOVENT DISKUS (fluticasone propionate inhalation powder) inhaler, the SERVENT DISKUS (salmeterol inhalation powder) inhaler, or the ADVAIR DISKUS (combination of fluticasone propionate and salmeterol inhalation powder) inhaler.

14.1 Asthma

Adult and Adolescent Subjects Aged 12 Years and Older: In clinical trials comparing fluticasone propionate and salmeterol inhalation powder with its individual components, improvements in most efficacy endpoints were greater with fluticasone propionate and salmeterol inhalation powder than with the use of either fluticasone propionate or salmeterol alone. In addition, clinical trials showed similar results between fluticasone propionate and salmeterol inhalation powder and the concurrent use of fluticasone propionate plus salmeterol at corresponding doses from separate inhalers.

Trials Comparing Fluticasone Propionate and Salmeterol Inhalation Powder with Fluticasone Propionate Alone or Salmeterol Alone: Three (3) double-blind, parallel-group clinical trials were conducted with fluticasone propionate and salmeterol inhalation powder in 1,208 adult and adolescent subjects (aged 12 years and older, baseline FEV₁ 63% to 72% of predicted normal) with asthma that was not optimally controlled on their current therapy. All treatments were inhalation powders given as one inhalation from another dry powder inhaler twice daily, and other maintenance therapies were discontinued.

- k. 14.2 Chronic Obstructive Pulmonary Disease: Revise the highlighted text to state “the dry powder inhaler.” We note that “the DISKUS inhaler” in the RLD labeling in this instance references the ADVAIR DISKUS (combination of fluticasone propionate and salmeterol inhalation powder) inhaler.

14.2 Chronic Obstructive Pulmonary Disease

36

The efficacy of fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg and fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg in the treatment of subjects with COPD was evaluated in 6 randomized, double-blind, parallel-group clinical trials in adult subjects aged 40 years and older. These trials were primarily designed to evaluate the efficacy of fluticasone propionate and salmeterol inhalation powder on lung function (3 trials), exacerbations (2 trials), and survival (1 trial).

Lung Function: Two of the 3 clinical trials primarily designed to evaluate the efficacy of fluticasone propionate and salmeterol inhalation powder on lung function were conducted in 1,414 subjects with COPD associated with chronic bronchitis. In these 2 trials, all the subjects had a history of cough productive of sputum that was not attributable to another disease process on most days for at least 3 months of the year for at least 2 years. The trials were randomized, double-blind, parallel-group, 24-week treatment duration. One trial evaluated the efficacy of fluticasone propionate and salmeterol inhalation powder 250 mcg/50 mcg compared with its components fluticasone propionate 250 mcg and salmeterol 50 mcg and with placebo, and the other trial evaluated the efficacy of fluticasone propionate and salmeterol inhalation powder 500 mcg/50 mcg compared with its components fluticasone propionate 500 mcg and salmeterol 50 mcg and with placebo. Trial treatments were inhalation powders given as one inhalation from another dry powder inhaler twice daily. Maintenance COPD therapies were discontinued, with the exception of theophylline. The subjects had a mean pre-bronchodilator FEV₁ of 41% and 20% reversibility at trial entry. Percent reversibility was calculated as 100 times (FEV₁ post-albuterol minus FEV₁ pre-albuterol)/FEV₁ pre-albuterol.

- l. Section 16 How Supplied/Storage and Handling: Remove the following statements to align with the RLD labeling



2. INSTRUCTIONS FOR USE (IFU)

3. CARTON LABELING

Refer to comments 2.a and 2.b. and revise accordingly.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. In addition, please provide a side-by-side comparison of your proposed labeling with the RLD labeling. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE-NA

The Division of Labeling has no further questions/comments at this time based on your labeling submissions dated (add date).

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

NA

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

The below comments are from the labeling review C3 based on the submission dated 3/9/2018. See cover letter dated 7/13/2018 for firm's responses on Instructions for Use (IFU).

LABELING

FDA COMMENT 1 – CONTAINER LABEL (INHALER LABEL)

The RLD container label (back panel) includes "Do not exhale into the mouthpiece or tip downward when in use." Revise to state "Do not exhale into the mouthpiece." We note your response (February 5, 2018 submission) stating that the statement "Do not tip downward when in use" is a DISKUS® specific instruction. However, the first part stating "Do no exhale into the mouthpiece" is applicable to your product, and needs to be added to be consistent with the RLD.

MYLAN RESPONSE

As requested by the Agency and in accordance with the RLD's container label, Mylan has included the statement "Do not exhale into the mouthpiece" on the proposed final printed inhaler labels (back panel). Please refer to [Section 1.14.2.1](#). A side by side comparison of Mylan's proposed final printed inhaler labels (back panel) to Mylan's previously submitted final printed inhaler labels (back panel) is provided in [Section 1.14.1.2 \(Container\)](#).

FDA COMMENT 2 - CARTON LABELING

- a. "Follow the 4 steps below each time you take a dose": Refer to comment 4 (IFU), and revise to be consistent with the RLD carton labeling.
- b. "Important Information": Refer to comment 4 (IFU), and revise to be consistent with the RLD carton labeling.

MYLAN RESPONSE

- a. In accordance with Comment 4 (IFU), Mylan has revised the previous wording of "*Follow the 4 steps below each time you take a dose*" on the back panel of the proposed final printed cartons to be consistent with the RLD cartons. The text now states: "*Instructions for using WIXELA™ INHUB™ Read the Patient Information that comes with WIXELA™ INHUB™ before you start using it and each time you get a refill. There may be new information.*" This also reflects revisions made to the IFU. Please refer to [Section 1.14.2.1](#). A side by side comparison of Mylan's proposed final printed cartons to Mylan's previously submitted final printed cartons is provided in [Section 1.14.1.2 \(Container\)](#).
- b. In accordance with comment 4 (IFU), Mylan has revised the "important information" section on the proposed final printed cartons to be consistent with the RLD cartons. Please note that the header for this section now reads as "Remember:" to be consistent with the RLD cartons. Please refer to [Section 1.14.2.1](#). A side by side comparison of Mylan's proposed final printed cartons to Mylan's previously submitted final printed cartons is provided in [Section 1.14.1.2 \(Container\)](#).

FDA COMMENT 3 - PRESCRIBING INFORMATION

In your August 28, 2017 resubmission, you proposed peak inspiratory flow (PIF) data from the most recently approved labeling for the RLD in the Description section of your product labeling. You indicate that your proposal is based on FDA’s recommendation described in the Agency’s July 7, 2017 Preliminary Meeting Comments. We note that you also have submitted data reflecting the flow profiles achieved in patient populations specifically with your device (see Mylan’s April 3, 2017 request for a face-to-face meeting). In your April 3, 2017 submission, you proposed to provide a summary of the *in vitro* equivalence testing in relation to the flow profiles achieved in patient populations with your specific device in your product labeling as an example of how healthcare providers may be informed of your product’s attributes. Upon further consideration of the Agency’s July 7, 2017 Preliminary Meeting Comments, please explain, whether it would be more appropriate for your product labeling to reflect PIF data from the RLD labeling or the PIF data available for your product. Please include in your response the scientific and regulatory justification for your proposal, taking into account the labeling requirements for ANDAs reflected in 21 C.F.R. 314.94(a)(8)(iv) and 21 C.F.R. 314.127(a)(7).

MYLAN RESPONSE

Mylan proposes that the label reflect the PIF data from the RLD labelling and based on the following scientific and regulatory justification:

-  (b) (4)
-
-

We would welcome any feedback OGD is able to provide in advance of the goal date. In light of the necessary lead times Mylan has already printed labelling in support of launch preparation activities and in order to be able to make this first generic product available to consumers at the earliest possible date upon approval.

The following text is included in the Wixela™ Inhub™ USPI contained in Section 1.14.1.2 (Labeling):

“In adult subjects with obstructive lung disease and severely compromised lung function (mean FEV1 20% to 30% of predicted), mean peak inspiratory flow (PIF) through the dry powder inhaler was 82.4 L/min (range: 46.1 to 115.3 L/min).

Inhalation profiles for adolescent (N = 13, aged 12 to 17 years) and adult (N = 17, aged 18 to 50 years) subjects with asthma inhaling maximally through the dry powder inhaler show mean PIF of 122.2 L/min (range: 81.6 to 152.1 L/min). Inhalation profiles for pediatric subjects with asthma inhaling maximally through the dry powder inhaler show a mean PIF of 75.5 L/min (range: 49.0 to 104.8 L/min) for the 4-year-old subject set (N = 20) and 107.3 L/min (range: 82.8 to 125.6 L/min) for the 8-year-old subject set (N = 20).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.”

Reviewer Comments:

Description/PIF data:

Applicant proposes to include the peak inspiratory flow (PIF) data from the RLD labeling in the Description Section of the ANDA labeling, with certain permissible labeling differences. Per the Agency's September 27, 2018 and October 2, 2018 requests, applicant also made the following changes to the Description Section of the labeling:

1. [REDACTED] (b) (4) was changed to "After the inhaler is **activated**, the powder **is dispersed** into the airstream created by the patient inhaling through the mouthpiece." (same as RLD labeling); and
2. "the dry powder inhaler" was changed to "another dry powder inhaler" ("DISKUS" in RLD labeling, but permissible labeling differences because applicant's product is [REDACTED] (b) (4))

The Agency's current thinking is that the labeling for ANDAs that reference Advair Diskus should include PIF data from the RLD labeling in the Description Section of the labeling.

Instructions for Use:

Firm includes the following response for Step 4: RLD dose counter information appears in Step 2 vs. Step 4 for this ANDA for consistency with Mylan's device design and operation. Mylan's dose counter will count down one dose in conjunction with the closure of Mylan's inhaler device: Acceptable.

FDA Comment 4b ii. Step 4:

- Your proposed differences in the illustration and instructions on how to close the mouthpiece cover are acceptable.
- All other proposed changes made to this section of the IFU not listed above should be revised to be consistent with the IFU for the RLD.

Mylan Response 4b ii. Step 4:

- Please note that the RLD's dose counter information appears in Step 2 of the RLD's IFU to coincide with the RLD's lever being slid to the correct position. For consistency with Mylan's inhaler device design and operation, Mylan's dose counter information is with the Step 4 instructions because Mylan's 'dose counter will count down one dose' in conjunction with the closure of Mylan's inhaler device.
- The IFU has been revised to be consistent with the RLD with the exception of the aforementioned dose counter information. Please refer to Section 1.14.1.2 (Labeling) for a side by side comparison of Mylan's proposed final IFU compared with the RLD.

After further consideration, additional comments will be made to more closely align the proposed labeling, IFU and carton labeling with the RLD labeling, IFU, and carton labeling. The additional comments related to the IFU were drafted in consultation with DCR.

After further consideration, RLD proprietary names, non-RLD proprietary names, and device proprietary names in ANDA labeling will be handled as follows:

- **The RLD proprietary name should be replaced with the ANDA established name. Units of measurement can be added to express the strength in the ANDA established name.**

- **Non-RLD proprietary names should be retained in the ANDA labeling.**
- **Device proprietary names should be changed in the ANDA labeling. Specifically, use of “the dry powder inhaler” is recommended only when the ADVAIR DISKUS inhaler is referenced in the RLD labeling. In all other instances, revise to use “a dry powder inhaler” including “the DISKHALER inhalation device.”**

Further, the APSD USP statement will remain the same as currently proposed in the Description section of the PI and on the container/carton labeling: (b) (4)

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: Carton labeling needs to be further revised per additional comments on the IFU.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

NA

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in [DLR's SharePoint Drug Facts](#)? NO

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on [OGD's SharePoint](#)? YES

If Yes, please explain.

CP	FDA-2009-P-0597	Multiple: Serevent Diskus, Flovent Diskus, Flovent HFA, Advair Diskus, and Advair HFA (Metered and powdered inhalation products)	Multiple: fluticasone propionate and salmeterol xinafoate; aerosol, Metered and Powder; Inhalation	Requests FDA to not approve any ANDA referencing inhalation products containing fluticasone propionate and/or salmeterol xinafoate unless conforms to the RLD: in patient instructions for use and handling, Q1/Q2 BE, successful clinical testing in pediatric and adults as part of BE, and successfully clinically tested in asthma and COPD patients.	020692 (serevent Diskus), 020833 (Flovent Diskus), 021433 (Flovent HFA), 021077 (Advair Diskus), and 21254 (Advair HFA)	No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead
No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence or Labeling		Petitioner is specifically referring to metered-dose inhalers (MDIs) and dry-powder inhalers (DPIs) with these active ingredients that treat asthma and chronic obstructive pulmonary disease (COPD). The petitioner provides the following NDAs as their applications that fall within under the category of Inhalation Products: 020692 (serevent Diskus), 020833 (Flovent Diskus), 021433 (Flovent HFA), 021077 (Advair Diskus), and 21254 (Advair HFA).			12/16/2009	Andrea Bautista

Is the drug product listed on the [Susceptibility Test Interpretive Criteria web page](#)? NO

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling
(Check the box used as the Model Labeling)

MOST RECENTLY APPROVED NDA MODEL LABELING

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)

NDA# /Supplement# (S-000 if original): 021077/S-056 and S-057

Supplement Approval Date: 12/20/2017

Proprietary Name: Advair Diskus®

Established Name: Fluticasone Propionate and Salmeterol Inhalation Powder

Description of Supplement:

These Prior Approval supplemental new drug applications provide for changes to the prescribing information to incorporate the results of the required safety trials with Advair Diskus and revised class labeling for inhaled corticosteroid/long-acting beta agonist combination products, including removal of the Boxed Warning for asthma-related death. These supplements also provide for replacement of the Medication Guide with the Patient Information leaflet and revised labeling in accordance with the Pregnancy and Lactation Labeling Rule (PLLR).

MOST RECENTLY APPROVED ANDA MODEL LABELING

ANDA#/Supplement# (S-000 if original): Click here to enter text.

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement:

TEMPLATE (e.g., BPCA, PREA, Carve-out): NA

OTHER (Describe): NA

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **NO**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

Applicant proposes to include the peak inspiratory flow (PIF) data from the RLD labeling in the Description Section of the ANDA labeling, with certain permissible labeling differences. See above for more information.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: AR-15]

Container



Foil Overwrap



Carton

ADVAIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

Remember:

- Always use the DISKUS in a level, flat position.
- Make sure the lever firmly clicks into place.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. Do not swallow the water.
- Do not take an extra dose, even if you did not taste or feel the powder.
- Do not take the DISKUS apart.
- Do not wash the DISKUS.
- Always keep the DISKUS in a dry place.
- Do not use the DISKUS with a spacer device.

For live assistance with using your ADVAIR DISKUS, call 1-800-884-0593. Visit www.advair.com

NDC 0173-0695-00

ADVAIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

FOR ORAL INHALATION ONLY

*Each blister contains 100 mcg of fluticasone propionate and 72.5 mcg of salmeterol xinafoate, equivalent to 50 mcg of salmeterol base, with lactose.

Rx only

100/50

1 DISKUS Inhalation Device
Containing 1 Foil Strip of 60 Blisters



Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in a dry place away from direct heat or sunlight. **Keep out of reach of children.** Discard ADVAIR DISKUS 1 month after opening the foil pouch or when the counter reads "0" (after all blisters have been used), whichever comes first. **Dosage:** Use only as directed by your doctor.

IMPORTANT: Read the accompanying Patient Information leaflet carefully for further information. Trademarks are owned by or licensed to the GSK group of companies. ©2018 GSK group of companies or its licensor. GlaxoSmithKline Research Triangle Park, NC 27709

For FREE information, please visit our website at: advair.com
Or call 888-825-5249



100/50
ADVAIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

Instructions for using ADVAIR DISKUS
Read the Patient Information that comes with ADVAIR DISKUS before you start using it and each time you get a refill. There may be new information.



Step 1. Open your ADVAIR DISKUS.

Hold the DISKUS in your left hand. Place the thumb of your right hand in the thumb grip and push it away from you as far as it will go until the mouthpiece snaps into place.



Step 2. Slide the lever until you hear it click.

Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the lever away from the mouthpiece as far as it will go until it clicks.



Step 3. Inhale your medicine.

Breathe out (exhale) as long as you can while you hold the DISKUS level and away from your mouth. Do not breathe into the mouthpiece.

Put the mouthpiece to your lips. Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.

Remove the DISKUS from your mouth and hold your breath for about 10 seconds, or for as long as is comfortable for you.

Breathe out slowly as long as you can.



The DISKUS delivers your dose of medicine as a very fine powder that you may or may not taste or feel. Do not take an extra dose from the DISKUS even if you do not taste or feel the medicine.

Step 4. Close the DISKUS. Make sure the DISKUS clicks shut and you cannot see the mouthpiece.

Step 5. Rinse your mouth with water after breathing in the medicine. Spit out the water. Do not swallow it.

Continued on side panel.

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Rev. 3/18

ADVAIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

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Instructions for using ADVAIR DISKUS

Read the Patient Information that comes with ADVAIR DISKUS before you start using it and each time you get a refill. There may be new information.



Step 1. Open your ADVAIR DISKUS.

Hold the DISKUS in your left hand. Place the thumb of your right hand in the thumb grip and push it away from you as far as it will go until the mouthpiece snaps into place.



Step 2. Slide the lever until you hear it click.

Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the lever away from the mouthpiece as far as it will go until it clicks.



Step 3. Inhale your medicine.

Breathe out (exhale) as long as you can while you hold the DISKUS level and away from your mouth. Do not breathe into the mouthpiece.

Put the mouthpiece to your lips. Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.

Remove the DISKUS from your mouth and hold your breath for about 10 seconds, or for as long as is comfortable for you.

Breathe out slowly as long as you can.

The DISKUS delivers your dose of medicine as a very fine powder that you may or may not taste or feel. Do not take an extra dose from the DISKUS even if you do not taste or feel the medicine.

Step 4. Close the DISKUS. Make sure the DISKUS clicks shut and you cannot see the mouthpiece.

Step 5. Rinse your mouth with water after breathing in the medicine. Spit out the water. Do not swallow it.

Continued on side panel.



For FREE information, please visit our website at: advair.com
Or call 888-825-5249

ADVAIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

NDC 0173-0695-00

gsk

ADVAIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

FOR ORAL INHALATION ONLY

*Each blister contains 100 mcg of fluticasone propionate and 72.5 mcg of salmeterol xinafoate, equivalent to 50 mcg of salmeterol base, with lactose.

Rx only

100/50

1 DISKUS Inhalation Device
Containing 1 Foil Strip of 60 Blisters

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in a dry place away from direct heat or sunlight. **Keep out of reach of children.** Discard ADVAIR DISKUS 1 month after opening the foil pouch or when the counter reads "0" (after all blisters have been used), whichever comes first.

Dosage: Use only as directed by your doctor.

IMPORTANT: Read the accompanying Patient Information leaflet carefully for further information.

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Research Triangle Park,
NC 27709

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3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 12/12/2018.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	YES		Fluticasone Propionate and Salmeterol Inhalation Powder	Packaging and Storage: Preserve in tight, light-resistant containers. Store at controlled room temperature, in a dry place away from direct heat or sunlight.
Not Yet Official	NA	NA	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **YES.**

Reviewer Comments:

The APSD USP statement will remain in the Description section of the proposed PI and on the proposed container/carton labeling as recommended by Chemistry: (b) (4)

(b) (4)

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 12/12/2018.

Table 3 provides Orange Book patents for the Model Labeling NDA 021077 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
NA						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

NA

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
M-214	12/20/2020	INFORMATION ADDED TO THE CLINICAL TRIALS SECTION OF THE LABELING REGARDING A POSTMARKETING SAFETY AND EFFICACY STUDY EVALUATING THE RISK OF SERIOUS ASTHMA-RELATED EVENTS	(b) (4)	2/26/2018	Carve-out

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **YES**

Reviewer Comments:

(b) (4)

(b) (4) **It is the Agency's current thinking that the applicant's proposed exclusivity carve-out is acceptable.**

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
 Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
 Are there changes to the manufacturer/distributor/packer statements? **NO**
 If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	Currently Proposed	Assessment
Wixela™ Inhub™ is a grey colored plastic inhaler containing two foil sealed discs, each disc containing 30 pre-metered doses. Each of the 60 doses contains a white to off white powder mix of micronized fluticasone propionate (100 mcg, 250 mcg, or 500 mcg) and micronized salmeterol xinafoate salt (72.5 mcg, equivalent to 50 mcg of salmeterol base) in 12.5 mg of formulation containing lactose monohydrate (which contains milk proteins). After the inhaler is prepared, the powder is ready to be dispersed into the airstream created by the patient inhaling through the mouthpiece.	Wixela™ Inhub™ is a grey colored plastic inhaler containing two foil sealed discs, each disc containing 30 pre-metered doses. Each of the 60 doses contains a white to off white powder mix of micronized fluticasone propionate (100 mcg, 250 mcg, or 500 mcg) and micronized salmeterol xinafoate salt (72.5 mcg, equivalent to 50 mcg of salmeterol base) in 12.5 mg of formulation containing lactose monohydrate (which contains milk proteins). After the inhaler is activated, the powder is dispersed into the airstream created by the patient inhaling through the mouthpiece.	No change in the inactives. The highlighted changes indicate revisions to be consistent with the RLD labeling.

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	Currently Proposed	Assessment

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

(b) (4) 	See below.	No change



Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment
 Manufactured for: Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A. Manufactured by: McDermott Laboratories Ltd. t/a Mylan Dublin Respiratory Unit 25 Baldoyle Industrial Estate, Grange Road, Baldoyle, Dublin 13, Ireland	 Manufactured for: Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A. Manufactured by: McDermott Laboratories Ltd. t/a Mylan Dublin Respiratory Unit 25 Baldoyle Industrial Estate, Grange Road, Baldoyle, Dublin 13, Ireland	No change

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline (e.g., OPQ, OB, DCR) reviewer(s):

Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

The APSD USP statement on the proposed PI and on the proposed container/carton labeling will remain the same as recommended by Chemistry: (b) (4)

(b) (4)

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item “Final, Draft, or “NA”. If you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	One inhaler	7/13/2018	Satisfactory
Blister	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Carton	Final	Containing one inhaler	7/13/2018	Revise
(Other – specify) Foil Pouch label	Final	Containing one inhaler	7/13/2018	Satisfactory

Table 9 Review Summary of Prescribing Information and Patient Labeling

	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	10/2018	10/4/2018	Revise
Medication Guide	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patient Information	Draft	10/2018	10/4/2018	Satisfactory

Instructions for Use	Draft	10/2018	10/4/2018	Revise
SPL Data Elements		10/2018	10/4/2018	Satisfactory



Juwon
Lee

Digitally signed by Juwon Lee
Date: 12/12/2018 02:48:07PM
GUID: 508da6f700027fdcd32f67dfe9fc22f8



Malik
Imam

Digitally signed by Malik Imam
Date: 12/12/2018 04:00:36PM
GUID: 508da70800028c685bf6578d234e223f

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	6/11/2018
ANDA Number(s)	208891
Review Number	3
Applicant Name	Mylan Pharmaceuticals Inc.
Established Name & Strength(s)	Fluticasone Propionate and Salmeterol Inhalation Powder USP, 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg/50 mcg
Proposed Proprietary Name	Wixela™ Inhub™ (Proprietary name expired: Request for review submitted 5/11/2018)
Submission Received Date	3/9/2018 (All other submissions after 3/9/2018 include no labeling)
Primary Labeling Reviewer	JuWon Lee, Pharm. D.
Secondary Labeling Reviewer	Keisha Redd, Pharm. D.
Review Conclusion ☐ ACCEPTABLE – No Comments. ☐ ACCEPTABLE – Include Post Approval Comments ☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant. ☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant †Theme - Choose an item. Justification for Major Deficiency - Choose an item. *Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.	

On Policy Alert List YES NO

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on 6/11/2018 based on your submission dated 3/9/2018:

1. CONTAINER LABEL (Inhaler label)

The RLD container label (back panel) includes “Do not exhale into the mouthpiece or tip downward when in use.” Revise to state “Do not exhale into the mouthpiece.” We note your response (February 5, 2018 submission) stating that the statement “Do not tip downward when in use” is a DISKUS® specific instruction. However, the first part stating “Do no exhale into the mouthpiece” is applicable to your product, and needs to be added to be consistent with the RLD.

2. CARTON LABELING

- a. “Follow the 4 steps below each time you take a dose”: Refer to comment 4 (IFU), and revise to be consistent with RLD carton labeling.
- b. “Important Information”: Refer to comment 4 (IFU), and revise to be consistent with RLD carton labeling.

3. PRESCRIBING INFORMATION

In your August 28, 2017 resubmission, you proposed peak inspiratory flow (PIF) data from the most recently approved labeling for the RLD in the Description section of your product labeling. You indicate that your proposal is based on FDA’s recommendation described in the Agency’s July 7, 2017 Preliminary Meeting Comments. We note that you also have submitted data reflecting the flow profiles achieved in patient populations specifically with your device (see Mylan’s April 3, 2017 request for a face-to-face meeting). In your April 3, 2017 submission, you proposed to provide a summary of the in vitro equivalence testing in relation to the flow profiles achieved in patient populations with your specific device in your product labeling as an example of how healthcare providers may be informed of your product’s attributes. Upon further consideration of the Agency’s July 7, 2017 Preliminary Meeting Comments, please explain, whether it would be more appropriate for your product labeling to reflect PIF data from the RLD labeling or the PIF data available for your product. Please include in your response the scientific and regulatory justification for your proposal, taking into account the labeling requirements for ANDAs reflected in 21 C.F.R. 314.94(a)(8)(iv) and 21 C.F.R. 314.127(a)(7).

4. INSTRUCTIONS FOR USE (IFU)

- a. Please replace the term “inhaler” with your device name “INHUB.”

b. We acknowledge that there are some design and operational differences between your product and the RLD. However, many of the differences between the Instructions for Use (IFU) for your product and the IFU for the RLD are not allowable differences in labeling under 21 CFR 314.94(a)(8)(iv). 21 CFR 314.94(a)(8)(iv) states that “Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under [21 CFR] §314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act.” Accordingly, please revise all sections of the IFU for your proposed product with respect to text, device illustrations, and organization of the tasks within the operating steps for dose administration, to be more consistent with the IFU of the RLD product. Specific recommendations for revisions to all sections of the IFU for your proposed product are listed below.

i. Header Section

The inclusion of two illustrations (closed and open position) of the Wixela Inhub inhaler in the IFU instead of one illustration of the inhaler as included in the RLD’s IFU, is acceptable. Your proposal to remove the text that informs user that the inhaler is for oral use only from the body of the IFU is not acceptable and should be revised. It is important that users of the device inhaler are instructed that the product is to be used for oral use only and by including this message only in the heading of the IFU, users may not see this important message. In addition, in the “Open Position” illustration, add the term “mouthpiece” with a line indicating the location on the WIXELA INHUB for increased patient clarity. This term is used throughout the IFU. All other proposed changes made to this section of the IFU not listed above should be revised to be consistent with the IFU for the RLD.

ii. Step 1

Your proposal to include an illustration to accompany the text for this step is acceptable. It is acceptable to remove the text that informs users to hold the inhaler in the left hand. The changes in the text on how to open the mouthpiece cover from “push the thumb grip to open the mouthpiece cover” in the Wixela Inhub to “lower the mouthpiece cover from top to bottom” in the proposed IFU is acceptable. All other proposed changes made to this section of the IFU not listed above should be revised to be consistent with the IFU for the RLD.

iii. Step 2

The removal of the text that instructs users to hold the inhaler in a flat and level position and to not tilt the inhaler in the IFU is acceptable. It is acceptable to remove the text that references an audible click when the lever has been pushed to the correct position and replace it with text informing users to push the yellow lever to the end of the purple arrows. We note that on the sample of the finished (to-be-marketed) product provided in your response to the Division of Clinical Review's Information Request (Sequence Number 0023, Date 12/18/2017), the color of the arrows on the Wixela Inhub inhaler is blue and not purple as stated in your proposed IFU. Please confirm that the correct color of the arrows on the commercial to-be-marketed version of the Wixela Inhub inhaler is stated in the IFU. All other proposed changes made to this section of the IFU not listed above should be revised to be consistent with the IFU for the RLD.

iv. Step 3

It is acceptable that the proposed IFU instructs users to hold the Wixela Inhub inhaler in a vertical position when inhaling the medication. All other proposed changes made to this section of the IFU not listed above should be revised to be consistent with the IFU for the RLD.

v. Step 4

Your proposed differences in the illustration and instructions on how to close the mouthpiece cover are acceptable. All other proposed changes made to this section of the IFU not listed above should be revised to be consistent with the IFU for the RLD.

vi. Step 5

The removal of Step 5 from the IFU for your proposed product is not acceptable. All proposed changes made to this section of the IFU should be revised to be consistent with the IFU for the RLD.

vii. Key Points Section

The inclusion of illustrations to show how the dose counter will appear on the Wixela Inhub inhaler is acceptable. The revision to the proposed IFU to accurately reflect the appearance of the dose counter is also acceptable. The removal of the text that informs users to hold the inhaler in a level, flat position and to push the lever until it clicks from the proposed IFU for the Wixela Inhub inhaler is acceptable. All other proposed changes made to this section of the IFU not listed above should be revised to be consistent with the IFU for the RLD.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia

– National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE-NA

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated (add date)

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
NA

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

The below comments are from the labeling review C2 (Addendum) based on the submission dated 8/28/2017.

Labeling Deficiencies determined as of 2/5/2018 based on your submission dated 8/28/2017:

FDA COMMENT 1

GENERAL COMMENTS

- a. We note that on December 16, 2009, Ropes & Gray, LLP, on behalf of GlaxoSmithKline, submitted a citizen petition to FDA (Docket No. FDA-2009-P-0597) regarding abbreviated new drug applications (ANDAs) that reference generic copies of oral inhalation products containing fluticasone propionate and/or salmeterol xinafoate. On December 5, 2017, Mylan Inc. submitted a citizen petition to FDA (Docket No. FDA-2017-P-6750) regarding ANDAs for fluticasone propionate and salmeterol xinafoate inhalation powder that rely on Advair Diskus as the reference listed drug (RLD). The issues raised by the above-referenced citizen petitions are under review by the Agency, and FDA has not made a final decision on these issues. The deficiency comments included in this communication do not represent a final decision by the Agency on the issues raised in the pending citizen petitions.
- b. We note that the Medication Guide (MG) has been replaced with Patient Information in the most recently approved reference listed drug (RLD) labeling, Advair Diskus®, NDA 021077/S-056 and 057, approved 12/20/2017. Please replace references to "Medication Guide" (MG) with "Patient Information" in your labels/labeling where applicable (i.e., "Read the accompanying Medication Guide...")
- c. The Orange Book has updated exclusivity (M-214) for the RLD. Address the new exclusivity and revise the insert labeling and Patient Information accordingly.

MYLAN RESPONSE

- a. Mylan acknowledges the Agency's comment.
- b. As requested by the Agency, Mylan's proposed prescribing information was revised pursuant to the CDER Internet Posting dated December 20, 2017 (NDA 021077/S-056 and S-057) which contained approved labeling revisions for the RLD, ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder) (Glaxo Grp Ltd). References to the "Medication Guide" were replaced with "Patient Information" accordingly. Please refer to [Section 1.14.2.2](#).
- c. As requested by the Agency, Mylan has provided a Patent Amendment in [Section 1.3.5.1](#) to address the M-214 exclusivity. As described in the Patent Amendment, Mylan's proposed labeling does not include information covered by the M-214 exclusivity. Please refer to [Section 1.14.2.2](#).

FDA COMMENT 2

CONTAINER LABEL (Inhaler label)

- a. Relocate the expression of strength to appear directly below the established name.
- b. Replace “30 days” with “1 month” to be consistent with RLD.
- c. The RLD container label (back panel) includes “Do not exhale into the mouthpiece or tip downward when in use.” Revise to include this statement to better align with RLD. Please provide rationale for any changes to the statement if needed.
- d. Revise to include a placement for lot number expiration date.

MYLAN RESPONSE

- a. As requested by the Agency, the expression of strength has been relocated to appear directly below the established name from the proposed container labels. Please refer to [Section 1.14.2.1](#).
- b. As requested by the Agency, the terminology has been revised to now read ‘1 month’ to be consistent with the RLD labeling. Please refer to [Section 1.14.2.1](#)
- c. Mylan acknowledges the Agency’s comment. There are a number of ‘do not’ statements included in the Instructions For Use (IFU) and on the side panel of the carton (see response to [question 4d](#)), this includes the text (b) (4) There is no evidence that the ‘do not’ statement relating to breathing into the inhaler is of any greater importance than other ‘do not’ statements included in the IFU or on the carton and there is no evidence within the Device Development Risk Management Program (Module 3, [Section 3.2.P.7.2.7](#)) of a residual risk associated with this potential misuse scenario. Therefore, in order not to suggest a hierarchy of warnings Mylan have not added this specific statement to the inhaler label.

The statement “Do not tip downward when in use” is a DISKUS[®] specific instruction; there is no requirement for this instruction in relation to the use of Mylan’s inhaler (b) (4)



- d. As requested by the Agency, Mylan’s proposed container labels include a place holder for printing of the lot number and expiration date on the non-varnished area. The lot number and expiration date will be printed in the designated location during the packaging process. Please refer to [Section 1.14.2.1](#).

FDA COMMENT 3

FOIL POUCH LABEL

Refer to comments 2.a and 2.b.

MYLAN RESPONSE

Please refer to Mylan’s responses to FDA Comments 2.a. and 2.b, above. Please refer to Section 1.14.2.1.

FDA COMMENT 4

CARTON LABELING

- a. Refer to comments 2.a and 2.b.
- b. Delete the Medication Guide statement on the principal display panel.
- c. Side panel:
Change “Follow the 4 steps below each time you take a dose” to “Instructions for using [Product Name]” followed by “Read the Patient Information that comes with...” to be consistent with the RLD Instructions for use: Refer to comment 7.b for instructions for use, and revise accordingly.
- d. Side panel including “Dose Counter” and “Important Information”: RLD includes the following information under the header “Remember:”

Remember:

- Always use the DISKUS in a level, flat position.
- Make sure the lever firmly clicks into place.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. Do not swallow the water.
- Do not take an extra dose, even if you did not taste or feel the powder.
- Do not take the DISKUS apart.
- Do not wash the DISKUS.
- Always keep the DISKUS in a dry place.
- Do not use the DISKUS with a spacer device.

Revise to better align with the above information. For example, RLD includes “Do not use the [inhaler name] with a spacer device” when your product includes “Do not use a spacer.” Please provide rationale for any information you choose to delete or change.

MYLAN RESPONSE

- a. Please refer to Mylan's responses to FDA Comments 2.a. and 2.b, above. Please refer to [Section 1.14.2.1](#).
- b. As requested by the Agency, the Medication Guide statement has been deleted on the proposed carton labels. Please refer to [Section 1.14.2.1](#).
- c. Mylan acknowledges the Agency's comment. The terminology "Follow the 4 steps below each time you take a dose" has been developed specifically during the Device Development program (inclusive of development of the IFU) to ensure that the instructions are clear and concise, and to reinforce the requirement to complete all 4 steps. This reinforcement was added following usability testing that included RLD users, where some RLD users reported not closing the mouthpiece cover of DISKUS[®] before storage. The IFU containing this statement was underwritten and confirmed as being acceptable and suitable for all intended users during the Human Factors Design Validation study, as described in Module 3, [Section 3.2.P.7.2.6](#) Design Validation. Mylan therefore proposes to maintain the current proposed terminology on the carton label and IFU.
- d. Mylan acknowledges the Agency's comment. Mylan has revised the carton side panel to incorporate all important information contained in the complete text of the IFU to better align with the statements in the same location on the RLD's carton. The text on the amended panel aligns with the text of Mylan's IFU therefore for further discussion on the comparison of instructional text please refer to the response to FDA Comment 7., below.

A side by side comparison of Mylan's proposed final printed container labels to Mylan's previously submitted final printed container labels is provided in [Section 1.14.1.2](#) (Container).

FDA COMMENT 5

PRESCRIBING INFORMATION

Revise your insert labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Advair Diskus[®], NDA 021077/S-056 and 057, approved 12/20/2017.

MYLAN RESPONSE

As requested by the Agency, Mylan's proposed prescribing information was revised pursuant to the CDER Internet Posting dated December 20, 2017 (NDA 021077/S-056 and S-057) which contained approved labeling revisions for the RLD, ADVAIR DISKUS[®] (fluticasone propionate and salmeterol inhalation powder) (Glaxo Grp Ltd). Please refer to [Section 1.14.2.2](#).

FDA COMMENT 6

Patient Information (previously Medication Guide)

Refer to comment 5.

MYLAN RESPONSE

Please refer to Mylan's response to FDA Comment 5, above. Please refer to [Section 1.14.2.2](#).

FDA COMMENT 7

Instructions for Use (IFU)

- a. Refer to comment 5.
- b. Although there are some design and operational differences between your product and the RLD, we believe it is possible to revise all sections of the Instructions for Use (IFU) of your proposed product with respect to text, device illustrations, and organization of the tasks within the operating steps for dose administration, to better align with the IFU of the RLD product. For example, the headers in the IFU of your proposed product should be revised to better align with the following headers in the IFU of the RLD product:

Instructions for Use

Title

For oral inhalation

“Read this Instructions for Use before you start using...”

Your [Product Name] inhaler

[High definition photograph of your inhaler]

Important information about your [Product Name] inhaler:

How to use your [Product Name] inhaler

Follow these steps every time you use [Product Name]

Step 1...Step 5

Also, note that the RLD includes 5 steps instead of 4 steps, and uses the word “1 month” instead of “30 days.”: Please revise accordingly.

- c. Title: Delete (b)(4) appearing next to “for oral inhalation.”

- a. Please refer to Mylan's response to FDA Comment 5, above and Mylan's response 7.b. below. Please also refer to [Section 1.14.2.2](#).
- b. Mylan acknowledges the Agency's comment. In accordance with 21 CFR Part 801.5; Medical devices; adequate directions for use, the Guidance *Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers* and EN ISO 62366:2009 the Instructions for Use (IFU) have been developed to provide the user with instructions that flow logically in brief simple language, highlighting desired information to meet the user need at the moment. Mylan has incorporated current best practice across the pharmaceutical and human factors industries in the design of the IFU whilst meeting the requirements of the *Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate for Powder/Inhalation* (FDA, September 2013) to present the external operating procedures of the CRC749 device in 4 steps: (1) Open, (2) Click, (3) Inhale, and (4) Close, noting that the header of step 2 in the CRC749 IFU reflects a more accurate description of the action required of the user i.e. "Push Down".

An example of the employment of current best practice is the use of line drawing illustrations throughout the IFU to give a consistent message and to ensure the omission of distinctive features where possible such as eyes and painted nails, that may detract the users' attention from the overall intent of the image. Mylan considers it very important to ensure alignment of important information within the specific sequence of use to ensure that the user receives the information at the point at which it is required, and therefore incorporated this best practice within the IFU.

Mylan's IFU has been presented to the Agency throughout the device development program and specifically in the Device Orientation Study Protocol (MGR000-1004) which incorporated all feedback from the Agency review (Request for Special Protocol Assessment, IND: 118769 Sequence: 0009 and controlled correspondence response dated February 9, 2015) prior execution of the study described in Module 3, [Section 3.2.P.7.2.6.1](#).

Mylan's IFU development program resulted in confirmation through Design Validation of the ability of the user to engage with the IFU in order to use the CRC749 inhaler safely and effectively:

- The Device Orientation study (MGR000-1004) demonstrated that patients (including current RLD patients) are able to use the CRC749 inhaler safely and effectively with and without the IFU.
- The Device Robustness Study (MGR001-1010) confirmed by inference that patients who chose to consult the IFU during home use were able to use the CRC749 safely and effectively (Module 3, [Section 3.2.P.7.2.6.2](#)).

As a result of recent advances in IFU development, there are minor differences between Mylan's IFU and that of the RLD. These differences were assessed through Threshold Analysis (Labelling Comparison) in accordance with the Draft Guidance *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry* (January 2017). The outcome of this Comparative Analysis (incorporating the Threshold Analysis (Labelling Comparison) was provided to the Agency in May 2017 (Sequence No. 0018) in response to the Agency's request and subsequently discussed during the meeting on July 13, 2017. The Comparative Analysis was also included in Mylan's response to the CRL (Sequence No. 0021). The Agency confirmed at the July 2017 meeting that FDA agreed with Mylan's

position that any differences between the RLD and CRC749, are considered minor relative to the risk profile of the product (see meeting minutes provided in Sequence No. 0020, Section 1.4.4).

In response to the Agency's request, Mylan has adjusted the IFU and to the associated text on the carton. These adjustments are reflected in the updated labelling provided. As a consequence of these changes the Threshold Analysis was revised and for the purposes of clarity to the reviewer, the outcome of the Threshold Analysis (Labelling Comparison) has been added to the justification of changes within Section 1.14.3.1 (Labelling) and both have been updated to include comparison of images within the IFUs.

Mylan's proposed differences between Mylan's IFU and that of the RLD do not negatively impact the user experience or ability to demonstrate safe and effective use of CRC749. These minor differences are reflective of best practice and have been underwritten and confirmed through acceptability of the current proposed IFU during the device development program, inclusive of the Threshold Analysis (Labelling Comparison) and through Design Validation (Section 3.2.P.7.2.6).

- c. As requested by the Agency, Mylan has amended the IFU title to remove the term (b) (4) Please refer to Section 1.14.2.2.

In accordance with the Agency's Guidance, *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (April 2005), Structured Product Labeling (SPL) for Wixela™ Inhub™ (fluticasone propionate and salmeterol inhalation powder, USP), 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg/50 mcg is provided in Section 1.14.2.3. As a review aid, Microsoft Word versions have also been provided for the proposed labeling components.

Mylan acknowledges that the Agency may request further changes to the labeling prior to approval. In addition, Mylan may have to revise our labeling pursuant to approved changes for the Reference Listed Drug. Mylan will monitor FDA's website for any approved labeling changes, where applicable, subject to the provisions of 505(j)(10)(A) which address late stage labeling changes by the RLD.

Reviewer Comments: Firm did not revise its IFUs as recommended. Consults to the Patient Labeling Team (PLT) and Division of Clinical Review (DCR) were completed (4/13/2018 and 6/4/2018) stating that the IFUs need to be revised to be more consistent with RLD. Container and carton labels need to be further revised. Deficiency language on PIF data (Description section of the PI) will be sent to the firm. See comments.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were NOT requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: Container/carton labels need to be further revised. See comments.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

NA

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review			
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES If Yes, please explain.			
CP	FDA-2009-P-0597	Multiple: Serevent Diskus, Flovent Diskus, Flovent HFA, Advair Diskus, and Advair HFA (Metered and powdered inhalation products) Multiple: fluticasone propionate and salmeterol xinafoate; aerosol, Metered and Powder; Inhalation	Requests FDA to not approve any ANDA referencing inhalation products containing fluticasone propionate and/or salmeterol xinafoate unless conforms to the RLD: in patient instructions for use and handling, Q1/Q2 BE, successful clinical testing in pediatric and adults as part of BE, and successfully clinically tested in asthma and COPD patients. Petitioner is specifically referring to metered-dose inhalers (MDIs) and dry-powder inhalers (DPIs) with these active ingredients that treat asthma and chronic obstructive pulmonary disease (COPD). The petitioner provides the following NDAs as their applications that fall within under the category of Inhalation Products: 020692 (serevent Diskus), 020833 (Flovent Diskus), 021433 (Flovent HFA), 021077 (Advair Diskus), and 21254 (Advair HFA).
No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence or Labeling		020602 (serevent Diskus), 020833 (Flovent Diskus), 021433 (Flovent HFA), 021077 (Advair Diskus), and 21254 (Advair HFA)	No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead 12/16/2009 Andrea Bautista
Is the drug product listed on the Susceptibility Test Interpretive Criteria web page? NO			

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)	
☒	MOST RECENTLY APPROVED NDA MODEL LABELING <i>(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)</i> NDA#/Supplement# (S-000 if original): 021077/S-056 and S-057 Supplement Approval Date: 12/20/2017 Proprietary Name: Advair Diskus® Established Name: Fluticasone Propionate and Salmeterol Inhalation Powder Description of Supplement: These Prior Approval supplemental new drug applications provide for changes to the prescribing information to incorporate the results of the required safety trials with Advair Diskus and revised class labeling for inhaled corticosteroid/long-acting beta agonist combination products, including removal of the Boxed Warning for asthma-related death. These supplements also provide for replacement of the Medication Guide with the Patient Information leaflet and revised labeling in accordance with the Pregnancy and Lactation Labeling Rule (PLLR).
☐	MOST RECENTLY APPROVED ANDA MODEL LABELING ANDA#/Supplement# (S-000 if original): Click here to enter text. Supplement Approval Date: Click here to enter text. Proprietary Name: Click here to enter text. Established Name: Click here to enter text. Description of Supplement:
☐	TEMPLATE (e.g., BPCA, PREA, Carve-out): NA

**Table 1: Review Model Labeling for Prescribing Information and Patient Labeling
(Check the box used as the Model Labeling)**

OTHER (Describe): NA

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **NO**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

Description section of the PI may need to be further revised. **Deficiency language on the PIF data will be sent to the firm.** See comments.

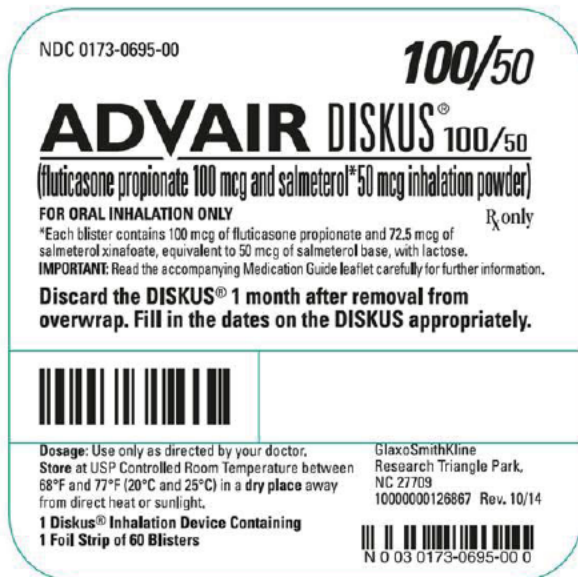
3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: AR-15]

Container



Foil Overwrap



Outside Copy

ADVAIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

Remember:

- Always use the DISKUS in a level, flat position.
- Make sure the lever firmly clicks into place.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. Do not swallow the water.
- Do not take an extra dose, even if you did not taste or feel the powder.
- Do not take the DISKUS apart.
- Do not wash the DISKUS.
- Always keep the DISKUS in a dry place.
- Do not use the DISKUS with a spacer device.

For live assistance with using your ADVAIR DISKUS, call 1-800-884-0593. Visit www.advair.com

NDC 0173-0695-00

ADVAIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

FOR ORAL INHALATION ONLY

*Each blister contains 100 mcg of fluticasone propionate and 72.5 mcg of salmeterol xinafoate, equivalent to 50 mcg of salmeterol base, with lactose.

Federal Law requires the dispensing of ADVAIR DISKUS with the Medication Guide inside the carton.

Rx only

100/50

ADVAIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

1 DISKUS[®] Inhalation Device Containing 1 Foil Strip of 60 Blisters

100/50

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0173-0695-00

ADVAIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

Instructions for using ADVAIR DISKUS
Read the Medication Guide that comes with ADVAIR DISKUS before you start using it and each time you get a refill. There may be new information.

Step 1. Open your ADVAIR DISKUS.
Hold the DISKUS in your left hand. Place the thumb of your right hand in the thumb grip and push it away from you as far as it will go until the mouthpiece snaps into place.

Step 2. Slide the lever until you hear it click.
Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the lever away from the mouthpiece as far as it will go until it clicks.

Step 3. Inhale your medicine.
Breathe out (exhale) as long as you can while you hold the DISKUS level and away from your mouth. Do not breathe into the mouthpiece.
Put the mouthpiece to your lips. Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.
Remove the DISKUS from your mouth and hold your breath for about 10 seconds, or for as long as is comfortable for you.
Breathe out slowly as long as you can.

The DISKUS delivers your dose of medicine as a very fine powder that you may or may not taste or feel. Do not take an extra dose from the DISKUS even if you do not taste or feel the medicine.

Step 4. Close the DISKUS. Make sure the DISKUS clicks shut and you cannot see the mouthpiece.

Step 5. Rinse your mouth with water after breathing in the medicine. Spit out the water. Do not swallow it.

Continued on side panel.

For **FREE** information, please visit our website at advair.com
Or call 888-825-5249

1000000126873 Rev. 10/14

0173-0695-00

GlaxoSmithKline Artwork Information Panel	Item Num 10000000
Market or Pack Owner: United States-USA	Market Tr Advair
Technical Reference No(s): 0003235 TS-000581 (do not include in technical reference sheet content ref(s))	Printing P N/A

Enlarged

ADVAIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in a **dry place** away from direct heat or sunlight. **Keep out of reach of children.** Discard ADVAIR DISKUS 1 month after opening the foil pouch or when the counter reads "0" (after all blisters have been used), whichever comes first.

Dosage: Use only as directed by your doctor.

IMPORTANT: Read the accompanying Medication Guide leaflet carefully for further information.

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GlaxoSmithKline
Research Triangle Park, NC 27709

For **FREE** information, please visit our website at:
advair.com
Or call 888-825-5249

0173-0695-00

Instructions for using ADVAIR DISKUS
Read the Medication Guide that comes with ADVAIR DISKUS before you start using it and each time you get a refill. There may be new information.

Step 1. Open your ADVAIR DISKUS.
Hold the DISKUS in your left hand. Place the thumb of your right hand in the thumb grip and push it away from you as far as it will go until the mouthpiece snaps into place.

Step 2. Slide the lever until you hear it click.
Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the lever away from the mouthpiece as far as it will go until it clicks.

Step 3. Inhale your medicine.
Breathe out (exhale) as long as you can while you hold the DISKUS level and away from your mouth. Do not breathe into the mouthpiece.
Put the mouthpiece to your lips. Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.
Remove the DISKUS from your mouth and hold your breath for about 10 seconds, or for as long as is comfortable for you.
Breathe out slowly as long as you can.

The DISKUS delivers your dose of medicine as a very fine powder that you may or may not taste or feel. Do not take an extra dose from the DISKUS even if you do not taste or feel the medicine.

Step 4. Close the DISKUS. Make sure the DISKUS clicks shut and you cannot see the mouthpiece.

Step 5. Rinse your mouth with water after breathing in the medicine. Spit out the water. Do not swallow it.

Continued on side panel.

ADVAIR DISKUS[®] 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

Remember:

- Always use the DISKUS in a level, flat position.
- Make sure the lever firmly clicks into place.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. Do not swallow the water.
- Do not take an extra dose, even if you did not taste or feel the powder.
- Do not take the DISKUS apart.
- Do not wash the DISKUS.
- Always keep the DISKUS in a dry place.
- Do not use the DISKUS with a spacer device.

For live assistance with using your ADVAIR DISKUS, call 1-800-884-0593. Visit www.advail.com

NDC 0173-0695-00

ADVAIR DISKUS[®] 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

FOR ORAL INHALATION ONLY

*Each blister contains 100 mcg of fluticasone propionate and 72.5 mcg of salmeterol xinafoate, equivalent to 50 mcg of salmeterol base, with lactose.

Federal Law requires the dispensing of ADVAIR DISKUS with the Medication Guide inside the carton.

R_x only

100/50



1 DISKUS[®] Inhalation Device
Containing 1 Foil Strip of 60 Blisters

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in a dry place away from direct heat or sunlight. **Keep out of reach of children.** Discard ADVAIR DISKUS 1 month after opening the foil pouch or when the counter reads "0" (after all blisters have been used), whichever comes first.

Dosage: Use only as directed by your doctor.

IMPORTANT: Read the accompanying Medication Guide leaflet carefully for further information.

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Research Triangle Park, NC 27709

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Or call 888-825-5249



1000000126873
Rev. 10/14

ADVAIR DISKUS[®] 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

100/50

1000000
0126873

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

The [USP](#) was searched on 6/11/2018.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Official Monograph	YES		Fluticasone Propionate and Salmeterol Inhalation Powder	Packaging and Storage: Preserve in tight, light-resistant containers. Store at controlled room temperature, in a dry place away from direct heat or sunlight
Pending Monograph Proposed	YES	8/1/2018	Fluticasone Propionate and Salmeterol Inhalation Powder	Packaging and Storage: Preserve in tight, light-resistant containers. Store at controlled room temperature, in a dry place away from direct heat or sunlight

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **YES**

Reviewer Comments: Labels and labeling include the statement “FDA approved Aerodynamic Particle Size Distribution test specifications differ from USP.”

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 6/11/2018.

Table 3 provides Orange Book patents for the Model Labeling NDA 021077 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
NA						

Reviewer Assessment:

Is the applicant’s “patent carve out” acceptable? **NA**

Reviewer Comments:

NA

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
M-214	12/20/2020	INFORMATION ADDED TO THE CLINICAL TRIALS SECTION OF THE LABELING REGARDING A POSTMARKETING SAFETY AND EFFICACY STUDY EVALUATING THE RISK OF SERIOUS ASTHMA-RELATED EVENTS	Mylan is not seeking approval for the indication covered by the exclusivity identified above, and will not include in its labeling information protected by such exclusivity. (b) (4) (b) (4)	2/26/2018	Carve-out

Reviewer Assessment:

Is the applicant’s “exclusivity carve out” acceptable? **YES**

Reviewer Comments:

Information regarding serious asthma-related events has been adequately carved-out from the Clinical Trials section of the PI.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**

Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**

Are there changes to the manufacturer/distributor/packer statements? **NO**

If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)

Previous Labeling Review	Currently Proposed	Assessment
Wixela™ Inhub™ is a grey colored plastic inhaler containing two foil sealed discs, each disc containing 30 pre-metered doses. Each of the 60 doses contains a white to off white powder mix of micronized fluticasone propionate (100 mcg, 250 mcg, or 500 mcg) and micronized salmeterol xinafoate salt (72.5 mcg, equivalent to 50 mcg of salmeterol base) in 12.5 mg of formulation containing lactose monohydrate (which contains milk proteins).	Wixela™ Inhub™ is a grey colored plastic inhaler containing two foil sealed discs, each disc containing 30 pre-metered doses. Each of the 60 doses contains a white to off white powder mix of micronized fluticasone propionate (100 mcg, 250 mcg, or 500 mcg) and micronized salmeterol xinafoate salt (72.5 mcg, equivalent to 50 mcg of salmeterol base) in 12.5 mg of formulation containing lactose monohydrate (which contains milk proteins).	No change

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

Previous Labeling Review	Currently Proposed	Assessment
See below	See below	No change





Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	Currently Proposed	Assessment

Table 7: Manufacturer/Distributor/Packer Statements

 Manufactured for: Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A. Manufactured by: McDermott Laboratories Ltd. t/a Mylan Dublin Respiratory Unit 25 Baldoyle Industrial Estate, Grange Road, Baldoyle, Dublin 13, Ireland	 Manufactured for: Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A. Manufactured by: McDermott Laboratories Ltd. t/a Mylan Dublin Respiratory Unit 25 Baldoyle Industrial Estate, Grange Road, Baldoyle, Dublin 13, Ireland	No change.

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline (e.g., OPQ, OB) reviewer(s):

Reviewer Comments:

Chemistry review is complete (5/23/2018) with no labeling-related issues: The updated statement on APSD is adequate.

Is the information accurate? Yes No

If “No,” explain.

Is the drug product subject of a USP monograph? Yes No

If “Yes,” state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Reviewer’s assessment (Review #2a): Mylan added a statement of APSD test pending, which is in line with DP Quality information. According to the archived Labeling Review Addendum (Dated of 02/06/2018), Labeling Review team is

aware of this USP pending statement, and no issue regarding this USP statement was raised in the updated list of deficiencies.

Review #2b: As highlighted, Mylan updated the USP statement for APSD testing, as requested during in-cycle review meeting on 3/1/2018.

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item “Final, Draft, or “NA”. If you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	One inhaler	3/9/2018	Revise
Blister	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Carton	Final	Containing one inhaler	3/9/2018	Revise
(Other – specify) Foil Pouch label	Final	Containing one inhaler	3/9/2018	Satisfactory

Table 9 Review Summary of Prescribing Information and Patient Labeling

	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	3/2018	3/9/2018	Revise
Medication Guide	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patient Information (Previously Medication Guide)	Draft	3/2018	3/9/2018	Satisfactory
Instructions for Use	Draft	3/2018	3/9/2018	Revise
SPL Data Elements		3/2018	3/9/2018	Satisfactory



Juwon
Lee

Digitally signed by Juwon Lee
Date: 6/19/2018 03:34:35PM
GUID: 508da6f700027fdcd32f67dfe9fc22f8



Keisha
Redd

Digitally signed by Keisha Redd
Date: 6/19/2018 05:23:28PM
GUID: 5511c09c0002a85ed531a9e88c322b6e

LABELING REVIEW

Division of Labeling Review
 Office of Regulatory Operations
 Office of Generic Drugs (OGD)
 Center for Drug Evaluation and Research (CDER)

Date of This Review	1/18/2018, 2/5/2018 (Addendum)
ANDA Number(s)	208891
Review Number	2
Applicant Name	Mylan Pharmaceuticals Inc.
Established Name & Strength(s)	Fluticasone Propionate and Salmeterol Inhalation Powder USP, 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg/50 mcg
Proposed Proprietary Name	Wixela™ Inhub™ (Proprietary name expired)
Submission Received Date	8/28/2017
Primary Labeling Reviewer	JuWon Lee, Pharm. D.
Secondary Labeling Reviewer	Keisha Redd, Pharm. D.
Review Conclusion ☐ ACCEPTABLE – No Comments. ☐ ACCEPTABLE – Include Post Approval Comments ☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant. ☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant †Theme - Choose an item. Justification for Major Deficiency - Choose an item. *Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.	
On Policy Alert List ☒ YES ☐ NO	

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined as of 2/5/2018 based on your submission dated 8/28/2017:

1. GENERAL COMMENTS

- a. We note that on December 16, 2009, Ropes & Gray, LLP, on behalf of GlaxoSmithKline, submitted a citizen petition to FDA (Docket No. FDA-2009-P-0597) regarding abbreviated new drug applications (ANDAs) that reference generic copies of oral inhalation products containing fluticasone propionate and/or salmeterol xinafoate. On December 5, 2017, Mylan Inc. submitted a citizen petition to FDA (Docket No. FDA-2017-P-6750) regarding ANDAs for fluticasone propionate and salmeterol xinafoate inhalation powder that rely on Advair Diskus as the reference listed drug (RLD). The issues raised by the above-referenced citizen petitions are under review by the Agency, and FDA has not made a final decision on these issues. The deficiency comments included in this communication do not represent a final decision by the Agency on the issues raised in the pending citizen petitions.
- b. We note that the Medication Guide (MG) has been replaced with Patient Information in the most recently approved reference listed drug (RLD) labeling, Advair Diskus®, NDA 021077/S-056 and 057, approved 12/20/2017. Please replace references to “Medication Guide” (MG) with “Patient Information” in your labels/labeling where applicable (i.e., “Read the accompanying Medication Guide...”)
- c. The Orange Book has updated exclusivity (M-214) for the RLD. Address the new exclusivity and revise the insert labeling and Patient Information accordingly.

2. CONTAINER LABEL (Inhaler label)

- a. Relocate the expression of strength to appear directly below the established name.
- b. Replace “30 days” with “1 month” to be consistent with RLD.
- c. The RLD container label (back panel) includes “Do not exhale into the mouthpiece or tip downward when in use.” **Revise to include this statement to better align with RLD.** Please provide rationale for any changes to the statement if needed.
- d. Revise to include a placement for lot number expiration date.

3. FOIL POUCH LABEL

Refer to comments 2.a and 2.b.

4. CARTON LABELING

- a. Refer to comments 2.a and 2.b.
- b. Delete the Medication Guide statement on the principal display panel.
- c. Side panel:
Change “Follow the 4 steps below each time you take a dose” to “Instructions for using [Product Name]” followed by “Read the Patient Information that comes with...” to be consistent with the RLD Instructions for use: Refer to comment 7.b for instructions for use, and revise accordingly.

- d. Side panel including “Dose Counter” and “Important Information”: RLD includes the following information under the header “Remember:”

Remember:

- Always use the DISKUS in a level, flat position.
- Make sure the lever firmly clicks into place.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. Do not swallow the water.
- **Do not** take an extra dose, even if you did not taste or feel the powder.
- **Do not** take the DISKUS apart.
- **Do not** wash the DISKUS.
- Always keep the DISKUS in a dry place.
- **Do not** use the DISKUS with a spacer device.

Revise to better align with the above information. For example, RLD includes “Do not use the [inhaler name] with a spacer device” when your product includes “Do not use a spacer.” Please provide rationale for any information you choose to delete or change.

5. PRESCRIBING INFORMATION

Revise your insert labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Advair Diskus®, NDA 021077/S-056 and 057, approved 12/20/2017.

6. Patient Information (previously Medication Guide)
Refer to comment 5.

7. Instructions for Use (IFU)

a. Refer to comment 5.

b. Although there are some design and operational differences between your product and the RLD, we believe it is possible to revise all sections of the Instructions for Use (IFU) of your proposed product with respect to text, device illustrations, and organization of the tasks within the operating steps for dose administration, to better align with the IFU of the RLD product. For example, the headers in the IFU of your proposed product should be revised to better align with the following headers in the IFU of the RLD product:

Instructions for Use

Title

For oral inhalation

“Read this Instructions for Use before you start using...”

Your [Product Name] inhaler

[High definition photograph of your inhaler]

Important information about your [Product Name] inhaler:

How to use your [Product Name] inhaler

Follow these steps every time you use [Product Name]

Step 1...Step 5

Also, note that the RLD includes 5 steps instead of 4 steps, and uses the word “1 month” instead of “30 days.”: Please revise accordingly.

c. Title: Delete “60 DOSE” appearing next to “for oral inhalation.”

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are

addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE-NA

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated (add date)

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
NA

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

The below comments are from the labeling review C1 based on the submission dated 12/29/2015:

FDA COMMENT 1 – GENERAL COMMENTS

- a. On December 16, 2009, Ropes & Gray LLP, on behalf of GlaxoSmithKline, submitted a citizen petition to FDA (Docket No. FDA-2009-P-0597) regarding applications that reference generic copies of oral inhalation products containing fluticasone propionate and/or salmeterol xinafoate. The issues raised by that petition are under review by the agency and FDA has not made a final decision on the issues the petition raises. These deficiency comments included in this communication/email reflect only our current thinking and this communication/email does not represent a final decision by the agency on the issues raised in the pending citizen petition. As such, your labeling may be subject to further revision as we complete our review of the issues the petition raises.
- b. Please note that USP monograph for Fluticasone Propionate and Salmeterol Inhalation Powder became official on August 1, 2016. Please submit any necessary changes (CMC, dissolution, and/or labeling) ensuring that your product meets the USP monograph per USP General Notices 3.10.10.
- c. Submit final labeling for the container (inhaler), foil pouch, and carton, true to size and color. Please also provide font information.

MYLAN RESPONSE 1

- a. Mylan acknowledges the Agency's comment. Given the lead times necessary to procure the various labelling components for this product, Mylan would like to request that any additional labelling comments be issued as Easily Correctable Deficiencies so that we can address them within the current review cycle.
- b. As described at the Face to Face Meeting on July 13, 2017, Mylan will petition the USP to include our in-house method in the USP monograph (e.g. as method II) in parallel with this review cycle. Accordingly, we have included the text "*USP Aerodynamic Size Distribution Test Pending.*" in the DESCRIPTION section of our proposed final printed insert. Please refer to [Section 1.14.2.2](#).
- c. As requested by the Agency, Mylan has provided proposed final printed container label PDFs (for the inhaler labels, foil pouches and cartons) that are true to size and color. Additionally, font information has been provided in the associated legends in the PDFs. Please refer to [Section 1.14.2.1](#).

FDA COMMENT 2 – PRESCRIBING INFORMATION

- a. Update your labeling in accordance with the most recently approved labeling for the Reference Listed Drug (RLD, NDA 021077/S-058, approved February 28, 2017).
- b. Description: We note that your proposed labeling currently includes the mean peak inspiratory flow (PIF) data of the RLD. Please explain the relevance of the PIF data of the RLD to your ANDA.

MYLAN RESPONSE 2

- a. As requested by the Agency, Mylan’s proposed prescribing information was revised pursuant to the CDER Internet Posting dated February 28, 2017 (NDA 021077/S-058) which contained approved labeling revisions for the RLD, ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder) (Glaxo Grp Ltd). Please refer to Section 1.14.2.2.
- b. Further to FDA’s comment number 10.4 of the Preliminary Meeting comments received on July 7, 2017, Mylan confirms that as per the recommendation from FDA the PIF data from the most recently approved labeling for the RLD is included in the product labeling included with this submission.

For ease of reference, FDA’s preliminary comment number 10.4 is included below:

“FDA Preliminary Comment no. 10.4:

Thank you for your response regarding our request to explain the relevance of the RLD’s PIF data to your ANDA. Upon further consideration, we recommend that the description section of your ANDA labeling (section 11) reflect the most recently approved labeling for the RLD (NDA 021077/S-058, approved February 28, 2017).”

FDA COMMENT 3 – PATIENT LABELING (Instructions for Use)

- a. Refer to comment 2.a.

- b.  (b) (4)

MYLAN RESPONSE 3

- a. As requested by the Agency, Mylan’s proposed patient labeling was revised pursuant to the CDER Internet Posting dated February 28, 2017 (NDA 021077/S-058) which contained approved labeling revisions for the RLD, ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder) (Glaxo Grp Ltd). In accordance with the Comparative Analysis included in response to Bioequivalence Question 47, store your inhaler “in a dry place” has been added to the instructions for step 4. Please refer to Section 1.14.2.2 for the revised patient labeling.

At the request of the Agency, both in the Complete Response Letter, dated March 28, 2017, question BE 47 (Device Orientation Study (MGR000-1004)) and in the pre-meeting correspondence dated May 10, 2017, Mylan conducted a Comparative Analysis in line with DRAFT guidance entitled *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January, 2017). The Comparative Analysis report includes a Threshold Analysis (labeling comparison). All differences in the labeling comparison were categorized as minor, when considered in the context of the overall risk profile of the product, such that any differences do not involve impact on the ability of the User to safely and effectively deliver a dose, even where there is no additional training or healthcare provider intervention prior to use. The Comparative Analysis is included in the response to Bioequivalence Question 47.

b.

(b) (4)

The content of the updated IFU, in which this statement was removed, was assessed in the labeling comparison threshold analysis of the comparative analysis conducted at the Agency's request for additional information regarding Mylan's face to face meeting request dated April 3rd, 2017. This update to the IFU has also been included as part of the review against the most recently approved labeling for the RLD ADVAIR DISKUS® in response to the Complete Response Letter, dated March 28, 2017, question LABELING 3.a (PATIENT LABELING (Instructions for Use)).

(b) (4)

FDA COMMENT 4 – MEDICATION GUIDE

Refer to comment 2.a.

MYLAN RESPONSE 4

As requested by the Agency, Mylan’s proposed medication guide was revised pursuant to the CDER Internet Posting dated February 28, 2017 (NDA 021077/S-058) which contained approved labeling revisions for the RLD, ADVAIR DISKUS[®] (fluticasone propionate and salmeterol inhalation powder) (Glaxo Grp Ltd). Please refer to [Section 1.14.2.2](#).

A side by side comparison of Mylan’s proposed final printed insert/medication guide/instructions for use to the RLD’s approved insert/medication guide/instructions for use is provided in [Section 1.14.3.1 \(Labeling\)](#).

In accordance with the Agency’s Guidance, *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (April 2005), Structured Product Labeling (SPL) for Wixela[™] Inhub[™] (fluticasone propionate and salmeterol inhalation powder, USP), 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg/50 mcg is provided in [Section 1.14.2.3](#). As a review aid, Microsoft Word versions have also been provided for the proposed labeling components.

FDA COMMENT 5 – CARTON LABELING

- a. Delete the asterisks (*) next to 50 mcg and before “Each dose of inhalation powder...”
- b. “Follow the 4 steps below each time you take a dose”: Refer to comment 3.a. for Instructions for Use and revise accordingly.

MYLAN RESPONSE 5

a. As requested by the Agency, the asterisks have been deleted accordingly from the proposed carton labels. Please refer to [Section 1.14.2.1](#).

b. As clarified in the [email correspondence dated August 15, 2017](#) from Mr. Andrew Potter, of your Office, the reference in the comment above should be to comment 3.b., not 3.a. Consistent with the RLD labeling and our response to FDA Comment 3.b. above, Mylan has removed reference to cleaning from our proposed carton labels. Please refer to [Section 1.14.2.1](#).

FDA COMMENT 6 – FOIL POUCH

Refer to comment 5. a.

MYLAN RESPONSE 6

As requested by the Agency, the asterisks have been deleted accordingly from the proposed foil pouch labels. Please refer to [Section 1.14.2.1](#).

A side by side comparison of Mylan’s proposed final printed container labels to Mylan’s previously submitted draft container labels is provided in [Section 1.14.1.2 \(Container\)](#).

Mylan acknowledges that the Agency may request further changes to the labeling prior to approval. In addition, Mylan may have to revise our labeling pursuant to approved changes for the Reference Listed Drug. Mylan will monitor FDA’s website for any approved labeling changes, where applicable, subject to the provisions of 505(j)(10)(A) which address late stage labeling changes by the RLD.

Reviewer Comments: The insert labeling needs to be updated to be in accordance with RLD labeling update (12/20/2017). See comments.

The following is the subject of this Addendum (2/5/2018):

Policy input (email dated 2/2/2015) has been addressed for pending Citizen Petitions on Instructions for Use. Disclaimer has been added in the General comments section as well as revisions to include “better align with RLD instructions for use” rather than using the word “similar to.”

Also, please note the following regarding the PIF data in the Description section of the PI:

The Agency continues to discuss whether PIF data should be included in the Prescribing Information section of the generic labeling for this drug product. The Agency will consider Mylan’s 8/28/2017 response to the PIF data labeling deficiency as part of those discussions. If appropriate, Mylan will be requested to update its labeling to reflect the Agency’s final thinking on this issue.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were NOT requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

(b) (4) has been added to container/carton labeling per FDA request (email dated 8/15/2017) in response to firm’s inquiry.

Final labeling for container/carton has been submitted per the previous request. Further revisions are necessary. See comments.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

NA

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in [DLR's SharePoint Drug Facts](#)? NO

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the [Policy Alert Tracker](#) on [OGD's SharePoint](#)? YES

If Yes, please explain.

CP	FDA-2009-P-0597	Multiple: Serevent Diskus, Flovent Diskus, Flovent HFA, Advair Diskus, and Advair HFA (Metered and powdered inhalation products)	Multiple: fluticasone propionate and salmeterol xinafoate; aerosol, Metered and Powder, Inhalation	Requests FDA to not approve any ANDA referencing inhalation products containing fluticasone propionate and/or salmeterol xinafoate unless conforms to the RLD: in patient instructions for use and handling, Q1/Q2 BE, successful clinical testing in pediatric and adults as part of BE, and successfully clinically tested in asthma and COPD patients.	020692 (Serevent Diskus), 020833 (Flovent Diskus), 021433 (Flovent HFA), 021077 (Advair Diskus), and 21254 (Advair HFA)	No Actions (AP/TA/CR) can be taken prior to contacting Policy Lead	No IR/ECDC for Labeling OBE Quality

No Actions (AP/TA/CR) can be taken prior to contacting Policy Lead	No IR/ECD/CC for: Labeling OBE Quality	10/20/17: Notice of Availability, Draft Bioequivalence Guidance: Product-Specific Guidances for Salmeterol Xinafoate and Fluticasone Propionate, 48823-48825 [2017-22735] Petitioner is specifically referring to metered-dose inhalers (MDIs) and dry-powder inhalers (DPIs) with these active ingredients that treat asthma and chronic obstructive pulmonary disease (COPD). The petitioner provides the following NDAs as their applications that fall within under the category of Inhalation Products: 020692 (serevent Diskus), 020833 (Flovent Diskus), 021433 (Flovent HFA), 021077 (Advair Diskus), and 21254 (Advair HFA).	12/16/2009	Andrea Bautista
Is the drug product listed on the Susceptibility Test Interpretive Criteria web page? NO				

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ MOST RECENTLY APPROVED <u>NDA</u> MODEL LABELING <i>(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)</i> NDA#/Supplement# (S-000 if original): 021077/S-056 and S-057 Supplement Approval Date: 12/20/2017 Proprietary Name: Advair Diskus® Established Name: Fluticasone Propionate and Salmeterol Inhalation Powder Description of Supplement: These Prior Approval supplemental new drug applications provide for changes to the prescribing information to incorporate the results of the required safety trials with Advair Diskus and revised class labeling for inhaled corticosteroid/long-acting beta agonist combination products, including removal of the Boxed Warning for asthma-related death. These supplements also provide for replacement of the Medication Guide with the Patient Information leaflet and revised labeling in accordance with the Pregnancy and Lactation Labeling Rule (PLLR).
☐ MOST RECENTLY APPROVED <u>ANDA</u> MODEL LABELING ANDA#/Supplement# (S-000 if original): Click here to enter text. Supplement Approval Date: Click here to enter text. Proprietary Name: Click here to enter text. Established Name: Click here to enter text. Description of Supplement:
☐ TEMPLATE (e.g., BPCA, PREA, Carve-out): NA
☐ OTHER (Describe): NA

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8) ? NO
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old) ? YES
Does the Model Labeling have combined insert labeling for multiple dosage forms? NO

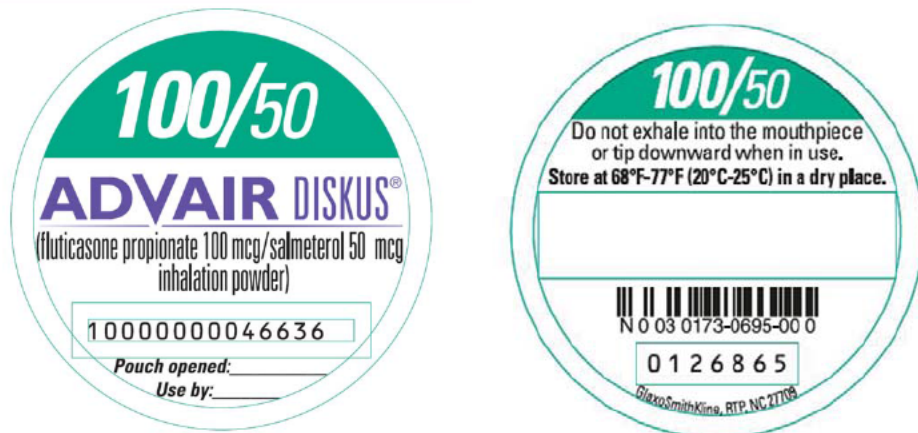
Reviewer Comments:

The insert labeling needs to be updated in accordance with RLD labeling update.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: AR-15]

Container



Overwrap



Carton

ADV AIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

Remember:

- Always use the DISKUS in a level, flat position.
- Make sure the lever firmly clicks into place.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. Do not swallow the water.
- Do not take an extra dose, even if you did not taste or feel the powder.
- Do not take the DISKUS apart.
- Do not wash the DISKUS.
- Always keep the DISKUS in a dry place.
- Do not use the DISKUS with a spacer device.

For live assistance with using your ADV AIR DISKUS, call 1-800-884-0593. Visit www.advair.com

Outside Copy

NDC 0173-0685-00

ADV AIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

FOR ORAL INHALATION ONLY

*Each blister contains 100 mcg of fluticasone propionate and 72.5 mcg of salmeterol xinafoate, equivalent to 50 mcg of salmeterol base, with lactose.

Federal Law requires the dispensing of ADV AIR DISKUS with the Medication Guide inside the carton.

Rx only



100/50

1 DISKUS Inhalation Device
Containing 1 Foil Strip of 60 Blisters

ADV AIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

100/50

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) (See USP Controlled Room Temperature). Store in a dry place away from direct heat or sunlight. **Keep out of reach of children.** Discard ADV AIR DISKUS 1 month after opening the foil pouch or when the counter reads "0" (after all blisters have been used), whichever comes first.

Dosage: Use only as directed by your doctor.

IMPORTANT: Read the accompanying Medication Guide **carefully** for further information.

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GlaxoSmithKline
Research Triangle Park, NC 27709

For **FREE** information, please visit our website at advair.com
Or call 888-825-5249



Instructions for using ADV AIR DISKUS
Read the Medication Guide that comes with ADV AIR DISKUS before you start using it and each time you get a refill. There may be new information.

- Step 1. Open your ADV AIR DISKUS.**
Hold the DISKUS in your left hand. Place the thumb of your right hand in the thumb grip and push it away from you as far as it will go until the mouthpiece snaps into place.
- Step 2. Slide the lever until you hear it click.**
Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the lever away from the mouthpiece as far as it will go until it clicks.
- Step 3. Inhale your medicine.**
Breathe out (exhale) as long as you can while you hold the DISKUS level and away from your mouth. Do not breathe into the mouthpiece.
Put the mouthpiece to your lips. Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.
Remove the DISKUS from your mouth and **hold your breath for about 10 seconds**, or for as long as is comfortable for you.
Breathe out slowly as long as you can.
The DISKUS delivers your dose of medicine as a very fine powder that you may or may not taste or feel. Do not take an extra dose from the DISKUS even if you do not taste or feel the medicine.
- Step 4. Close the DISKUS.** Make sure the DISKUS clicks shut and you cannot see the mouthpiece.
- Step 5. Rinse your mouth with water after breathing in the medicine.** Spit out the water. Do not swallow it.

Continued on side panel.

Instructions for use

GlaxoSmithKline	Item Num
Artwork Information Panel	10000000
Market or Pack Owner: United States-USA	Market Tr Advair
Technical Reference No(s): 0003235 TS-000581 (do not include the technical reference desc/ version ref/L)	Printing P N/A

ADV AIR DISKUS[®] 100/50
(fluticasone propionate 100 mcg and
salmeterol 50 mcg inhalation powder)

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) (See USP Controlled Room Temperature). Store in a dry place away from direct heat or sunlight. Keep out of reach of children.

Discard ADVAIR DISKUS 1 month after opening the foil pouch or when the counter reads "0" (after all Diskus have been used), whichever comes first.

Dosage: Use only as directed by your doctor.

IMPORTANT: Read the accompanying Medication Guide leaflet carefully for further information.

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GlaxoSmithKline
Research Triangle Park,
NC 27709

For FREE information,
please visit our website at:

advair.com

Or call 888-825-5249



Instructions for using ADVAIR DISKUS

Read the Medication Guide that comes with ADVAIR DISKUS before you start using it and each time you get a refill. There may be new information.



Step 1. Open your ADVAIR DISKUS.

Hold the DISKUS in your left hand. Place the thumb of your right hand in the thumb grip and push it away from you as far as it will go until the mouthpiece snaps into place.



Step 2. Slide the lever until you hear it click.

Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the lever away from the mouthpiece as far as it will go until it clicks.



Step 3. Inhale your medicine.

Breathe out (exhale) as long as you can while you hold the DISKUS level and away from your mouth. Do not breathe into the mouthpiece.

Put the mouthpiece to your lips. Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.

Remove the DISKUS from your mouth and hold your breath for about 10 seconds, or for as long as is comfortable for you.

Breathe out slowly as long as you can.



The DISKUS delivers your dose of medicine as a very fine powder that you may or may not taste or feel. Do not take an extra dose from the DISKUS even if you do not taste or feel the medicine.

Step 4. Close the DISKUS. Make sure the DISKUS clicks shut and you cannot see the mouthpiece.

Step 5. Rinse your mouth with water after breathing in the medicine. Spit out the water. Do not swallow it.

Continued on side panel.

Outside Copy

ADVAIR DISKUS[®] 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

Remember:

- Always use the DISKUS in a level, flat position.
- Make sure the lever firmly clicks into place.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. Do not swallow the water.
- Do not take an extra dose, even if you did not taste or feel the powder.
- Do not take the DISKUS apart.
- Do not wash the DISKUS.
- Always keep the DISKUS in a dry place.
- Do not use the DISKUS with a spacer device.

For live assistance with using your ADVAIR DISKUS, call 1-800-884-0593. Visit www.advair.com

NDC 0173-0695-00

ADVAIR DISKUS[®] 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

FOR ORAL INHALATION ONLY

*Each blister contains 100 mcg of fluticasone propionate and 72.5 mcg of salmeterol xinafoate, equivalent to 50 mcg of salmeterol base, with lactose.

Federal Law requires the dispensing of ADVAIR DISKUS with the Medication Guide inside the carton.

R_x only

100/50



1 DISKUS[®] Inhalation Device
Containing 1 Foil Strip of 60 Blisters

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in a dry place away from direct heat or sunlight. Keep out of reach of children. Discard ADVAIR DISKUS 1 month after opening the foil pouch or when the counter reads "0" (after all blisters have been used), whichever comes first. **Dosage:** Use only as directed by your doctor.

IMPORTANT: Read the accompanying Medication Guide leaflet carefully for further information.

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GlaxoSmithKline
Research Triangle Park,
NC 27709

For FREE information, please visit our website at advair.com
Or call 888-825-5249



0173-0695-00 0

10000000126873
Rev. 10/14

ADVAIR DISKUS[®] 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

100/50

1000000
0126873

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

The USP was searched on 2/5/2018.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Official Monograph	YES		Fluticasone Propionate and Salmeterol Inhalation Powder	Packaging and Storage: Preserve in tight, light-resistant containers. Store at controlled room temperature, in a dry place away from direct heat or sunlight.
Pending Monograph Proposed	YES	5/1/2018	Fluticasone Propionate and Salmeterol Inhalation Powder	Packaging and Storage: Preserve in tight, light-resistant containers. Store at controlled room temperature, in a dry place away from direct heat or sunlight.

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **YES**

Reviewer Comments:

“USP Aerodynamic Size Distribution Test Pending” has been added to container/carton labeling per FDA request (email dated 8/15/2017) in response to firm’s inquiry.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 2/5/2018.

Table 3 provides Orange Book patents for the Model Labeling 021077 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
NA						

Reviewer Assessment:

Is the applicant’s “patent carve out” acceptable? **NA**

Reviewer Comments:

NA

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
M-214	12/20/2020	INFORMATION ADDED TO THE CLINICAL TRIALS SECTION OF THE LABELING REGARDING A POSTMARKETING SAFETY AND EFFICACY STUDY EVALUATING THE RISK OF SERIOUS ASTHMA-RELATED EVENTS	Not submitted. See comments.	NA	NA

Reviewer Assessment:

Is the applicant’s “exclusivity carve out” acceptable? **NA**

Reviewer Comments:

Firm needs to address this new exclusivity.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
 Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**

Are there changes to the manufacturer/distributor/packer statements? **YES**
 If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)

Previous Labeling Review	Currently Proposed	Assessment
Wixela™ Inhub™ is a grey colored plastic inhaler containing two foil sealed discs, each disc containing 30 pre-metered doses. Each of the 60 doses contains a white to off white powder mix of micronized fluticasone propionate (100 mcg, 250 mcg, or 500 mcg) and micronized salmeterol xinafoate salt (72.5 mcg, equivalent to 50 mcg of salmeterol base) in 12.5 mg of formulation containing lactose monohydrate (which contains milk proteins).	Wixela™ Inhub™ is a grey colored plastic inhaler containing two foil sealed discs, each disc containing 30 pre-metered doses. Each of the 60 doses contains a white to off white powder mix of micronized fluticasone propionate (100 mcg, 250 mcg, or 500 mcg) and micronized salmeterol xinafoate salt (72.5 mcg, equivalent to 50 mcg of salmeterol base) in 12.5 mg of formulation containing lactose monohydrate (which contains milk proteins).	No changes

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

Previous Labeling Review	Currently Proposed	Assessment
See below	See below	USP designation added: Acceptable.





Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment
 Mylan® Manufactured for: Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A. Manufactured by: Mylan Dublin Respiratory Unit 25, Baldoyle Industrial Estate, Grange Road, Baldoyle, Dublin 13, Ireland	 Mylan® Manufactured for: Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A. Manufactured by: McDermott Laboratories Ltd. Mylan Dublin Respiratory Unit 25 Baldoyle Industrial Estate, Grange Road, Baldoyle, Dublin 13, Ireland	Acceptable.

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline (e.g., OPQ, OB) reviewer(s):

Reviewer Comments:

Chemistry review is complete (3/27/2017) with no labeling-related issues.

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: NONE.

Satisfactory from Quality perspective.

List of Deficiencies: None.

Primary Drug Product Reviewer Name and Date: Fang Yuan, 10/4/2016.

Secondary Drug Product Reviewer Name and Date: Dhaval K. Gaglani, 1/22/2017

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item ‘Final, Draft, or ‘NA’. If you enter ‘NA’ under the second column, you do NOT need to enter ‘NA’ for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container (Inhaler)	Final	One inhaler	8/28/2017	Revise
Blister	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Carton	Final	Containing one inhaler	8/28/2017	Revise
(Other – specify) Foil Pouch label	Final	Containing one inhaler	8/28/2017	Revise
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	8/2017	8/28/2017	Revise
Medication Guide	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patient Information (previously Medication Guide)	Draft	8/2017	8/28/2017	Revise
Instructions for Use	Draft	8/2017	8/28/2017	Revise
SPL Data Elements		8/2017	8/28/2017	Satisfactory



Juwon
Lee

Digitally signed by Juwon Lee
Date: 2/05/2018 04:57:51PM
GUID: 508da6f700027fdcd32f67dfe9fc22f8



Keisha
Redd

Digitally signed by Keisha Redd
Date: 2/06/2018 07:14:26AM
GUID: 5511c09c0002a85ed531a9e88c322b6e

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	1/18/2018
ANDA Number(s)	208891
Review Number	2
Applicant Name	Mylan Pharmaceuticals Inc.
Established Name & Strength(s)	Fluticasone Propionate and Salmeterol Inhalation Powder USP, 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg/50 mcg
Proposed Proprietary Name	Wixela™ Inhub™ (Proprietary name expired)
Submission Received Date	8/28/2017
Primary Labeling Reviewer	JuWon Lee, Pharm. D.
Secondary Labeling Reviewer	Keisha Redd, Pharm. D.
Review Conclusion ☐ ACCEPTABLE – No Comments. ☐ ACCEPTABLE – Include Post Approval Comments ☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant. ☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant †Theme - Choose an item. Justification for Major Deficiency - Choose an item. *Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.	
On Policy Alert List ☒ YES ☐ NO	

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on 1/19/2018 based on your submission dated 8/28/2017:

1. GENERAL COMMENTS

- a. We note that the Medication Guide (MG) has been replaced with Patient Information in the most recently approved reference listed drug (RLD) labeling, Advair Diskus®, NDA 021077/S-056 and 057, approved 12/20/2017. Please replace references to “Medication Guide” (MG) with “Patient Information” in your labels/labeling where applicable (i.e., “Read the accompanying Medication Guide...”)
- b. The Orange Book has updated exclusivity (M-214) for the RLD. Address the new exclusivity and revise the insert labeling and Patient Information accordingly.

2. CONTAINER LABEL (Inhaler label)

- a. Relocate the expression of strength to appear directly below the established name.
- b. Replace “30 days” with “1 month” to be consistent with RLD.
- c. The RLD container label (back panel) includes “Do not exhale into the mouthpiece or tip downward when in use.” Revise to include this statement, or similar information as applicable to your product. Please provide rationale for any changes to the statement.
- d. Revise to include a placement for lot number expiration date.

3. FOIL POUCH LABEL

Refer to comments 2.a and 2.b.

4. CARTON LABELING

- a. Refer to comments 2.a and 2.b.
- b. Delete the Medication Guide statement on the principal display panel.
- c. Side panel:
Change “Follow the 4 steps below each time you take a dose” to “Instructions for using [Product Name]” followed by “Read the Patient Information that comes with...” to be consistent with the RLD Instructions for use: Refer to comment 7.b for instructions for use, and revise accordingly.
- d. Side panel including “Dose Counter” and “Important Information”: RLD includes the following information under the header “Remember:”

Remember:

- Always use the DISKUS in a level, flat position.
- Make sure the lever firmly clicks into place.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. Do not swallow the water.
- **Do not** take an extra dose, even if you did not taste or feel the powder.
- **Do not** take the DISKUS apart.
- **Do not** wash the DISKUS.
- Always keep the DISKUS in a dry place.
- **Do not** use the DISKUS with a spacer device.

Revise to include the same or similar information as applicable to your product. Please provide rationale for any information you choose to delete or change. Ensure to use the same wording as RLD when applicable. For example, RLD includes “Do not use the [inhaler name] with a spacer device” when your product includes “Do not use a spacer.”

5. PRESCRIBING INFORMATION

Revise your insert labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Advair Diskus[®], NDA 021077/S-056 and 057, approved 12/20/2017.

6. Patient Information (previously Medication Guide)

Refer to comment 5.

7. Instructions for Use (IFU)

a. Refer to comment 5.

b. Despite the design and operational differences between your product and the RLD, we believe it is possible to revise all sections of the Instructions for Use (IFU) of your proposed product with respect to text, device illustrations, and organization of the tasks within the operating steps for dose administration, to make the IFU of your product more similar to the IFU of the RLD product. For example, we note that your device is different from RLD, but the headers used in the Instructions for Use should contain similar information as applicable to your product as follows:

Instructions for Use

Title

For oral inhalation

“Read this Instructions for Use before you start using...”

Your [Product Name] inhaler

[High definition photograph of your inhaler]

Important information about your [Product Name] inhaler:

How to use your [Product Name] inhaler

Follow these steps every time you use [Product Name]

Step 1...Step 5

Also, note that the RLD includes 5 steps instead of 4 steps, and uses the word “1 month” instead of “30 days.”: Please revise accordingly.

c. Title: Delete (b) (4) appearing next to “for oral inhalation.”

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are

addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE-NA

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated (add date)

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
NA

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

The below comments are from the labeling review C1 based on the submission dated 12/29/2015:

FDA COMMENT 1 – GENERAL COMMENTS

- a. On December 16, 2009, Ropes & Gray LLP, on behalf of GlaxoSmithKline, submitted a citizen petition to FDA (Docket No. FDA-2009-P-0597) regarding applications that reference generic copies of oral inhalation products containing fluticasone propionate and/or salmeterol xinafoate. The issues raised by that petition are under review by the agency and FDA has not made a final decision on the issues the petition raises. These deficiency comments included in this communication/email reflect only our current thinking and this communication/email does not represent a final decision by the agency on the issues raised in the pending citizen petition. As such, your labeling may be subject to further revision as we complete our review of the issues the petition raises.
- b. Please note that USP monograph for Fluticasone Propionate and Salmeterol Inhalation Powder became official on August 1, 2016. Please submit any necessary changes (CMC, dissolution, and/or labeling) ensuring that your product meets the USP monograph per USP General Notices 3.10.10.
- c. Submit final labeling for the container (inhaler), foil pouch, and carton, true to size and color. Please also provide font information.

MYLAN RESPONSE 1

- a. Mylan acknowledges the Agency's comment. Given the lead times necessary to procure the various labelling components for this product, Mylan would like to request that any additional labelling comments be issued as Easily Correctable Deficiencies so that we can address them within the current review cycle.
- b. As described at the Face to Face Meeting on July 13, 2017, Mylan will petition the USP to include our in-house method in the USP monograph (e.g. as method II) in parallel with this review cycle. Accordingly, we have included the text "*USP Aerodynamic Size Distribution Test Pending.*" in the DESCRIPTION section of our proposed final printed insert. Please refer to [Section 1.14.2.2](#).
- c. As requested by the Agency, Mylan has provided proposed final printed container label PDFs (for the inhaler labels, foil pouches and cartons) that are true to size and color. Additionally, font information has been provided in the associated legends in the PDFs. Please refer to [Section 1.14.2.1](#).

FDA COMMENT 2 – PRESCRIBING INFORMATION

- a. Update your labeling in accordance with the most recently approved labeling for the Reference Listed Drug (RLD, NDA 021077/S-058, approved February 28, 2017).
- b. Description: We note that your proposed labeling currently includes the mean peak inspiratory flow (PIF) data of the RLD. Please explain the relevance of the PIF data of the RLD to your ANDA.

MYLAN RESPONSE 2

- a. As requested by the Agency, Mylan’s proposed prescribing information was revised pursuant to the CDER Internet Posting dated February 28, 2017 (NDA 021077/S-058) which contained approved labeling revisions for the RLD, ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder) (Glaxo Grp Ltd). Please refer to Section 1.14.2.2.
- b. Further to FDA’s comment number 10.4 of the Preliminary Meeting comments received on July 7, 2017, Mylan confirms that as per the recommendation from FDA the PIF data from the most recently approved labeling for the RLD is included in the product labeling included with this submission.

For ease of reference, FDA’s preliminary comment number 10.4 is included below:

“FDA Preliminary Comment no. 10.4:

Thank you for your response regarding our request to explain the relevance of the RLD’s PIF data to your ANDA. Upon further consideration, we recommend that the description section of your ANDA labeling (section 11) reflect the most recently approved labeling for the RLD (NDA 021077/S-058, approved February 28, 2017).”

FDA COMMENT 3 – PATIENT LABELING (Instructions for Use)

- a. Refer to comment 2.a.

b.

(b) (4)

MYLAN RESPONSE 3

- a. As requested by the Agency, Mylan’s proposed patient labeling was revised pursuant to the CDER Internet Posting dated February 28, 2017 (NDA 021077/S-058) which contained approved labeling revisions for the RLD, ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder) (Glaxo Grp Ltd). In accordance with the Comparative Analysis included in response to Bioequivalence Question 47, store your inhaler “in a dry place” has been added to the instructions for step 4. Please refer to Section 1.14.2.2 for the revised patient labeling.

At the request of the Agency, both in the Complete Response Letter, dated March 28, 2017, question BE 47 (Device Orientation Study (MGR000-1004)) and in the pre-meeting correspondence dated May 10, 2017, Mylan conducted a Comparative Analysis in line with DRAFT guidance entitled *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January, 2017). The Comparative Analysis report includes a Threshold Analysis (labeling comparison). All differences in the labeling comparison were categorized as minor, when considered in the context of the overall risk profile of the product, such that any differences do not involve impact on the ability of the User to safely and effectively deliver a dose, even where there is no additional training or healthcare provider intervention prior to use. The Comparative Analysis is included in the response to Bioequivalence Question 47.

b.

(b) (4)

The content of the updated IFU, in which this statement was removed, was assessed in the labeling comparison threshold analysis of the comparative analysis conducted at the Agency's request for additional information regarding Mylan's face to face meeting request dated April 3rd, 2017. This update to the IFU has also been included as part of the review against the most recently approved labeling for the RLD ADVAIR DISKUS® in response to the Complete Response Letter, dated March 28, 2017, question LABELING 3.a (PATIENT LABELING (Instructions for Use)).

(b) (4)

FDA COMMENT 4 – MEDICATION GUIDE

Refer to comment 2.a.

MYLAN RESPONSE 4

As requested by the Agency, Mylan’s proposed medication guide was revised pursuant to the CDER Internet Posting dated February 28, 2017 (NDA 021077/S-058) which contained approved labeling revisions for the RLD, ADVAIR DISKUS[®] (fluticasone propionate and salmeterol inhalation powder) (Glaxo Grp Ltd). Please refer to [Section 1.14.2.2](#).

A side by side comparison of Mylan’s proposed final printed insert/medication guide/instructions for use to the RLD’s approved insert/medication guide/instructions for use is provided in [Section 1.14.3.1 \(Labeling\)](#).

In accordance with the Agency’s Guidance, *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (April 2005), Structured Product Labeling (SPL) for Wixela[™] Inhub[™] (fluticasone propionate and salmeterol inhalation powder, USP), 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg/50 mcg is provided in [Section 1.14.2.3](#). As a review aid, Microsoft Word versions have also been provided for the proposed labeling components.

FDA COMMENT 5 – CARTON LABELING

- a. Delete the asterisks (*) next to 50 mcg and before “Each dose of inhalation powder...”
- b. “Follow the 4 steps below each time you take a dose”: Refer to comment 3.a. for Instructions for Use and revise accordingly.

MYLAN RESPONSE 5

a. As requested by the Agency, the asterisks have been deleted accordingly from the proposed carton labels. Please refer to [Section 1.14.2.1](#).

b. As clarified in the [email correspondence dated August 15, 2017](#) from Mr. Andrew Potter, of your Office, the reference in the comment above should be to comment 3.b., not 3.a. Consistent with the RLD labeling and our response to FDA Comment 3.b. above, Mylan has removed reference to cleaning from our proposed carton labels. Please refer to [Section 1.14.2.1](#).

FDA COMMENT 6 – FOIL POUCH

Refer to comment 5. a.

MYLAN RESPONSE 6

As requested by the Agency, the asterisks have been deleted accordingly from the proposed foil pouch labels. Please refer to [Section 1.14.2.1](#).

A side by side comparison of Mylan’s proposed final printed container labels to Mylan’s previously submitted draft container labels is provided in [Section 1.14.1.2 \(Container\)](#).

Mylan acknowledges that the Agency may request further changes to the labeling prior to approval. In addition, Mylan may have to revise our labeling pursuant to approved changes for the Reference Listed Drug. Mylan will monitor FDA’s website for any approved labeling changes, where applicable, subject to the provisions of 505(j)(10)(A) which address late stage labeling changes by the RLD.

Reviewer Comments: The insert labeling needs to be updated to be in accordance with RLD labeling update (12/20/2017). See comments.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were NOT requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

(b) (4) has been added to container/carton labeling per FDA request (email dated 8/15/2017) in response to firm's inquiry.

Final labeling for container/carton has been submitted per the previous request. Further revisions are necessary. See comments.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

NA

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review								
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES If Yes, please explain.								
CP	FDA-2009-P-0597	Multiple: Serevent Diskus, Flovent Diskus, Flovent HFA, Advair Diskus, and Advair HFA (Metered and powdered inhalation products)	Multiple: Fluticasone propionate and salmeterol xinafoate, aerosol, Metered and Powder, Inhalation	Requests FDA to not approve any ANDA referencing inhalation products containing fluticasone propionate and/or salmeterol xinafoate unless conforms to the RLD: in patient instructions for use and handling, Q1/Q2 BE, successful clinical testing in pediatric and adults as part of BE, and successfully clinically tested in asthma and COPD patients.		020692 (Serevent Diskus), 020833 (Flovent Diskus), 021433 (Flovent HFA), 021077 (Advair Diskus), and 21254 (Advair HFA)	No Actions (AP/TA/CR) can be taken prior to contacting Policy Lead	No IR/ECD/CC for: Labeling OBE Quality
No Actions (AP/TA/CR) can be taken prior to contacting Policy Lead	No IR/ECD/CC for: Labeling OBE Quality	10/20/17: Notice of Availability, Draft Bioequivalence Guidance: Product-Specific Guidances for Salmeterol Xinafoate and Fluticasone Propionate, 48823-48825 [2017-22735] Petitioner is specifically referring to metered-dose inhalers (MDIs) and dry-powder inhalers (DPIs) with these active ingredients that treat asthma and chronic obstructive pulmonary disease (COPD). The petitioner provides the following NDAs as their applications that fall within under the category of Inhalation Products: 020692 (Serevent Diskus), 020833 (Flovent Diskus), 021433 (Flovent HFA), 021077 (Advair Diskus), and 21254 (Advair HFA).			12/16/2009	Andrea Bautista		

Is the drug product listed on the [Susceptibility Test Interpretive Criteria web page](#)? NO

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling
(Check the box used as the Model Labeling)

MOST RECENTLY APPROVED NDA MODEL LABELING

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): 021077/S-056 and S-057

Supplement Approval Date: 12/20/2017

Proprietary Name: Advair Diskus®

Established Name: Fluticasone Propionate and Salmeterol Inhalation Powder

Description of Supplement:

These Prior Approval supplemental new drug applications provide for changes to the prescribing information to incorporate the results of the required safety trials with Advair Diskus and revised class labeling for inhaled corticosteroid/long-acting beta agonist combination products, including removal of the Boxed Warning for asthma-related death. These supplements also provide for replacement of the Medication Guide with the Patient Information leaflet and revised labeling in accordance with the Pregnancy and Lactation Labeling Rule (PLLR).

MOST RECENTLY APPROVED ANDA MODEL LABELING

ANDA#/Supplement# (S-000 if original): [Click here to enter text.](#)

Supplement Approval Date: [Click here to enter text.](#)

Proprietary Name: [Click here to enter text.](#)

Established Name: [Click here to enter text.](#)

Description of Supplement:

TEMPLATE (e.g., BPCA, PREA, Carve-out): NA

OTHER (Describe): NA

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **NO**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

The insert labeling needs to be updated in accordance with RLD labeling update.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: AR-15]

Container



Overwrap





ADVAIR DISKUS[®] 100/50
(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

ADVAIR DISKUS[®] 100/50
(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

Remember:

- Always use the DISKUS in a level, flat position.
- Make sure the lever firmly clicks into place.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. Do not swallow the water.
- Do not take an extra dose, even if you did not taste or feel the powder.
- Do not take the DISKUS apart.
- Do not wash the DISKUS.
- Always keep the DISKUS in a dry place.
- Do not use the DISKUS with a spacer device.

For live assistance with using your ADVAIR DISKUS, call 1-800-884-0593. Visit www.advair.com

NDC 0173-0695-00

ADVAIR DISKUS[®] 100/50
(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

FOR ORAL INHALATION ONLY

*Each blister contains 100 mcg of fluticasone propionate and 72.5 mcg of salmeterol xinafoate, equivalent to 50 mcg of salmeterol base, with lactose.

Federal Law requires the dispensing of ADVAIR DISKUS with the Medication Guide inside the carton.



1 DISKUS[®] Inhalation Device
Containing 1 Foil Strip of 60 Blisters

Store at room temperature between 88°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) (See USP Controlled Room Temperature). Store in a dry place away from direct heat or sunlight. Keep out of reach of children. Discard ADVAIR DISKUS 1 month after opening the foil pouch or when the counter reads "0" (after all blisters have been used), whichever comes first. Dosage: Use only as directed by your doctor.

IMPORTANT: Read the accompanying Medication Guide leaflet carefully for further information.

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GlaxoSmithKline
Research Triangle Park, NC 27709

For FREE information, please visit our website at advair.com
Or call 888-825-5249



Instructions for using ADVAIR DISKUS
Read the Medication Guide that comes with ADVAIR DISKUS before you start using it and each time you get a refill. There may be new information.

- Step 1. Open your ADVAIR DISKUS.**
Hold the DISKUS in your left hand. Place the thumb of your right hand in the thumb grip and push it away from you as far as it will go until the mouthpiece snaps into place.
- Step 2. Slide the lever until you hear it click.**
Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the lever away from the mouthpiece as far as it will go until it clicks.
- Step 3. Inhale your medicine.**
Breathe out (exhale) as long as you can while you hold the DISKUS level and away from your mouth. Do not breathe into the mouthpiece.
Put the mouthpiece to your lips. Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.
Remove the DISKUS from your mouth and hold your breath for about 10 seconds, or for as long as is comfortable for you.
Breathe out slowly as long as you can.
- Step 4. Close the DISKUS.** Make sure the DISKUS clicks shut and you cannot see the mouthpiece.
- Step 5. Rinse your mouth with water after breathing in the medicine.** Spit out the water. Do not swallow it.

Continued on side panel.

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Rev. 10/14

ADV AIR DISKUS[®] 100/50
(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)



1000000
0126873

GlaxoSmithKline Artwork Information Panel	Item Num 10000000
Market or Pack Owner: United States-USA	Market Tr Advair
Technical Reference No(s): 0003235 TS-000581 (do NOT include the technical reference desc(version ref(s))	Printing P N/A

Instructions for use



ADV AIR DISKUS[®] 100/50
(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

Store at room temperature between 88°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) (See USP Controlled Room Temperature). Store in a dry place away from direct heat or sunlight. Keep out of reach of children. Discard ADVAIR DISKUS 1 month after opening the foil pouch or when the counter reads "0" (after all blisters have been used), whichever comes first. Dosage: Use only as directed by your doctor.

IMPORTANT: Read the accompanying Medication Guide leaflet carefully for further information.

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GlaxoSmithKline
Research Triangle Park, NC 27709

For FREE information, please visit our website at advair.com
Or call 888-825-5249



Instructions for using ADVAIR DISKUS
Read the Medication Guide that comes with ADVAIR DISKUS before you start using it and each time you get a refill. There may be new information.

- Step 1. Open your ADVAIR DISKUS.**
Hold the DISKUS in your left hand. Place the thumb of your right hand in the thumb grip and push it away from you as far as it will go until the mouthpiece snaps into place.
- Step 2. Slide the lever until you hear it click.**
Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the lever away from the mouthpiece as far as it will go until it clicks.
- Step 3. Inhale your medicine.**
Breathe out (exhale) as long as you can while you hold the DISKUS level and away from your mouth. Do not breathe into the mouthpiece.
Put the mouthpiece to your lips. Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.
Remove the DISKUS from your mouth and hold your breath for about 10 seconds, or for as long as is comfortable for you.
Breathe out slowly as long as you can.
- Step 4. Close the DISKUS.** Make sure the DISKUS clicks shut and you cannot see the mouthpiece.
- Step 5. Rinse your mouth with water after breathing in the medicine.** Spit out the water. Do not swallow it.

Continued on side panel.

The DISKUS delivers your dose of medicine as a very fine powder that you may or may not taste or feel. Do not take an extra dose from the DISKUS even if you do not taste or feel the medicine.

Outside Copy

ADVAIR DISKUS[®] 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

Remember:

- Always use the DISKUS in a level, flat position.
- Make sure the lever firmly clicks into place.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. Do not swallow the water.
- Do not take an extra dose, even if you did not taste or feel the powder.
- Do not take the DISKUS apart.
- Do not wash the DISKUS.
- Always keep the DISKUS in a dry place.
- Do not use the DISKUS with a spacer device.

For live assistance with using your ADVAIR DISKUS, call 1-800-884-0593. Visit www.advail.com

NDC 0173-0695-00

ADVAIR DISKUS[®] 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

FOR ORAL INHALATION ONLY

*Each blister contains 100 mcg of fluticasone propionate and 72.5 mcg of salmeterol xinafoate, equivalent to 50 mcg of salmeterol base, with lactose.

Federal Law requires the dispensing of ADVAIR DISKUS with the Medication Guide inside the carton.

R_x only

100/50



1 DISKUS[®] Inhalation Device
Containing 1 Foil Strip of 60 Blisters

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in a dry place away from direct heat or sunlight. Keep out of reach of children. Discard ADVAIR DISKUS 1 month after opening the foil pouch or when the counter reads "0" (after all blisters have been used, whichever comes first). **Dosage:** Use only as directed by your doctor.

IMPORTANT: Read the accompanying Medication Guide leaflet carefully for further information.

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Research Triangle Park,
NC 27709

For FREE information, please visit our website at advair.com
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10000000126873
Rev. 10/14

ADVAIR DISKUS[®] 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

100/50

1000000
0126873

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

The USP was searched on 1/18/2018.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Official Monograph	YES		Fluticasone Propionate and Salmeterol Inhalation Powder	Packaging and Storage: Preserve in tight, light-resistant containers. Store at controlled room temperature, in a dry place away from direct heat or sunlight.
Pending Monograph Proposed	YES	5/1/2018	Fluticasone Propionate and Salmeterol Inhalation Powder	Packaging and Storage: Preserve in tight, light-resistant containers. Store at controlled room temperature, in a dry place away from direct heat or sunlight.

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **YES**

Reviewer Comments:

(b) (4) been added to container/carton labeling per FDA request (email dated 8/15/2017) in response to firm's inquiry.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 1/18/2018.

Table 3 provides Orange Book patents for the Model Labeling 021077 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
NA						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

NA

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
M-214	12/20/2020	INFORMATION ADDED TO THE CLINICAL TRIALS SECTION OF THE LABELING REGARDING A POSTMARKETING SAFETY AND EFFICACY STUDY EVALUATING THE RISK OF SERIOUS ASTHMA-RELATED EVENTS	Not submitted. See comments.	NA	NA

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

Firm needs to address this new exclusivity.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**

Are there changes to the manufacturer/distributor/packer statements? **YES**
 If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)

Previous Labeling Review	Currently Proposed	Assessment
Wixela™ Inhub™ is a grey colored plastic inhaler containing two foil sealed discs, each disc containing 30 pre-metered doses. Each of the 60 doses contains a white to off white powder mix of micronized fluticasone propionate (100 mcg, 250 mcg, or 500 mcg) and micronized salmeterol xinafoate salt (72.5 mcg, equivalent to 50 mcg of salmeterol base) in 12.5 mg of formulation containing lactose monohydrate (which contains milk proteins).	Wixela™ Inhub™ is a grey colored plastic inhaler containing two foil sealed discs, each disc containing 30 pre-metered doses. Each of the 60 doses contains a white to off white powder mix of micronized fluticasone propionate (100 mcg, 250 mcg, or 500 mcg) and micronized salmeterol xinafoate salt (72.5 mcg, equivalent to 50 mcg of salmeterol base) in 12.5 mg of formulation containing lactose monohydrate (which contains milk proteins).	No changes

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

Previous Labeling Review	Currently Proposed	Assessment
See below	See below	USP designation added: Acceptable.





Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment
 Mylan® Manufactured for: Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A. Manufactured by: Mylan Dublin Respiratory Unit 25, Baldoyle Industrial Estate, Grange Road, Baldoyle, Dublin 13, Ireland	 Mylan® Manufactured for: Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A. Manufactured by: McDermott Laboratories Ltd. Mylan Dublin Respiratory Unit 25 Baldoyle Industrial Estate, Grange Road, Baldoyle, Dublin 13, Ireland	Acceptable.

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline (e.g., OPQ, OB) reviewer(s):

Reviewer Comments:

Chemistry review is complete (3/27/2017) with no labeling-related issues.

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: NONE.

Satisfactory from Quality perspective.

List of Deficiencies: None.

Primary Drug Product Reviewer Name and Date: Fang Yuan, 10/4/2016.

Secondary Drug Product Reviewer Name and Date: Dhaval K. Gaglani, 1/22/2017

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item ‘Final, Draft, or ‘NA’. If you enter ‘NA’ under the second column, you do NOT need to enter ‘NA’ for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container (Inhaler)	Final	One inhaler	8/28/2017	Revise
Blister	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Carton	Final	Containing one inhaler	8/28/2017	Revise
(Other – specify) Foil Pouch label	Final	Containing one inhaler	8/28/2017	Revise
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	8/2017	8/28/2017	Revise
Medication Guide	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patient Information (previously Medication Guide)	Draft	8/2017	8/28/2017	Revise
Instructions for Use	Draft	8/2017	8/28/2017	Revise
SPL Data Elements		8/2017	8/28/2017	Satisfactory



Keisha
Redd

Digitally signed by Keisha Redd
Date: 1/25/2018 11:40:05AM
GUID: 5511c09c0002a85ed531a9e88c322b6e



Juwon
Lee

Digitally signed by Juwon Lee
Date: 1/29/2018 05:02:41PM
GUID: 508da6f700027fdcd32f67dfe9fc22f8

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: April 13, 2018

To: Chi-Ann (Ruby) Wu, PharmD, MPH
Director
**Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon Williams, MSN, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)

Drug Name (established name): WIXELA INHUB (fluticasone propionate and salmeterol inhalation powder)

Dosage Form and Route: for oral inhalation use

Application Type/Number: ANDA 208891

Applicant: Mylan Pharmaceuticals, Inc.

1 INTRODUCTION

On December 29, 2015, Mylan Pharmaceuticals, Inc. submitted for the Agency's review an original abbreviated new drug application (ANDA) for WIXELA INHUB (fluticasone propionate and salmeterol inhalation powder). The reference listed drug (RLD) is ADVAIR DISKUS (fluticasone propionate and salmeterol inhalation powder). The Agency issued a Complete Response (CR) letter on March 28, 2017. The Applicant resubmitted the application on August 28, 2017. The Applicant is seeking approval of WIXELA INHUB (fluticasone propionate and salmeterol inhalation powder) indicated for:

- Treatment of asthma in patients aged 4 years and older.
- Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD).

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Labeling Review, Office of Regulatory Operations, Office of Generic Drugs on March 29, 2018 for DMPP to review the Applicant's proposed Instructions for Use (IFU).

2 MATERIAL REVIEWED

- Draft WIXELA INHUB (fluticasone propionate and salmeterol inhalation powder) IFU received on August 28, 2017 and received by DMPP on April 2, 2018.
- Draft WIXELA INHUB (fluticasone propionate and salmeterol inhalation powder) WIXELA INHUB Prescribing Information (PI) received on August 28, 2017 and received by DMPP on April 2, 2018.
- Approved comparator labeling ADVAIR DISKUS (fluticasone propionate and salmeterol inhalation powder) dated December 20, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 10.

In our review of the IFU we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the IFU is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 208991

PROPRIETARY NAME REVIEW(s)

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	August 9, 2018
Application Type and Number:	ANDA 208891
Product Name and Strength:	Wixela Inhub (fluticasone propionate and salmeterol) Inhalation Powder, 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg /50 mcg
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Mylan Pharmaceuticals Inc.
Panorama #:	2018-23036994
DMEPA Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD
DMEPA Associate Director:	Mishale Mistry, PharmD, MPH

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Wixela Inhub, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively. The Applicant submitted an addendum to their previously reviewed external name study, conducted by Addison Whitney, for this proposed proprietary name.^a

1.1 REGULATORY HISTORY

The Applicant previously submitted the proposed proprietary name, Wixela Inhub*** on September 2, 2015 and we found the name acceptable under IND 118769 on January 12, 2016.^a

On February 17, 2016 the Applicant submitted the proposed proprietary name, Wixela Inhub*** under ANDA 208891 and on July 14, 2016^b we found the name acceptable. However, on June 27, 2018, the application received a complete response (CR). The Applicant submitted their response to the CR on July 13, 2018.

Thus, the Applicant submitted the name, Wixela Inhub***, for review on July 19, 2018.

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on July 19, 2018.

- Intended Pronunciation: wicks-EL-uh IN-hub
- Active Ingredient: Fluticasone propionate and Salmeterol
- Indication of Use: treatment of asthma in patients aged 4 years and older and maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD).
- Route of Administration: Oral inhalation
- Dosage Form: Inhalation Powder
- Strength: 100 mcg/50 mcg, 250 mcg /50 mcg and 500 mcg /50 mcg
- Dose and Frequency: 1 inhalation twice daily
- How Supplied: disposable grey colored plastic dry powder inhaler containing two foil sealed discs, providing a total of 60 pre-metered doses. Each of the 60 doses contains a white to off white powder for oral inhalation. The inhaler is packaged in a moisture-protective foil pouch.

^a Owens, L. Proprietary Name Review for Wixela Inhub (IND 118769) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JAN 12 Panorama No. 2015-1367944

^b Owens, L. Proprietary Name Memo for Wixela Inhub (ANDA208891) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JUL 14 Panorama No. 2016- 2811220

- Storage: 20°C to 25°C (68°F to 77°F). Store in a dry place away from direct heat and sunlight
- Reference Listed Drug/Reference Product: Advair Diskus NDA 021077

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) concurred with the findings of OPDP's assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proprietary name^c.

2.2.2 Components of the Proposed Proprietary Name

This proprietary name is comprised of a root name and a modifier. The Applicant did not provide a derivation or intended meaning for the proposed name, Wixela Inhub in their submission. We evaluated the modifier 'Inhub' in our previous review and found it to be acceptable for this product.^d We agree with our previous assessment and maintain our decision.

2.2.3 Comments from Other Review Disciplines at Initial Review

In response to the OSE, August 1, 2018 e-mail, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) did not forward any comments or concerns relating to the proposed proprietary name at the initial phase of the review.

2.2.4 FDA Name Simulation Studies

Fifty-seven (n=57) practitioners participated in DMEPA's prescription studies. The responses did not overlap with any currently marketed products nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. Appendix B contains the results from the verbal and written prescription studies.

^c USAN stem search conducted on August 2, 2018

^d Owens, L. Proprietary Name Review for Wixela Inhub (IND 118769) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JAN 12Panorama No. 2015-1367944

2.2.5 *Phonetic and Orthographic Computer Analysis (POCA) Search Results*

Our POCA search identified 59 names with the combined score of $\geq 55\%$ or individual orthographic or phonetic score of $\geq 70\%$. We had identified and evaluated some of the names in our previous proprietary name review. We re-evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding the acceptability of the name. We note that none of the product characteristics have changed and we agree with the findings from our previous review for the names evaluated previously. Therefore, we identified 32 names not previously analyzed. These names are included in Table 1 below.

2.2.6 *Names Retrieved for Review Organized by Name Pair Similarity*

Table 1 lists the number of names retrieved from our POCA search and the Addison Whitney external study Addendum. These name pairs are organized as highly similar, moderately similar or low similarity for further evaluation.

Table 1. Similarity Category	Number of Names
Highly similar name pair: combined match percentage score $\geq 70\%$	1
Moderately similar name pair: combined match percentage score $\geq 55\%$ to $\leq 69\%$	30
Low similarity name pair: combined match percentage score $\leq 54\%$	4

2.2.7 *Safety Analysis of Names with Potential Orthographic, Spelling, and Phonetic Similarities*

Our analysis of the 35 names contained in Table 1 determined none of the names will pose a risk for confusion as described in Appendices C through H.

3 CONCLUSION

The proposed proprietary name is acceptable.

If you have any questions or need clarifications, please contact Michael Sinks, OSE project manager, at 240-402-2684.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Wixela Inhub, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your submission, received on July 19, 2018, are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. **USAN Stems** (<http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page>)

USAN Stems List contains all the recognized USAN stems.

2. *Phonetic and Orthographic Computer Analysis (POCA)*

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at <http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther biological>).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (<http://www.nlm.nih.gov/research/umls/rxnorm/overview.html#>).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment:** For prescription drug products, OPDP assesses the name for misbranding concerns. For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment:** The safety assessment is conducted by DMEPA, and includes the following:
 - a. **Preliminary Assessment:** We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.[°]

[°] National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	Is the proposed name obviously similar in spelling and pronunciation to other names?
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	Are there inert or inactive ingredients referenced in the proprietary name?
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	Does the proprietary name include combinations of active ingredients?
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	Is there a United States Adopted Name (USAN) stem in the proprietary name?
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	Is this proprietary name used for another product that does not share at least one common active ingredient?
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	Is this a proprietary name of a discontinued product?
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

- b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 55% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:
- Highly similar pair: combined match percentage score $\geq 70\%$.
 - Moderately similar pair: combined match percentage score $\geq 55\%$ to $\leq 69\%$.
 - Low similarity: combined match percentage score $\leq 54\%$.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names are further evaluated to identify the presence of attributes that are known to cause name confusion.
 - Name attributes: We note that the beginning of the drug name plays a significant role in contributing to confusion. Additionally, drug name pairs that start with the same first letter and contain a shared letter string of at least 3 letters in both names are major contributing factor in the confusion of drug names^f. We evaluate all moderately similar names retrieved from POCA to identify the above attributes. These names are further evaluated to identify overlapping or similar strengths or doses.
 - Product attributes: Moderately similar names of products that have overlapping or similar strengths or doses represent an area for concern for FDA. The dose and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and the information can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form) may be limited when the strength or dose overlaps. DMEPA reviews such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).
- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

^f Shah, M, Merchant, L, Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

- c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

- d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is $\geq 70\%$).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair does not share a common strength or dose.			
<u>Orthographic Checklist</u>		<u>Phonetic Checklist</u>	
Y/N	Do the names begin with different first letters? <i>Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.</i>	Y/N	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? <i>*FDA considers the length of names different if the names differ by two or more letters.</i>	Y/N	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as <i>z</i> and <i>f</i>), is there a different number or placement of upstroke/downstroke letters present in the names?	Y/N	Do the syllables have different phonologic processes, such as vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	Y/N	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is $\geq 55\%$ to $\leq 69\%$).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: • Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. • Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names <u>with</u> overlapping or similar strengths or doses.

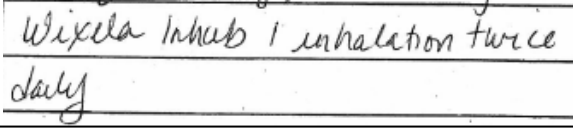
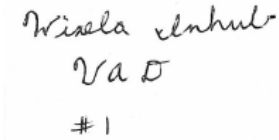
	Orthographic Checklist (Y/N to each question) • Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. • Considering variations in scripting of some letters (such as <i>z</i> and <i>f</i>), is there a different number or placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted?	Phonetic Checklist (Y/N to each question) • Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such as vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is $\leq 54\%$).

Names with low similarity are generally acceptable unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Wixela Inhub Study (Conducted on May 11, 2018)

Handwritten Medication Order/Prescription	Verbal Prescription
Medication Order: 	Wixela Inhub UAD #1
Outpatient Prescription: 	

Study Name: Wixela Inhub

As of Date 8/2/2018

292 People Received Study
57 People Responded

Study Name: Wixela Inhub

Total	17	19	21	
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL
VIXELA INHUB	0	1	0	1
WECZELA XR INHUB	0	1	0	1
WEXLAR INHUB	0	1	0	1
WICKCELLA INHUB	0	1	0	1
WICKSELLA INHUB	0	1	0	1
WINELA INHALER	4	0	0	4
WINELA INHUB	3	0	0	3
WINXELA INHUB VAD	1	0	0	1
WISELA INHALER	1	0	0	1
WISELA INHUB	1	0	0	1
WITSELLA INHUB	0	1	0	1
WIXCELLA ENHUB	0	1	0	1
WIXCELLA ENTAUB	0	1	0	1

WIXELA	0	0	16	16
WIXELA INHAB	0	0	2	2
WIXELA INHALER	3	0	0	3
WIXELA INHOP	0	1	0	1
WIXELA INHUB	4	3	2	25
WIXELLA INHUB	0	7	0	7
WIXILA	0	0	1	1

Appendix C: Highly Similar Names (e.g., combined POCA score is $\geq 70\%$)

No.	Proposed name: Wixela Inhub Established name: Fluticasone Propionate and Salmeterol Inhaler Dosage form: Dry Powder Inhaler Strength(s): 100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg Usual Dose: 1 inhalation twice daily <i>Mark all proposed PNs with ***</i>	POCA Score (%)	Orthographic and/or phonetic differences in the names sufficient to prevent confusion Other prevention of failure mode expected to minimize the risk of confusion between these two names.
1.	Wixela***	100	Root name of the proposed name under review

Appendix D: Moderately Similar Names (e.g., combined POCA score is $\geq 55\%$ to $\leq 69\%$) with no overlap or numerical similarity in Strength and/or Dose-N/A

Appendix E: Moderately Similar Names (e.g., combined POCA score is $\geq 55\%$ to $\leq 69\%$) with overlap or numerical similarity in Strength and/or Dose

No.	Proposed name: Wixela Inhub Established name: Fluticasone Propionate and Salmeterol Inhaler Dosage form: Dry Powder Inhaler Strength(s): 100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg Usual Dose: 1 inhalation twice daily <i>Mark all proposed PNs with ***</i>	POCA Score (%)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
2.	Ibsrela***	62	This name pair has sufficient orthographic and phonetic differences.

Appendix F: Low Similarity Names (e.g., combined POCA score is $\leq 54\%$)

No.	Name	POCA Score (%)
3.	Wilate	45
4.	(b) (4)	(b) (4)
5.	Ruxolitinib	35
6.	(b) (4)	(b) (4)

Appendix G: Names not likely to be confused or not used in usual practice settings for the reasons described.

No.	Name	POCA Score (%)	Failure preventions
7.			(b) (4)
8.	Lexxel	58	Brand discontinued with no generic equivalents available.
9.	Wixela Inhub ***	58	Name is the subject of this review. Our POCA search was conducted for the root name 'Wixela***'
10.	Oxeladin	56	Product is discontinued with no generics

Appendix H: Names not likely to be confused due to absence of attributes that are known to cause name confusion^g.

No.	Name	POCA Score (%)
11.	Exildra***	62
12.	Ex-Lax	62
13.	Flexall	59
14.	Paxil	58
15.	Naxcel	58
16.	Vanex- LA	57
17.	Execlear	57
18.	Trexall	56
19.	Conex LA	56
20.	Zotex LA	56
21.	Dynex LA	56
22.	Oxalate	56
23.	Dexilant	56
24.	Banex- LA	56
25.	Entex LA	56
26.	Fenex- LA	56
27.	Medex- LA	56
28.	Virx Gel	56
29.	Elixiral	56
30.	Amitex LA	56
31.	Ami-Tex LA	56

^g Shah, M, Merchant, L, Chan, I, and Taylor, K. Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

No.	Name	POCA Score (%)
32.	(b) (4)	
33.	Excenel	55
34.	Laxilose	55
35.	Lexinal	55

(

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISSA C OWENS
08/10/2018

SARAH K VEE
08/10/2018

MISHALE P MISTRY
08/10/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 208891

CHEMISTRY REVIEW(s)

Recommendation: Approval

**A/NDA 208891
Review #3**

Drug Name/Dosage Form	Fluticasone Propionate and Salmeterol Powder for Inhalation
Strength	100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg
Route of Administration	Inhalation
Rx/OTC Dispensed	Rx
Applicant	Mylan Pharmaceuticals Inc.
US agent, if applicable	N/A

SUBMISSIONS REVIEWED (Review #1)	DOCUMENT DATE
New ANDA (SD #0000)	12/29/2015
Multiple categories/Subcategories (SD #0001)	02/16/2016
SUBMISSIONS REVIEWED (Review #2a)	
Meeting/Meeting Request (SD #0016), post-CR meeting package	4/3/2017
Meeting/Meeting Request (SD #0017), post-CR meeting package	4/4/2017
Multiple Categories/Subcategories (SD #0019), post-CR meeting minutes	8/7/2017
Multiple Categories/Subcategories (SD #0020), post-CR meeting minutes	8/22/2017
Multiple Categories/Subcategories (SD #0015), P4 filling batch submission package	3/2/2017
Multiple Categories/Subcategories (SD #0021), CRL responses	8/28/2017
Meeting/Meeting Request (SD #0022), in-cycle meeting	10/19/2017
Multiple Categories/Subcategories (SD #0025), in-cycle meeting agenda	02/16/2018
SUBMISSIONS REVIEWED (Review #2b)	
Multiple Categories/Subcategories (SD #0031), Mylan's in-cycle meeting minutes	03/16/2018
Multiple Categories/Subcategories (SD #0034), IR response	03/23/2018
Multiple Categories/Subcategories (SD #0035), FDA's in-cycle meeting minutes	04/19/2018
SUBMISSIONS REVIEWED (Review #3)	
Multiple Categories/Subcategories (SD #0041), post-CR T-con request	06/29/2018
Multiple Categories/Subcategories (SD #0042), post-CR T-con meeting minutes (Mylan)	07/11/2018
Multiple Categories/Subcategories (SD #0043), CRL responses	07/13/2018
Multiple Categories/Subcategories (SD #0045), CRL responses	09/05/2018
Multiple Categories/Subcategories (SD #0051), IRL responses	11/30/2018

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Roger Farr	Benjamin Lim
Drug Product	Fang Yuan	Dhaval Gaglani
Process	Brian Rogers	Sharmista Chatterjee
Microbiology	N/A	
Facility	Zhong Li	Zhihao Peter Qiu
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Candice Cottle-Delisle	
Application Technical Lead	Dhaval Gaglani	
Laboratory (OTR)	N/A	
ORA Lead	Mike Tollon/Caryn McNab	
Environmental	N/A	

Quality Review Data Sheet

[IQA Review Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF # (b) (4)	Type	Holder	Item Referenced (b) (4)	Status	Date Review Completed	Comments
	Type II			Adequate	8/20/2018	No pending Quality Amendments
	Type II			Adequate	5/11/2018	
	Type III			Adequate	5/24/2018	
	Type III			Not reviewed.		Sufficient information was submitted in ANDA application.
	Type IV			Not reviewed.		

B. Other Documents: IND, RLD, or sister applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	021077 Advair Diskus by GSK	NDA

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A.			
Pharmacology/Toxicology	N/A.			
CDRH	Adequate	Approval	8/23/2018	Elizabeth Katz
Clinical	N/A.			
Other	N/A.			

Executive Summary

[IQA Review Guide Reference](#)

I. Recommendations and Conclusion on Approvability

The ANDA is adequate based on outcome of IQA team review-including product, process, and facility. OPQ recommends approval.

II. Summary of Quality Assessments

A. Product Overview

Final recommended dissolution method/specification acknowledged by Firm?	BC	N/A
Are there comparability protocols provided? If yes, how many?	BC	No
If USP monograph exists, do the specifications conform to the current USP?	BC	*(see comments)
Is the application compliant with USP <232/233> requirements or ICH Q3D (regarding elemental impurities)?	BC	Yes

***: USP published a pending drug product monograph for Fluticasone Propionate and Salmeterol Inhalation Powder on 12/13/18. Mylan's proposed APSD test specification is in-line with Test 2 of the pending drug product monograph.**

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of asthma in patients aged 4 years and older, and maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD).
Duration of Treatment	Refer to physician's recommendation for duration of treatment.
Maximum Daily Dose	1 mg of Fluticasone Propionate; 0.1 mg of Salmeterol.
Alternative Methods of Administration	None.

B. Quality Assessment Overview

A. Drug Substance, Drug Product and Labeling: Adequate

Drug Substances:

[Redacted content] (b) (4)

Drug Product:

- The proposed product is a fixed dose combination product, i.e., FP and salmeterol (Sal, as xinafoate salt) inhalation powder for oral use in the CRC749 device. CRC749 is a passive (breath-actuated) multi-dose inhaler containing 60 pre-metered doses. The doses are contained within two foil sealed Discs each with 30 pre-metered doses. The grey, molded plastic inhaler has an integral dose counter and is disposable., with three strengths proposed to be marketed, 100/50 mcg, 250/50 mcg and 500/50 mcg.

[Redacted content] (b) (4)



Dhaval
Gaglani

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Date: 1/29/2019 01:36:20PM
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PROCESS

Product Background: **RLD - ADVAIR DISKUS (NDA 21077)**
First Generic

The drug product is a fixed dose combination product of fluticasone propionate (FP) and salmeterol (as xinafoate, SX) inhalation powder for oral use in the CRC749 device. CRC749 is a passive (breath-actuated) multi dose inhaler containing 60 pre-metered doses. The doses are contained within two foil sealed Discs each with 30 pre-metered doses. The grey, molded plastic inhaler has an integral dose counter and is disposable. The applicant proposes to market three strengths of inhaler, 100/50, 250/50, and 500/50 µg/dose of FP and SX, respectively.

Fluticasone propionate is a corticosteroid. It exhibits polymorphism.

(b) (4)

(b) (4)

ANDA: **208891**

Drug Product Name/Strength: **Fluticasone Propionate/Salmeterol Xinafoate**
100/50 mcg, 250/50 mcg, 500/50 mcg Inhalation Powder (MGR001)

Route of Administration: **Oral Inhalation**

Applicant Name: **Mylan Pharmaceuticals Inc.**

Review Recommendation: **Approvable from a Process Perspective**

Review Summary:

(b) (4)

(b) (4)



Brian
Rogers

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Sharmista
Chatterjee

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DP Quality Adequate.

DRUG SUBSTANCE

IQA Review Guide Reference

Product Background:

Fluticasone Propionate and Salmeterol Inhalation Powder USP, 100/50 mcg, 250/50 mcg and 500/50 mcg is indicated for the treatment of asthma in patients aged 4 yrs and older, and maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). Not indicated for relief of acute bronchospasm.

Maximum daily dose (MDD) is calculated as 1 mg for fluticasone propionate (FP) and 0.1 mg for salmeterol (Sal), based on the maximum dose (**500/50 mcg twice daily**) indicated for treatment of asthma in patients aged 12 years and older.

ICH Impurity thresholds:

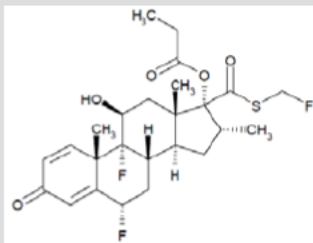
	ICH Impurity Threshold for Fluticasone Propionate (MDD = 1 mg)		
	Report	Identification	Qualification
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.1%	0.5%	1.0%

	ICH Impurity Threshold for Salmeterol Xinafoate (MDD = 0.1 mg)		
	Report	Identification	Qualification
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.1%	1.0%	1.0%

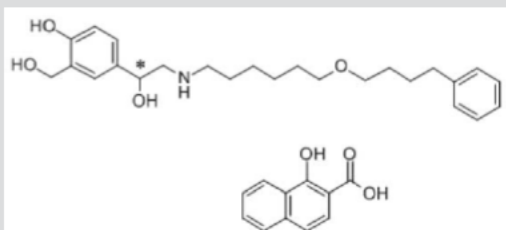
ANDA #208891: Review #3

Chemical Name and Structure:

Fluticasone Propionate (FP)



Salmeterol Xinafoate (SX)



(b) (4)



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Gaglani

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Date: 1/29/2019 11:26:16AM

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PROCESS

Product Background: **RLD - ADVAIR DISKUS (NDA 21077)**
First Generic

The drug product is a fixed dose combination product of fluticasone propionate (FP) and salmeterol (as xinafoate, SX) inhalation powder for oral use in the CRC749 device. CRC749 is a passive (breath-actuated) multi dose inhaler containing 60 pre-metered doses. The doses are contained within two foil sealed Discs each with 30 pre-metered doses. The grey, molded plastic inhaler has an integral dose counter and is disposable. The applicant proposes to market three strengths of inhaler, 100/50, 250/50, and 500/50 µg/dose of FP and SX, respectively.

Fluticasone propionate is a corticosteroid. It exhibits polymorphism. (b) (4)

(b) (4)

ANDA: **208891**

Drug Product Name/Strength: **Fluticasone Propionate/Salmeterol Xinafoate**
100/50 mcg, 250/50 mcg, 500/50 mcg Inhalation Powder (MGR001)

Route of Administration: **Oral Inhalation**

Applicant Name: **Mylan Pharmaceuticals Inc.**

Review Recommendation: **Approvable from a Process Perspective**

(b) (4)



Brian
Rogers

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Sharmista
Chatterjee

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FACILITIES

ANDA: 208891

Drug Product Name / Strength: Fluticasone Propionate/Salmeterol – 100/50 mcg, 250/50 mcg, 500/50 mcg Inhalation Powder

Route of Administration: Inhalation (oral)

Applicant Name: Mylan Pharmaceuticals Inc.

Review Summary:

Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing risks that prevent approval of this application. Based on the firm inspectional history and EIR reviews, the manufacturing facilities as listed below for ANDA 208891 are found to be acceptable.

List Submissions being reviewed (table): ANDA-208891-ORIG-1-AMEND-22

Highlight Key Outstanding Issues from Last Cycle: DP facility unacceptable

Concise Description Outstanding Issues Remaining: N/A

3.2.S.2 Manufacture

Summary of Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
			(b) (4)	Acceptable
				Acceptable



Zhong
Li

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Date: 1/31/2018 03:22:17PM
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Zhihao Peter
Qiu

Digitally signed by Zhihao Peter Qiu
Date: 1/31/2018 03:23:07PM
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Dhaval
Gaglani

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Date: 1/29/2019 08:08:56PM

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DP Quality Adequate.

DRUG SUBSTANCE

IQA Review Guide Reference

Product Background:

Fluticasone Propionate and Salmeterol Inhalation Powder USP, 100/50 mcg, 250/50 mcg and 500/50 mcg is indicated for the treatment of asthma in patients aged 4 yrs and older, and maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). Not indicated for relief of acute bronchospasm.

Maximum daily dose (MDD) is calculated as 1 mg for fluticasone propionate (FP) and 0.1 mg for salmeterol (Sal), based on the maximum dose (**500/50 mcg twice daily**) indicated for treatment of asthma in patients aged 12 years and older.

ICH Impurity thresholds:

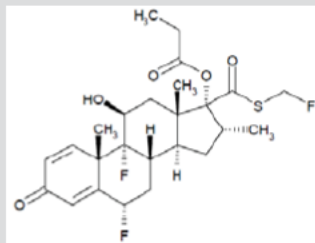
	ICH Impurity Threshold for Fluticasone Propionate (MDD = 1 mg)		
	Report	Identification	Qualification
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.1%	0.5%	1.0%

	ICH Impurity Threshold for Salmeterol Xinafoate (MDD = 0.1 mg)		
	Report	Identification	Qualification
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.1%	1.0%	1.0%

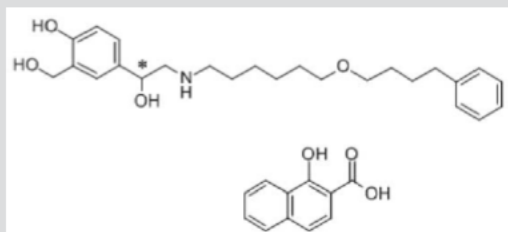
ANDA #208891: Review #3

Chemical Name and Structure:

Fluticasone Propionate (FP)



Salmeterol Xinafoate (SX)



(b) (4)



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Gaglani

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Recommendation: Minor

**A/NDA 208891
Review #2b**

Drug Name/Dosage Form	Fluticasone Propionate And Salmeterol Powder for Inhalation
Strength	100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg
Route of Administration	Inhalation
Rx/OTC Dispensed	Rx
Applicant	Mylan Pharmaceuticals Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Multiple categories/subcategories (please refer to the DP review for further reference)	2018	

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Roger Farr	Benjamin Lim
Drug Product	Fang Yuan	Dhaval Gaglani
Process	Brian Rogers	Sharmista Chatterjee
Microbiology		N/A
Facility	Zhong Li	Zhihao Peter Qiu
Biopharmaceutics		N/A
Regulatory Business Process Manager		Candice Cottle-Delisle
Application Technical Lead		Dhaval Gaglani
Laboratory (OTR)		N/A
ORA Lead		Mike Tollon/CarynMcNab
Environmental		N/A

Abbreviated Executive Summary **Addendum**

IQA Review Guide Reference

Per inter-office (OPQ, OGD and OCC) discussion on 06/13/2018, quality data from device orientation study will be used as critical evidence in support of adequate performance of CRC749 device at the intended and incorrect in-use orientation. To support the statement, both APSD and Delivered Dose Uniformity (DDU) data generated at different in-use orientations should be available to justify “adequate performance”. Since Mylan only submitted DDU data, Drug Product Quality Review team added a new deficiency to request APSD data from device orientation study in to the list of deficiencies in this Addendum.

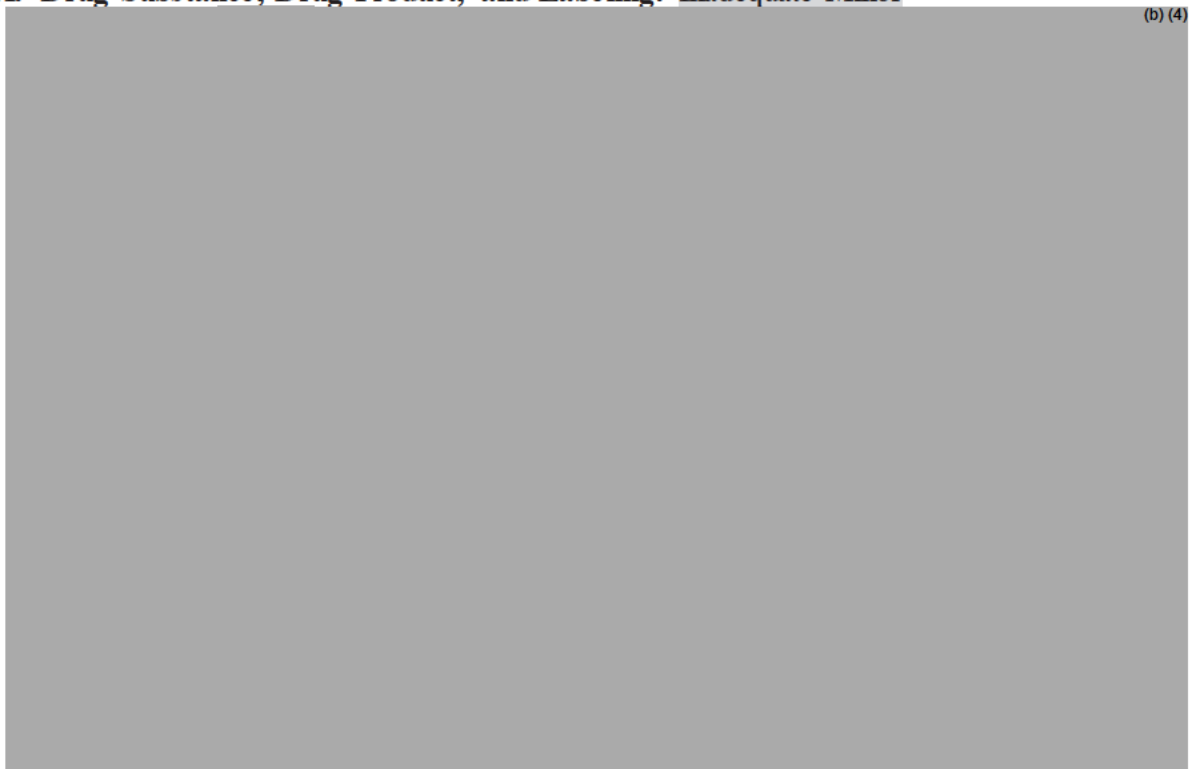
Type II DMF (b) (4) has a quality amendment submitted on 6/11/2018, that will be reviewed next cycle.

I. Recommendations and Conclusion on Approvability

The application is not recommended for approval due to quality related deficiencies summarized under “list of deficiencies for CR”. OPQ recommends issuing a Complete Response Letter – **Minor**.

II. Quality Assessment Overview

A. Drug Substance, Drug Product, and Labeling: **Inadequate-Minor**



Drug Product: The proposed product is a fixed dose combination product, i.e., fluticasone propionate (FP) and salmeterol (as xinafoate) inhalation powder for oral

use in the CRC749 device. CRC749 is a passive (breath-actuated) multi-dose inhaler containing 60 pre-metered doses. The doses are contained within two foil sealed Discs each with 30 pre-metered doses. The grey, molded plastic inhaler has an integral dose counter and is disposable, with three strengths proposed to be marketed, 100/50 mcg, 250/50 mcg and 500/50 mcg.

(b) (4)





Dhaval
Gaglani

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Review Addendum to DRUG PRODUCT CHAPTER

ANDA 208891: Review#2

Drug Product Name / Strength: Fluticasone Propionate and Salmeterol Inhalation Powder USP, 100/50 mcg, 250/50 mcg and 500/50 mcg

Route of Administration: Inhalation

Applicant Name: Mylan Pharmaceuticals Inc.

(b) (4)



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Gaglani

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Date: 6/22/2018 08:11:41AM

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Recommendation: Minor

**A/NDA 208891
Review #2b**

Drug Name/Dosage Form	Fluticasone Propionate And Salmeterol Powder for Inhalation
Strength	100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg
Route of Administration	Inhalation
Rx/OTC Dispensed	Rx
Applicant	Mylan Pharmaceuticals Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Multiple categories/subcategories (please refer to the DP review for further reference)	2018	

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Roger Farr	Benjamin Lim
Drug Product	Fang Yuan	Dhaval Gaglani
Process	Brian Rogers	Sharmista Chatterjee
Microbiology		N/A
Facility	Zhong Li	Zhihao Peter Qiu
Biopharmaceutics		N/A
Regulatory Business Process Manager		Candice Cottle-Delisle
Application Technical Lead		Dhaval Gaglani
Laboratory (OTR)		N/A
ORA Lead		Mike Tollon/CarynMcNab
Environmental		N/A

Abbreviated Executive Summary

[IQA Review Guide Reference](#)

I. Recommendations and Conclusion on Approvability

The application is not recommended for approval due to quality related deficiencies summarized under “list of deficiencies for CR”. OPQ recommends issuing a Complete Response Letter – **Minor**.

II. Quality Assessment Overview

A. Drug Substance, Drug Product, and Labeling: Inadequate-Minor

Type II DMFs

(b) (4)

adequate. Both

FP and SX have official USP Monographs:

(b) (4)

(b) (4)

(b) (4)

Drug Product: The proposed product is a fixed dose combination product, i.e., fluticasone propionate (FP) and salmeterol (as xinafoate) inhalation powder for oral use in the CRC749 device. CRC749 is a passive (breath-actuated) multi-dose inhaler containing 60 pre-metered doses. The doses are contained within two foil sealed Discs each with 30 pre-metered doses. The grey, molded plastic inhaler has an integral dose counter and is disposable, with three strengths proposed to be marketed, 100/50 mcg, 250/50 mcg and 500/50 mcg.

Compendial status: FP and Sal Inhalation Powder has a USP Monograph.

(b) (4)



Dhaval
Gaglani

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Color codes of Review #2:

For ease of reading review, Review #2b including the Firm's updates and Reviewer's assessment are provided below previous Deficiencies per Review #2a. No updates are made in context of Review #2a.

Orange: Old deficiencies per Review #2a.

Purple: The firm's IR responses and updated information, as well as Reviewer's assessment in Review #2b.

Maroon: Any identified remaining issues in assessment section of Review #2b.

Red: New deficiencies per Review #2b.

DRUG SUBSTANCE

[IQA Review Guide Reference](#)

Product Background:

Fluticasone Propionate and Salmeterol Inhalation Powder USP, 100/50 mcg, 250/50 mcg and 500/50 mcg is indicated for the treatment of asthma in patients aged 4 yrs and older, and maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). Not indicated for relief of acute bronchospasm.

Maximum daily dose (MDD) is calculated as 1 mg for fluticasone propionate (FP) and 0.1 mg for salmeterol (Sal), based on the maximum dose (**500/50 mcg twice daily**) indicated for treatment of asthma in patients aged 12 years and older.

ICH Impurity thresholds:

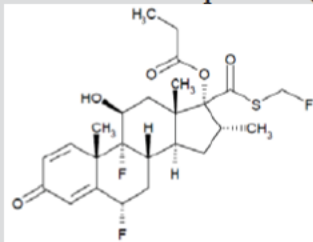
	ICH Impurity Threshold for Fluticasone Propionate (MDD = 1 mg)		
	Report	Identification	Qualification
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.1%	0.5%	1.0%

	ICH Impurity Threshold for Salmeterol Xinafoate (MDD = 0.1 mg)		
	Report	Identification	Qualification
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.1%	1.0%	1.0%

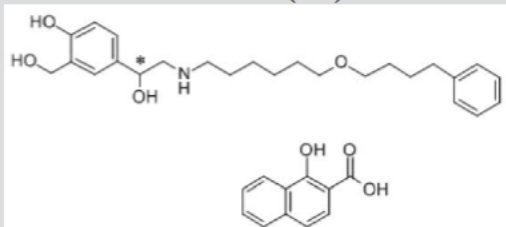
ANDA 208891: [Review#2a](#), [Review #2b](#)

Chemical Name and Structure:

Fluticasone Propionate (FP)



Salmeterol Xinafoate (SX)



(b) (4)

Review Recommendation: Adequate

Theme (ANDA only): N/A

Justification (ANDA only): N/A

Review Summary:

- ***Compendial status:*** Both FP and SX have official USP Monographs (b) (4)

(b) (4)

LABELING

[IQA Review Guide Reference](#)

{For ANDA only}

R Regional Information

1.14 Labeling

Updated as of 08/28/2018, and 03/23/2018

Labeling & Package Insert

DESCRIPTION section

(b) (4)

Is the information accurate? Yes No

If "No," explain.

Is the drug product subject of a USP monograph? Yes No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Reviewer's assessment (Review#2a): Mylan added a statement of APSD test pending, which is in line with DP Quality information. According to the archived Labeling Review Addendum (Dated of 02/06/2018), Labeling Review team is

aware of this USP pending statement, and no issue regarding this USP statement was raised in the updated list of deficiencies.

Review #2b: As highlighted, Mylan updated the USP statement for APSD testing, as requested during in-cycle review meeting on 3/1/2018.

HOW SUPPLIED section



- i) Is the information accurate? Yes No
- ii) Are the storage conditions acceptable? Yes No

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? Yes No N/A

If "No," explain.

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

None.

Review #2a and Review #2b: There are also no comments left to Chemistry Reviewer by Labeling Review team in the Labeling Review Addendum (date of 02/06/2018). **No further updates as of 5/22/2018.**

List of Deficiencies: None.

Primary Drug Product Reviewer Name and Date: Fang Yuan, 01/26/2018, 2/20/2018 (Review #2a); 4/18/2018 (Review #2b)

Secondary Drug Product Reviewer Name and Date: Dhaval K. Gaglani, 2/16/2018, 2/22/2018 (Review #2a); 5/7/2018 (Review #2b)



Dhaval
Gaglani

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Fang
Yuan

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Date: 6/12/2018 11:35:05AM

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PROCESS

Product Background: **RLD - ADVAIR DISKUS (NDA 21077)**
First Generic

The drug product is a fixed dose combination product of fluticasone propionate (FP) and salmeterol (as xinafoate, SX) inhalation powder for oral use in the CRC749 device. CRC749 is a passive (breath-actuated) multi dose inhaler containing 60 pre-metered doses. The doses are contained within two foil sealed Discs each with 30 pre-metered doses. The grey, molded plastic inhaler has an integral dose counter and is disposable. The applicant proposes to market three strengths of inhaler, 100/50, 250/50, and 500/50 µg/dose of FP and SX, respectively.

Fluticasone propionate is a corticosteroid. It exhibits polymorphism. (b) (4)

(b) (4)

ANDA: **208891**

Drug Product Name/Strength: **Fluticasone Propionate/Salmeterol Xinafoate**
100/50 mcg, 250/50 mcg, 500/50 mcg Inhalation Powder (MGR001)

Route of Administration: **Oral Inhalation**

Applicant Name: **Mylan Pharmaceuticals Inc.**

Review Recommendation: **Not Approvable from a Process Perspective - Minor**

(b) (4)



Brian
Rogers

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Sharmista
Chatterjee

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Date: 5/11/2018 12:17:54PM
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FACILITIES

ANDA: 208891

Drug Product Name / Strength: Fluticasone Propionate/Salmeterol – 100/50 mcg, 250/50 mcg, 500/50 mcg Inhalation Powder

Route of Administration: Inhalation (oral)

Applicant Name: Mylan Pharmaceuticals Inc.

Review Summary:

Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing risks that prevent approval of this application. Based on the firm inspectional history and EIR reviews, the manufacturing facilities as listed below for ANDA 208891 are found to be acceptable.

List Submissions being reviewed (table): ANDA-208891-ORIG-1-AMEND-22

Highlight Key Outstanding Issues from Last Cycle: DP facility unacceptable

Concise Description Outstanding Issues Remaining: N/A

3.2.S.2 Manufacture

Summary of Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
(b) (4)			(b) (4)	Acceptable
				Acceptable



Zhong
Li

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Date: 1/31/2018 03:22:17PM
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Zhihao Peter
Qiu

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 208891

BIOEQUIVALENCE REVIEW(s)

**Addendum to Clinical Bioequivalence Review
Amendment 22**

ANDA number	208891
Drug Product	Fluticasone Propionate and Salmeterol Inhalation Powder 100/50µg, 250/50µg, and 500/50µg
Applicant Name	Mylan Pharmaceuticals Inc.
Treatment Indication	1) Treatment of asthma in patients aged 4 years and older 2) Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD)
Reference Listed Drug (RLD)	Advair Diskus® (Fluticasone Propionate and Salmeterol Xinafoate) 100/50µg, 250/50µg, and 500/50µg)
NDA number for RLD	NDA 021077 (approved on 8/24/2000)
RLD Applicant Name	Glaxo Group LTD
Original Submission Date	December 29, 2015

Materials Reviewed	• Original ANDA submission: 12/29/2015 • ANDA amendment: 4/3/2017 (Request for a Post Complete Response Scientific Meeting), 4/4/2017 (Post Complete Response Clarification Request Written Responses Requested), 8/7/2017 (Sponsor Minutes – Post Complete Response Scientific Meeting), 8/28/2017 (Resubmission – 1st Major Complete Response Amendment), 12/18/2017 (Information Request Response to Division of Clinical Review), 2/1/2018 (Information Request Response to Division of Clinical Review), 2/26/2018 (Information Request Response to Division of Clinical Review), 3/15/2018 (Clinical Amendment), 3/22/2018 (Information Request Response to Division of Clinical Review), 4/26/2018 (Information Request Response to Division of Clinical Review), 5/25/2018 (Information Request Response to Division of Clinical Review), 6/7/2018 (Information Request Response to Division of Clinical Review) • FDA Complete Response letter signed by Denise Toyer McKan on 3/28/2017 • FDA Face-to-Face Meeting Minutes for Post Complete Response Scientific Meeting held on 7/13/2017 • FDA Face-to-Face Meeting Minutes for Mid-Cycle Review Meeting held on 3/1/2018 • FDA Statistical Review by Cynthia Liu, Ph.D. completed on 8/12/2016 • FDA Statistical Review and Evaluation by Youngsook Lee, Ph.D. completed on 6/12/2018 • OSIS EIR Cover Memo by Xingfang Li, MD, RAC completed on 10/25/2016 • OSIS Consult Response by Xingfang Li, MD, RAC completed on 4/5/2018 • Reserve Sample Memorandum by Sarah Yim, M.D. completed on 6/26/2018 • Division of Bioequivalence Review for Dry Powder Inhaler Products by Tian Ma, Ph.D. completed on 3/22/2017 • Clinical Review of Drug-Device Combination Product by Michael Spagnola, M.D. completed on 6/26/2018 • Clinical Consult Review by Sarah H. Seung, Pharm.D. and Sunny Tse, Ph.D. completed on 1/23/2017 • FDA Draft Product Specific Guidance for Fluticasone Propionate; Salmeterol Xinafoate Recommended September 2013 • NDA 021077 Submission and Clinical Review
Primary Reviewer	Michael Spagnola, M.D. Medical Officer Division of Clinical Review (DCR), Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Secondary Reviewer	Carol Kim, Pharm.D. Acting ANDA Team Leader, DCR, OB, OGD
Tertiary Reviewer	Mark Ritter, M.D. Associate Division Director, DCR, OB, OGD
Date of Completion	January 28, 2019
DCR Conclusion	DCR concludes that the Clinical Endpoint Bioequivalence Study (MGR001-3001) demonstrates that the test product is bioequivalent to the reference product.
Deficiency Classification	☐ Major ☐ Minor ☒ N/A (Review is Adequate)

This is an addendum to the Clinical Bioequivalence Review completed by Michael Spagnola, M.D. on June 27, 2018 which evaluated the bioequivalence study with clinical endpoint (Study MGR001-3001) to ensure that Mylan Pharmaceuticals Inc.’s Fluticasone Propionate and Salmeterol Inhalation Powder 100/50µg is bioequivalent to the reference listed drug (RLD), Advair Diskus® Fluticasone Propionate and Salmeterol Xinafoate 100/50µg (NDA 021077 approved on 08/24/2000). The addendum provides clarification for Section 2.7, “Formulation”, of the Clinical Bioequivalence Review for ANDA 208891 completed on June 27, 2018.

The formulation for the Reference Product (Advair Diskus® Fluticasone Propionate and Salmeterol Xinafoate 100/50µg) is presented in Table 1.

Table 1: Reference Product Formulation

Components	100/50 mcg	250/50 mcg	500/50 mcg
	per blister	per blister	per blister
Salmeterol xinafoate, (micronized)	72.5 mcg ¹	72.5 mcg ¹	72.5 mcg ¹
Fluticasone propionate (micronized)	100 mcg ²	250 mcg ²	500 mcg ²
Lactose monohydrate ³	to 12.5 mg	to 12.5 mg	to 12.5 mg

¹72.5 mcg salmeterol xinafoate is equivalent to 50 mcg

(b) (4)

Source: NDA 021077, Module 3.2.P.2 Pharmaceutical Development

Formulation of Test Product and Placebo

The formulation for the Test product (MGR001 100/50) is presented in Table 2.

Ingredients	Function	Test Amount (mg, %)	
		mg	%w/w
Salmeterol xinafoate	Active		(b) (4)
Fluticasone propionate	Active		
Lactose monohydrate	Excipient		

(b) (4)

(b) (4)¹

Reviewer's Comments: *The test product is qualitatively (Q1) and quantitatively (Q2) the same compared to the RLD.*

According to the FDA Draft Product Specific Guidance for Fluticasone Propionate; Salmeterol Xinafoate, the test product is recommended to be Q1 and Q2 the same as the R product. According to the Product Specific Guidance, Q1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product, and Q2 (quantitative sameness) means that concentrations of inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.² The test product contains Lactose monohydrate

(b) (4)

(b) (4).

The final acceptability of the formulation is deferred to the Division of Bioequivalence and the final acceptability of the active ingredients is deferred to the Office of Pharmaceutical Quality.

¹ <\\cdsesub1\evsprod\anda208891\0024\m1\us\12-cover-letters\cover-letter-0024-information-request-response-20180201.pdf>, Comment 2, Table 2

² <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM367643.pdf>



Michael
Spagnola

Digitally signed by Michael Spagnola
Date: 1/29/2019 01:19:09PM
GUID: 56f3fc6e00e3bf2df523cd48bdc61031



Carol
Kim

Digitally signed by Carol Kim
Date: 1/29/2019 01:22:01PM
GUID: 508da70a00028df5288765ab0807f9a5



Mark
Ritter

Digitally signed by Mark Ritter
Date: 1/29/2019 01:28:57PM
GUID: 508da6e80002732e6afdd41c9bb5d417

Addendum to Division of Bioequivalence (DB) Review for Dry Inhaler Products (ANDA 208891)

From: Tian Ma, Vipra Kundoor, Bing Li

To: ANDA 208891

Subject: clarifications to DB Review dated 5/31/2018

This addendum clarifies certain aspects of the Division of Bioequivalence (DB) Review dated 5/31/2018. This addendum was prepared in consultation and agreement with the Office of Generic Drug Policy (OGDP), Office of Research and Standards (ORS), and other relevant components.

- The review refers to two fasting pharmacokinetic studies on the 250/50mcg strength that were determined by DB to be unacceptable (studies MGR001-1005 and MGR001-1014). Mylan conducted another fasting pharmacokinetic study on the 250/50mcg strength (study MGR001-1016) which was determined to be acceptable by DB. Study MGR001-1016 was determined to have an appropriate study design, and used test product manufactured (b) (4). (b) (4). DB determined that it was appropriate to rely on study MGR001-1016 to support the demonstration of bioequivalence for this ANDA.
- Equivalence of single actuation content (SAC) was based on the population bioequivalence (PBE) analysis consistent with the draft product-specific guidance for fluticasone propionate; salmeterol xinafoate (draft PSG). Although not referenced in the draft PSG, the review also considered the geometric mean of % label claim data. This geometric mean data were evaluated as supportive for equivalent SAC; when data did not fall within a particular range, the review determines that the issue will not be pursued further. This was not intended to mean that data were disregarded, but rather that the data did not undermine the overall conclusion of equivalence for SAC.
- Equivalence of aerodynamic particle size distribution (APSD) was based on the PBE of impactor-sized mass consistent with the draft PSG. In addition, the mass balance accountability, and cascade impactor (CI) profiles representing drug deposition on the individual stages of the CI along with the mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle mass (FPM) were considered and evaluated as supportive evidence during the course of review consistent with the draft PSG. When data did not fall within a particular range, the review determines that an issue will not be pursued further. This was not intended to mean that data were disregarded, but rather that the data did not undermine the overall conclusion of equivalence for APSD. To clarify, all the data were considered in making the overall conclusions regarding equivalence for APSD.

- APSD is part of the in vitro BE study that supports an overall BE of the product. DB consulted ORS

(b) (5)

(b) (5)

(b) (5) This further evaluation will inform the utility of, and any modifications to, the analyses from a regulatory perspective. FDA intends to update the draft PSG if, and when, appropriate.

**DIVISION OF BIOEQUIVALENCE REVIEW FOR DRY POWDER INHALER
PRODUCTS**

ANDA No.	208891		
Drug Product Name	Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder		
Strength(s)	0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ 0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation		
Applicant Name	Mylan Pharmaceuticals Inc.		
Applicant Address	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310		
US Agent Name and the Mailing Address	Wayne Talton, Head of Global Regulatory Affairs wayne.talton@mylan.com OR Beth Britton, Senior Director of Regulatory Affairs beth.britton@mylan.com		
US agent's Telephone Number	(304) 554-6551 (WT) (304) 554-6184 (BB)		
US Agent's Fax Number	(304) 285-6407		
Original Submission Date(s)	December 29, 2015 February 15, 2016 (concentration data, graphs and SAS output for pharmacokinetic studies; tabular listing of all clinical studies; information on unblinding, randomization and datasets for the pharmacodynamic study) September 22, 2016 (Response to ECD/Bioequivalence) January 12, 2017 (Response to ECD/Bioequivalence) March 2, 2017 (Bridging in vitro BE studies) August 28, 2017 (Resubmission/After Action- Complete; Bioequivalence/Other) March 22, 2018 (Bioequivalence/Response to Discipline Review Letter)		
Submission Date(s) of Amendment(s) Under Review	July 13, 2018 (b) (4) (b) (4)		
Primary Reviewer	Tian Ma, Ph.D.		
Secondary Reviewer	Vipra Kundoor, Ph.D.		
Tertiary Reviewer	Bing V. Li, Ph.D.		
Study Number (s)	MGR001-1006	MGR001-1007	MGR001-1016
Study Type (s)	Fasting	Fasting	Fasting (repeat)
Strength (s)	100/50 mcg ¹	500/50 mcg	250/50 mcg
Clinical Site	Worldwide Clinical Trials Early Phase Services, LLC		
Clinical Site Address	2455 NE Loop 410, Suite 150 San Antonio, Texas 78217		

¹ From now on in this review, product strength of “x/y mcg” will be used to indicate the strength of fluticasone propionate and salmeterol xinafoate (EQ y mcg base) per inhalation, respectively.

Analytical Site	Mylan Pharmaceuticals Inc.		
Analytical Site Address	Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505		
Study Number (s)	MGR001-1005	MGR001-1014	
Study Type (s)	Fasting (failed, but was used in pooled analysis by the applicant with MGR001-1014)	Fasting(failed, but was used in pooled analysis by the applicant with MGR001-1005)	
Strength (s)	250/50 mcg	250/50 mcg	
Clinical Site	Worldwide Clinical Trials Early Phase Services, LLC		
Clinical Site Address	2455 NE Loop 410, Suite 150 San Antonio, Texas 78217		
Analytical Site	Mylan Pharmaceuticals Inc.		
Analytical Site Address	Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505		
Study Number (s)	057755-02-04	MGF-PRO-2015-080	057755-02-07
Study Type (s)	In Vitro BE [single actuation content (SAC) and aerodynamic particle size distribution (APSD)]	In Vitro BE (SAC and APSD)	In Vitro BE (SAC and APSD)
Strength (s)	100/50 mcg	250/50 mcg	500/50 mcg
Analytical Site	(b) (4)	Mylan Global Respiratory Group	(b) (4)
Analytical Site Address	(b) (4)	IPC008, Discovery Park House, Floor 3 Sandwich, Kent. CT13 9ND. UK	(b) (4)
Study Number (s)	MGR-REP-2015-092	MGR-PRO-REP-2015-103	MGR-REP-2015-093
Study Type (s)	Pressure Differential (4 kPa) (SAC and APSD)	Pressure Differential (4 kPa) (SAC and APSD)	Pressure Differential (4 kPa) (SAC and APSD)
Strength (s)	100/50 mcg	250/50 mcg	500/50 mcg
Analytical Site	(b) (4)	Mylan Global Respiratory Group	(b) (4)
Analytical Site Address	(b) (4)	IPC008, Discovery Park House, Floor 3 Sandwich, Kent. CT13 9ND. UK	(b) (4)
Study Number (s)	MGR-PRO-2016-106	MGR-PRO-2016-107	MGR-PRO-2016-108
Study Type (s)	In vitro bridging (SAC and APSD)	In vitro bridging (SAC and APSD)	In vitro bridging (SAC and APSD)
Strength (s)	100/50 mcg	250/50 mcg	500/50 mcg
Analytical Site	Mylan Global Respiratory Group	Mylan Global Respiratory Group	(b) (4)

Analytical Site Address	IPC008, Discovery Park House, Floor 3 Sandwich, Kent. CT13 9ND. UK	IPC008, Discovery Park House, Floor 3 Sandwich, Kent. CT13 9ND. UK	(b) (4)
Study Number (s)	MGR000-1003		
Study Type (s)	Flow Profiling		
Strength (s)	N/A (empty inhaler which did not contain drug or placebo)		
Clinical Site	Site	Principal Investigator	Address
	1	Dominik Kappeler	Inamed Clinical Unit, 82131 Gauting, Germany
	2	Isabelle Schenkenberger	Clinical Research Berlin GbR; 10787 Berlin, Germany
	3	Prof. Dr. med. Walter Dorsch	Practice for Child and Adolescent Medicine, Allergy, Pediatric Pulmonology, Naturopathic, 81379 Munich, Germany
	4	Dr. med. Manfred Praun	Practice for Child and Adolescent Medicine Dr. Praun & Dr. Stiebing, 82205 Gilching, Germany
	5 (not activated)	Prof. Dr. med. Stefan Zielen	University Hospital Johann Wolfgang Goethe-Universität Frankfurt/Main, Centre for children and adolescents, Departement of paediatric pneumology, allergology and cystic fibrosis, 60590 Frankfurt/Main, Germany
Clinical Site Address	Please see table above		
OSI Status	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete ☐ N/A (Waiver) ²	<u>Post October 1, 2014 ANDAs</u> ☐ To Be Determined by OSIS ☐ Pending ☒ Complete	
Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☐ Not granted ☒ N/A		
QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ N/A		
Formulation	☒ Adequate ☐ Inadequate		

² Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A		
BE Guidance Version Used for Evaluation of Current ANDA	Draft Guidance on Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder (Recommended Sep 2013)		
Deficiency Classification	☐ Major (Deficiencies to be communicated by CR) ☐ Minor ☒ N/A (Review is Adequate)		
Overall Review Result	☒ Adequate ☐ Inadequate		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1,2,10,14,22	Fasting	100/50 mcg	ACCEPTABLE
1,2,10,14,22	Fasting	500/50 mcg	ACCEPTABLE
22,34	Fasting	250/50 mcg	ACCEPTABLE
1,2,10,14	Fasting (Failed, but was used in pooled analysis by the applicant with MGR001-1014)	250/50 mcg	N/A (for information)
1,2,10,14	Fasting (Failed, but was used in pooled analysis by the applicant with MGR001-1005)	250/50 mcg	N/A (for information)
1,10,14,22,34	In Vitro BE (SAC and APSD)	100/50 mcg	ACCEPTABLE
1,10,14,22,34	In Vitro BE (SAC and APSD)	250/50 mcg	ACCEPTABLE
1,10,14,22,34	In Vitro BE (SAC and APSD)	500/50 mcg	ACCEPTABLE
1,10,14,22,34	Pressure Differential (4 kPa) (SAC and APSD)	100/50 mcg	ACCEPTABLE
1,10,14,22,34	Pressure Differential (4 kPa) (SAC and APSD)	250/50 mcg	ACCEPTABLE
1,10,14,22,34	Pressure Differential (4 kPa) (SAC and APSD)	500/50 mcg	ACCEPTABLE
16,34	In Vitro BE (SAC and APSD) Bridging	100/50 mcg	ACCEPTABLE
16,34	In Vitro BE (SAC and APSD) Bridging	250/50 mcg	ACCEPTABLE
16,34	In Vitro BE (SAC and APSD) Bridging	500/50 mcg	ACCEPTABLE
1,2,10,22	Flow Profiling	N/A (empty inhaler which did not contain drug or placebo)	N/A (for information)

1 EXECUTIVE SUMMARY

This is a review of an amendment.

On 12/29/2015, Mylan Pharmaceuticals Inc. has submitted the current application for Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder, 0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ 0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation. The test product, also refers to as MGR001 by the applicant, contains fluticasone propionate (FP) and salmeterol xinafoate (SX) inhalation powder in CRC749 inhaler device. The reference standard (RS) is Advair Diskus® 100/50 (fluticasone propionate and salmeterol xinafoate), 0.1 mg/EQ 0.05 mg base per inhalation; Advair Diskus® 250/50 (fluticasone propionate and salmeterol xinafoate), 0.25 mg/EQ 0.05 mg base per inhalation; and Advair Diskus® 500/50 (fluticasone propionate and salmeterol xinafoate), 0.5 mg/EQ 0.05 mg base per inhalation manufactured by GLAXO GRP LTD (approved on August 24, 2000 under NDA 021077). The reference-listed drug (RLD) is the same as the RS.

Please refer to the 5/31/2018 bioequivalence (BE) review³ for the submission history of this ANDA. Please note that the application was found acceptable from Division of Bioequivalence's perspective in the aforementioned BE review as amended. However, the application was found inadequate from multiple other disciplines such as Process in Office of Pharmaceutical Quality (OPQ). Therefore, a complete response (CR) letter was issued to the applicant on 6/27/2018⁴.

In the current CR response dated 7/13/2018, the applicant stated that, in response to a Process CR deficiency regarding the [REDACTED] (b) (4)

[REDACTED]. It is noted that the nominal amount of each active pharmaceutical ingredient (API) and excipient remain the same as the formulation submitted in the original submission, which was considered acceptable from BE perspective. It is also noted that there is no change in RLD formulation since the original BE review.⁶ Therefore, the current test formulation remains acceptable.

In addition, based on the applicant's response, it appears that the drug product specification has been updated. The reviewer communicated with the Drug Product reviewer regarding whether these exhibit batches are still acceptable to be used in the in vitro and in vivo BE studies based

³ GDRP: ANDA-208891-ORIG-1-AMEND-22, Bioequivalence Review, A208891N000DB-Review01-08282017.docx, 5/31/2018.

⁴ GDRP: ANDA-208891-ORIG-1-AMEND-22, Upload Final Decision, A208891N000DPM-CompleteResponse02.docx, 6/27/2018.

⁵ GS Review: ANDA 208891, Resubmission/After Action- Complete, 7/13/2018 (Module 1.2\Cover Letter..., p. 39-40 of 50).

⁶ The most recent annual report [GS Review: NDA 021077, New/Annual Report, 7/19/2018 (Module 1.13.5\Drug Product Index of Approved Changes, p. 1 of 4)] and the annual report referenced in the original BE review [GS Review: NDA 021077, New/Annual Report, 7/20/2016 (Module 1.13.5\Drug Product Index of Approved Changes, p. 1 of 4)] has the same information regarding RLD formulation.

on the updated specification. According to the Drug Product reviewer⁷, the updates of product specification in the current amendment do not affect the acceptability of these exhibit batches. Therefore, this updated product specification does not affect the BE study outcome.

The application remains **acceptable**.

2 APPENDIX

2.1 Process Deficiency in the 6/27/2018 CR Letter⁸

(b) (4)



⁷ \\fda.gov\wodc\CDER\OGD\All\OGDS11\DIVISION\BIO\BIO1\Email Reference\208891 Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder\RE [REDACTED] (b) (4)

(b) (4)

⁸ GS Review: ANDA 208891, Resubmission/After Action- Complete, 7/13/2018 (Module 1.2\Cover Letter..., p. 39-40 of 50).

⁹ Emphasized by the reviewer.

¹⁰ Emphasized by the reviewer.

2.2 Original Formulation of the Test Product (commercial batch)¹¹ (from the applicant's batch formula in the original submission dated 12/29/2015)

Ingredients	Commercial Batch Formula per Strength			Quality standard
	MGR001 100/50	MGR001 250/50	MGR001 500/50 (b) (4)	
Salmeterol Xinafoate ^{1,2}				USP
Fluticasone Propionate ²				USP
Lactose monohydrate (b) (4)				USP
(b) (4)				(b) (4)
Total Weight (Batch Size)				--

(b) (4)

2.3 Current Formulation of the Test Product (commercial batch)¹²

Ingredients	Commercial Batch Formula per Strength			Quality standard
	MGR001 100/50	MGR001 250/50	MGR001 500/50 (b) (4)	
Salmeterol Xinafoate ¹				USP
Fluticasone Propionate ¹				USP
Lactose monohydrate (b) (4)				USP
(b) (4)				(b) (4)
Total Weight (Batch Size)				--

(b) (4)

Reviewer's Comments:

- For the original formulation of the test product, (b) (4) (b) (4) (please see highlighted in Section 2.2). As detailed in the original BE review¹³, the acceptability of this overage was deferred to OPQ, and the original formulation of the test product was considered acceptable from BE perspective.
- As detailed in Section 2.1, in the 6/27/2018 CR letter, Process reviewer commented that the applicant's data (b) (4) (b) (4) In the current CR response submitted on 7/13/2018, the applicant

¹¹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.3.2\Batch Formula, p. 1 of 2).

¹² GS Review: ANDA 208891, Resubmission/After Action- Complete, 7/13/2018 (Module 3.2.P.3.2\Batch Formula, p. 1 of 2).

¹³ GDRP: ANDA-208891-ORIG-1, Bioequivalence Primary Review, A208891N000DB_N12292015, 3/22/2017.

•

¹⁴ The most recent annual report [GS Review: NDA 021077, New/Annual Report, 7/19/2018 (Module 1.13.5\Drug Product Index of Approved Changes, p. 1 of 4)] and the annual report referenced in the original BE review [GS Review: NDA 021077, New/Annual Report, 7/20/2016 (Module 1.13.5\Drug Product Index of Approved Changes, p. 1 of 4)] has the same information regarding RLD formulation.

¹⁵ \\fda.gov\wodc\CDER\OGD\All\OGDS11\DIVISION\BIO\BIO1\Email Reference\208891 Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder\RE [REDACTED] (b) (4)

(b) (4)

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 208891
APPLICANT: Mylan Pharmaceuticals Inc.
DRUG PRODUCT: Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate)
Inhalation Powder, 0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ
0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation

The Division of Bioequivalence I (DBI) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{ See appended electronic signature page }

Bing V. Li, Ph.D.
Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

2.4 Outcome Page

Completed Assignment for 208891 ID: 36100

Reviewer: Ma, Tian

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder, 0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ 0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>		
36100	7/13/2018	BIO	ANDA Amendment [1]	1	1	Edit	Delete
36100	7/13/2018	Parallel	Study Amendment [1]	1	1	Edit	Delete
				Total:	2		

**Clinical Bioequivalence Review
Amendment 22**

ANDA number	208891
Drug Product	Fluticasone Propionate and Salmeterol Inhalation Powder 100/50µg, 250/50µg, and 500/50µg
Applicant Name	Mylan Pharmaceuticals Inc.
Treatment Indication	1) Treatment of asthma in patients aged 4 years and older 2) Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD)
Reference Listed Drug (RLD)	Advair Diskus® (Fluticasone Propionate and Salmeterol Xinafoate) 100/50µg, 250/50µg, and 500/50µg)
NDA number for RLD	NDA 021077 (approved on 8/24/2000)
RLD Applicant Name	Glaxo Group LTD
Original Submission Date	December 29, 2015

Materials Reviewed	• Original ANDA submission: 12/29/2015 • ANDA amendment: 4/3/2017 (Request for a Post Complete Response Scientific Meeting), 4/4/2017 (Post Complete Response Clarification Request Written Responses Requested), 8/7/2017 (Sponsor Minutes – Post Complete Response Scientific Meeting), 8/28/2017 (Resubmission – 1st Major Complete Response Amendment), 12/18/2017 (Information Request Response to Division of Clinical Review), 2/1/2018 (Information Request Response to Division of Clinical Review), 2/26/2018 (Information Request Response to Division of Clinical Review), 3/15/2018 (Clinical Amendment), 3/22/2018 (Information Request Response to Division of Clinical Review), 4/26/2018 (Information Request Response to Division of Clinical Review), 5/25/2018 (Information Request Response to Division of Clinical Review), 6/7/2018 (Information Request Response to Division of Clinical Review) • FDA Complete Response letter signed by Denise Toyer McKan on 3/28/2017 • FDA Face-to-Face Meeting Minutes for Post Complete Response Scientific Meeting held on 7/13/2017 • FDA Face-to-Face Meeting Minutes for Mid-Cycle Review Meeting held on 3/1/2018 • FDA Statistical Review by Cynthia Liu, Ph.D. completed on 8/12/2016 • FDA Statistical Review and Evaluation by Youngsook Lee, Ph.D. completed on 6/12/2018 • OSIS EIR Cover Memo by Xingfang Li, MD, RAC completed on 10/25/2016 • OSIS Consult Response by Xingfang Li, MD, RAC completed on 4/5/2018 • Reserve Sample Memorandum by Sarah Yin, M.D. completed on 6/26/2018 • Division of Bioequivalence Review for Dry Powder Inhaler Products by Tian Ma, Ph.D. completed on 3/22/2017 • Clinical Review of Drug-Device Combination Product by Michael Spagnola, M.D. completed on 6/26/2018 • Clinical Consult Review by Sarah H. Seung, Pharm.D. and Sunny Tse, Ph.D. completed on 1/23/2017 • FDA Draft Product Specific Guidance for Fluticasone Propionate; Salmeterol Xinafoate Recommended September 2013 • NDA 021077 Submission and Clinical Review
Primary Reviewer	Michael Spagnola, M.D. Medical Officer Division of Clinical Review (DCR), Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Secondary Reviewer	Carol Kim, Pharm.D. Acting ANDA Team Leader, DCR, OB, OGD
Tertiary Reviewer	Mark Ritter, M.D. Associate Division Director, DCR, OB, OGD
Date of Completion	June 27, 2018
GDUFA Goal Date	June 27, 2018
DCR Conclusion	DCR concludes that the Clinical Endpoint Bioequivalence Study (MGR001-3001) demonstrates that the test product is bioequivalent to the reference product.

Deficiency Classification

- Major
- Minor
- N/A (Review is Adequate. See Section 3 of this review for non-deficiency comments to be provided to the Applicant by the RPM.)

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1 Executive Summary

1.1 Approval Recommendation

The study MGR001-3001 is adequate to support approval of the application pending satisfactory approval recommendations from the other disciplines on the review team.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

This review evaluates the study data submitted to ensure that Mylan Pharmaceuticals Inc.'s ("Applicant") Fluticasone Propionate and Salmeterol Inhalation Powder 100/50µg is bioequivalent to the reference listed drug (RLD), Advair Diskus® Fluticasone Propionate and Salmeterol Xinafoate 100/50µg (NDA 021077 approved on 08/24/2000).

On December 29, 2015, the Applicant submitted ANDA 208891 for Fluticasone Propionate and Salmeterol Inhalation Powder 100/50µg, 250/50µg, and 500/50µg as a generic version of the RLD, Advair Diskus® Fluticasone Propionate and Salmeterol Xinafoate 100/50µg, 250/50µg, and 500/50µg. On March 28, 2017, the Agency issued a Complete Response (CR) letter to the Applicant for ANDA 208891 and the Applicant submitted a Major Complete Response Amendment (Amendment 22) on August 28, 2017. In support of an approval for this ANDA, the Applicant conducted a bioequivalence study with clinical endpoint (Study MGR001-3001) in the treatment of asthma in 1128 subjects. Study MGR001-3001 was evaluated during this review.

There are no other ANDAs for this drug product filed prior to the current ANDA and therefore, this is a potential first generic for this drug product.

1.2.2 Comparative Efficacy

Study MGR001-3001 was a multicenter, double-blinded, double-dummy design, randomized, placebo-controlled, parallel-group study in 1128 male and non-pregnant female subjects ≥ 18 years of age with a clinical diagnosis of asthma. Following a single-blind placebo run-in period, subjects were randomized to receive one of three treatments: MGR001 100/50 containing Fluticasone Propionate 100 mcg and Salmeterol Xinafoate 50 mcg in a CRC749 inhaler (Test product), Advair Diskus® Fluticasone Propionate and Salmeterol Xinafoate 100/50µg (Reference product), or Placebo lactose (Placebo). The study subjects orally inhaled one puff of the study drug twice a day for 28 (± 2) days. The co-primary endpoints were 1) change from baseline in FEV₁ AUEC₀₋₁₂ measured on Day 1 and 2) change from baseline in pre-morning dose (trough) FEV₁ measured on Day 29.

A total of 1122 subjects were included in the Applicant's Full Analysis Set (FAS) and 1105 subjects were included in the Applicant's Per Protocol Set (PPS). The fact that the number of subjects in the Applicant's PPS was almost the same as the number of subjects in the Applicant's FAS reflected the Applicant's pre-specified PPS definition, which was defined as all subjects in the Full Analysis Set who had not violated, or deviated from, the protocol in such a way that could have affected the outcome of the FEV₁ assessments for *both* primary endpoints. Because two different treatments/endpoints are being evaluated at the Day 1 and Day 29 timepoints, FDA

concluded that the Applicant's definition was not conservative and could potentially obscure the assessment of bioequivalence because the PPS could include subjects who violated or deviated from the protocol in a way that could have affected the outcome of *one* of the endpoints. Therefore, the FDA reviewer adjusted the PPS using a more typical Per Protocol selection approach, and evaluated separate per protocol populations for the Day 1 and Day 29 endpoints, and a single combined per protocol population. The most common reasons for subject adjustments included Day 29 (Visit 5) out of time window spirometry assessments, Day 29 (Visit 5) out of window study visit, failure to meet Inclusion Criterion 6 (post bronchodilator percent reversibility), and failure to meet double-blind study treatment period study drug compliance. Of the 1128 subjects randomized into the study, 1028, 775, and 765 subjects were included in the FDA Day 1 Per Protocol, FDA Day 29 Per Protocol, and FDA Per Protocol populations, respectively.

According to the Applicant's and FDA's statistical analyses, the data shows that the test product is bioequivalent to the reference product for both co-primary endpoints. According to the FDA's statistical analysis, the mean change from baseline in FEV₁ AUEC₀₋₁₂ measured on Day 1 using the FDA Day 1 Per Protocol population is 3.9315 L.hr for the test product and 3.5459 L.hr for the reference product and the mean change from baseline in trough FEV₁ measured on Day 29 using the FDA Day 29 Per Protocol population is 0.2905 L for the test product and 0.2750 L for the reference product. The 90% CI for the test/reference ratio of the mean change from baseline in FEV₁ AUEC₀₋₁₂ measured on Day 1 using the FDA Day 1 Per Protocol population is (100.7%, 122.2%) which is within the bioequivalence limits of [80%, 125%] and the 90% CI for the test/reference ratio of the mean change from baseline in trough FEV₁ measured on Day 29 using the FDA Day 29 Per Protocol population is (92.0%, 122.4%) which is within the bioequivalence limits of [80%, 125%]. Both the test product and reference product are shown to be statistically superior to the placebo ($p \leq 0.0001$) in the FDA Modified Intent-to-treat (mITT) population for both co-primary endpoints.

According to the Office of Study Integrity and Surveillance's (OSIS) Establishment Inspection Report (EIR) Cover Memo dated October 25, 2016, the data from the clinical endpoint study (MGR001-3001) was not accepted for further agency review. Two significant findings detailed in the OSIS EIR Cover Memo (inspection report) included failure to maintain a sealed randomization schedule including blinding codes in possession of the clinical site prior to the dosing of subjects and failure of the clinical sites to retain reserve samples from subsequent shipments of the drug product. Based on additional information that Mylan provided in their Compete Response Amendment and Information Request responses, OSIS concluded in their consult response dated April 5, 2018 that Mylan had provided information to show that subjects were dosed with the study products as reported. Following several internal meetings between OGD and OSIS, OGD and OSIS concluded that the reserve samples were adequate to verify the authenticity of the study products and were representative of the study product used in the clinical endpoint study. OGD and OSIS determined that Study MGR001-3001 met 21 CFR 320.38 and 21 CFR 320.63 despite not retaining reserve samples from every shipment to every clinical site as recommended in the FDA Guidance "Handling and Retention of BA and BE Testing Samples" (May 2004). (Retention Sample BE Guidance). To the extent Mylan's approach to retaining reserve samples is not consistent with the Retention Sample BE Guidance, a departure from the guidance is appropriate because Mylan has demonstrated that its approach satisfied the applicable statutory and regulatory standards. OSIS and OGD concluded that the data from all clinical sites in the clinical endpoint study are acceptable for further agency review.

1.2.3 Comparative Safety

Study MGR001-3001 showed no clinically significant difference in the safety profile between the test product and the RLD. A total of 1127 subjects in the Safety Set were exposed to the study medication on at least one occasion. Subjects orally inhaled one puff of the study drug twice a day for 28 (±2) days. The percentage of subjects who experienced at least one AE was similar in the test group (14.1%) compared to the reference group (14.6%) and the placebo group (14.6%). The proportion of mild, moderate and severe AEs reported was similar between the test group and the reference group. Most adverse events were considered not related to the study drugs. The AEs experienced by at least 1% of the subjects in the test group were upper respiratory infection and asthma. There were no deaths or serious adverse events in the study. During screening and the single-blind placebo run-in period, two subjects (b) (6) (b) (6). Subject (b) (6) did not take a single dose of the placebo treatment and Subject (b) (6) discontinued from the study on (b) (6) after taking 31 doses of the placebo medication after it was determined that Subject (b) (6) (b) (6). Both subjects were withdrawn from the study and neither subject entered the double-blind treatment period or received any doses of the study medication.

2 Clinical Review

2.1 Introduction and Background

2.1.1 Summary of Drug Information¹

Reference Listed Drug	Advair Diskus® (Fluticasone Propionate and Salmeterol Xinafoate) 100/50µg, 250/50µg, and 500/50µg
RLD Applicant name	Glaxo Group LTD
NDA #	021077
Date of RLD Approval	8/24/2000
Approved Indications	1) Twice-daily treatment of asthma in patients aged 4 years and older 2) Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD)
Recommended Dosing/ Dosing considerations	• Treatment of asthma in patients aged 12 years and older: 1 inhalation of ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, or ADVAIR DISKUS 500/50 twice daily. Starting dosage is based on asthma severity • Treatment of asthma in patients aged 4 to 11 years: 1 inhalation of ADVAIR DISKUS 100/50 twice daily • Maintenance treatment of COPD: 1 inhalation of Advair DISKUS 250/50 twice daily More frequent administration or a greater number of inhalation (more than 1 inhalation twice daily) of the prescribed strength of ADVAIR DISKUS is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol.

¹ https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021077s056s057lbl.pdf

Absorption	Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Trials using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (less than 1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed. Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and eliminated independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Following administration of ADVAIR DISKUS to healthy adult subjects, peak plasma concentrations of salmeterol were achieved in about 5 minutes.
Mechanism of Action	Fluticasone propionate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma. Inflammation is also a component in the pathogenesis of COPD. In contrast to asthma, however, the predominant inflammatory cells in COPD include neutrophils, CD8+ T-lymphocytes, and macrophages. The effects of corticosteroids in the treatment of COPD are not well defined and inhaled corticosteroids and fluticasone propionate when used apart from ADVAIR DISKUS are not indicated for the treatment of COPD. Salmeterol is a selective LABA. The pharmacologic effects of beta2-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells. In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D₂, from human lung.
Boxed Warnings	None

Use in specific populations

- **Pregnancy:** There are no randomized clinical studies of ADVAIR DISKUS or individual monoproducts, fluticasone propionate and salmeterol xinafoate, in pregnant women. There are clinical considerations with the use of ADVAIR DISKUS in pregnant women. In animals, teratogenicity characteristic of corticosteroids, decreased fetal body weight and/or skeletal variations, in rats, mice, and rabbits were observed with subcutaneously administered maternal toxic doses of fluticasone propionate less than the maximum recommended human daily inhaled dose (MRHDID) on a mcg/m^2 basis. However, fluticasone propionate administered via inhalation to rats decreased fetal body weight, but did not induce teratogenicity at a maternal toxic dose less than the MRHDID on a mcg/m^2 basis. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. Oral administration of salmeterol to pregnant rabbits caused teratogenicity characteristic of beta-adrenoceptor stimulation at maternal doses approximately 50 times the MRHDID on an AUC basis. These adverse effects generally occurred at large multiples of the MRHDID when salmeterol was administered by the oral route to achieve high systemic exposures. No such effects occurred at an oral salmeterol dose approximately 20 times the MRHDID.
- **Lactation:** There are no available data on the presence of fluticasone propionate or salmeterol in human milk, the effects on the breastfed child, or the effects on milk production. Other corticosteroids have been detected in human milk. However, fluticasone propionate and salmeterol concentrations in plasma after inhaled therapeutic doses are low and therefore concentrations in human breast milk are likely to be correspondingly low. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ADVAIR DISKUS and any potential adverse effects on the breastfed child from ADVAIR DISKUS or from the underlying maternal condition.
- **Pediatric Use:** Use of ADVAIR DISKUS 100/50 in patients aged 4 to 11 years is supported by extrapolation of efficacy data from older subjects and by safety and efficacy data from a trial of ADVAIR DISKUS 100/50 in children with asthma aged 4 to 11 years. The safety and effectiveness of ADVAIR DISKUS in children with asthma younger than 4 years have not been established. ICS, including fluticasone propionate, a component of ADVAIR DISKUS, may cause a reduction in growth velocity in children and adolescents. The growth of pediatric patients receiving orally inhaled corticosteroids, including ADVAIR DISKUS, should be monitored.
- **Geriatric Use:** Clinical trial of ADVAIR DISKUS for asthma did not include sufficient numbers of subjects aged 65 years and older to determine whether older subjects with asthma respond differently than younger subjects. Of the total number of subjects in clinical trials receiving ADVAIR DISKUS for COPD, 1,621 were aged 65 years and older and 379 were aged 75 years and older. Subjects with COPD aged 65 years and older had a higher incidence of serious adverse events compared with subjects younger than 65 years. Although the distribution of adverse events was similar in the 2 age groups, subjects older than 65 years experienced more severe events. In two 1-year trials, the excess risk of pneumonia that was seen in subjects treated with ADVAIR DISKUS compared with those treated with salmeterol was greater in subjects older than 65 years than in subjects younger than 65 years. As with other products containing beta2-agonists, special caution should be observed when using ADVAIR DISKUS in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta2-agonists. Based on available data for ADVAIR DISKUS or its active components, no adjustment of dosage of ADVAIR DISKUS in geriatric patients is warranted.
- **Hepatic Impairment:** Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in patients with hepatic impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.
- **Renal Impairment:** Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in patients with renal impairment.

Warnings and Precautions	• LABA monotherapy increases the risk of serious asthma-related events • Do not initiate in acutely deteriorating asthma or COPD. Do not use to treat acute symptoms. • Do not use in combination with an additional medicine containing a LABA because of risk of overdose. • <i>Candida albicans</i> infection of the mouth and pharynx may occur. Monitor patients periodically. Advise the patient to rinse his/her mouth with water without swallowing after inhalation to help reduce the risk. • Increased risk of pneumonia in patients with COPD. Monitor patients for signs and symptoms of pneumonia. • Potential worsening of infections (e.g., existing tuberculosis; fungal, bacterial, viral, or parasitic infection; ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. • Risk of impaired adrenal function when transferring from systemic corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to ADVAIR DISKUS. • Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue ADVAIR DISKUS slowly. • If paradoxical bronchospasm occurs, discontinue ADVAIR DISKUS and institute alternative therapy. • Use with caution in patients with cardiovascular or central nervous system disorders because of beta-adrenergic stimulation. • Assess for decrease in bone mineral density initially and periodically thereafter. • Monitor growth of pediatric patients. • Close monitoring for glaucoma and cataracts is warranted. • Be alert to eosinophilic conditions, hypokalemia, and hyperglycemia. • Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis.
Contraindications	• Primary treatment of status asthmaticus or acute episodes of asthma or COPD requiring intensive measures. • Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone propionate, salmeterol, or any of the excipients.
Commonly reported Adverse Events	Most common adverse reactions (incidence $\geq 3\%$) include: • Asthma: Upper respiratory tract infection or inflammation, pharyngitis, dysphonia, oral candidiasis, bronchitis, cough, headaches, nausea and vomiting. • COPD: Pneumonia, oral candidiasis, throat irritation, dysphonia, viral respiratory infections, headaches, musculoskeletal pain.

Reviewer’s Comments: *On December 20, 2017, the Boxed Warning about asthma related death was removed from the drug label of Advair® after a review of four large clinical safety trials showed that treating asthma with long-acting beta agonists (LABA) in combination with inhaled corticosteroids (ICS) does not result in significantly more serious asthma related side effects than treatment with inhaled corticosteroids alone.*

2.1.2 Regulatory Background

Mylan Pharmaceuticals Inc. (“Applicant”) submitted ANDA 208891 on 12/29/2015 for Fluticasone Propionate and Salmeterol Inhalation Powder 100/50µg and 250/50µg as a generic version of the RLD, Advair Diskus® (NDA 021077, Glaxo Group LTD). On 3/28/2017, the Agency issued a Complete Response letter to the Applicant for ANDA 208891 and the Applicant submitted a Major Complete Response Amendment (Amendment 22) on 8/28/2017.

In support of their application, the Applicant submitted the results of one bioequivalence study with clinical endpoints (MGR001-3001).

2.1.2.1 Guidance on Drug Product

A FDA Draft Product Specific Guidance for establishing bioequivalence for this drug product is available². Table 2.1 provides a brief overview of the draft guidance recommendations.

Table 2.1: Drug Product Draft Guidance

Draft Guidance	Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate
Date Posted	September 2013
Recommended Studies	1. Single actuation content (SAC) 2. Aerodynamic particle size distribution (APSD) 3. Fasting single-dose, two-way crossover pharmacokinetic (PK) bioequivalence study 4. Clinical endpoint study
Clinical Endpoint Study Recommendations	Clinical endpoint study is recommended to be conducted for the lowest strength of the T and R products. Study design: A randomized, multiple-dose, placebo-controlled, parallel group design consisting of a 2 week run-in period followed by a 4-week treatment period of the placebo, T or R product Strength: 100/50 (fluticasone propionate 100 mcg and salmeterol 50 mcg powder for inhalation) Dose: 100/50, twice daily Subjects: Males and non-pregnant females with asthma Additional comments: • Inclusion criteria should, at minimum, include: a. Male or female subjects (≥ 12 years of age) of non-child bearing potential or of child bearing potential committing to consistent and correct use of an acceptable method of birth control. b. Diagnosed with asthma as defined by the National Asthma Education and Prevention Program (NAEPP) at least 12 weeks prior to screening. c. Pre-bronchodilator FEV₁ of $\geq 40\%$ and $\leq 85\%$ of the predicted value during the screening visit and on the first day of treatment. d. Currently non-smoking; had not used tobacco products (i.e., cigarettes, cigars, pipe tobacco) within the past year, and had ≤ 10 pack-years of historical use. e. $\geq 15\%$ reversibility of FEV₁ within 30 minutes following 360 mcg of albuterol inhalation (pMDI). f. Able to discontinue their asthma medications (inhaled corticosteroids and long-acting β agonists) during the run-in period and for remainder of the study. g. Able to replace current short-acting β agonists (SABAs) with salbutamol/albuterol inhaler for use as needed for the duration of the study (subjects should be able to withhold all inhaled SABAs for at least 6 hours

² <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM367643.pdf>

- prior to lung function assessments on study visits).
- h. Able to continue the following medications without a significant adjustment of dosage, formulation, dosing interval for the duration of the study, and judged able by the investigator to withhold them for the specified minimum time intervals prior to each clinic visit:
- short-acting forms of theophylline 12 hours
 - twice-a-day controlled-release forms of theophylline 24 hours
 - once-a-day controlled-release forms of theophylline 36 hours
- i. Able to discontinue the following medications for the specified minimum time intervals prior to the run-in period and for the remainder of the study, if the study is conducted in the US:
- oral corticosteroids 1 month
 - parenteral corticosteroids 1 month
 - oral short-acting β -agonists 12 hours
- j. Willingness to give their (and in the case of a minor their parent/guardian was able to give) written informed consent to participate in the study.

- Exclusion criteria should, at minimum, include:
 - a. Life-threatening asthma, defined as a history of asthma episode(s) requiring intubation, and/or associated with hypercapnoea; respiratory arrest or hypoxic seizures, asthma related syncopal episode(s), or hospitalizations within the past year or during the run-in period.
 - b. Evidence or history of clinically significant disease or abnormality including congestive heart failure, uncontrolled hypertension, uncontrolled coronary artery disease, myocardial infarction, or cardiac dysrhythmia. In addition, historical or current evidence of significant hematologic, hepatic neurologic, psychiatric, renal, or other diseases that in the opinion of the investigator, would put the patient at risk through study participation, or would affect the study analyses if the disease exacerbated during the study.
 - c. Hypersensitivity to any sympathomimetic drug (e.g., salmeterol or albuterol) or any inhaled, intranasal, or systemic corticosteroid therapy.
 - d. Medication(s) with the potential to affect the course of asthma or to interact with sympathomimetic amines, e.g.:
 - β -blockers
 - oral decongestants
 - benzodiazepines
 - digitalis
 - phenothiazines
 - polycyclic antidepressants
 - Monoamine oxidase inhibitors
 - e. Viral or bacterial, upper or lower respiratory tract infection or sinus or middle ear infection within 4 weeks prior to the screening visit or during the run-in period.
 - f. Factors (e.g., infirmity, disability or geographic location) that the investigator felt would likely limit the patient's compliance with the study protocol or scheduled clinic visits.

- The study is recommended to begin with a placebo run-in period (at least 2 weeks in duration) to wash out any pre-study corticosteroids/ long acting bronchodilators and to establish FEV₁ baseline values.
- The study protocol should provide a definition of compliant subjects (e.g., used

	at least 75% and no more than 125% of study drug doses) and specify how compliance will be verified (e.g., by the use of subject diaries). • To ensure adequate study sensitivity, the T and R products should both be statistically superior to placebo ($p < 0.05$) with regard to the BE study primary endpoints. • It is the sponsor's responsibility to enroll a sufficient number of subjects for the study to demonstrate BE of the T to the R product. • The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both. • All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the T and R products.
Primary Endpoints	1. Area under the serial FEV₁-time curve calculated from time zero to 12 hours (AUC_{0-12h}) on the first day of the treatment 2. FEV₁ measured in the morning prior to the dosing of inhaled medications on the last day of a 4-week treatment. The above two primary endpoints should be baseline adjusted (change from baseline). A FEV₁ baseline is defined as the average of pre-dose FEV₁ values of at least two time points measured in the morning of the first day of a 4 week treatment period. Sampling is recommended to correspond to the same time of day as used on the last day of a 4-week treatment. On the first day of the treatment, FEV₁ should be determined at 0, 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 hour post-dose. Equivalence based on: T/R ratio for the primary endpoints. The 90% CIs for the T/R ratios for the primary endpoints should fall within the limits of 80.00-125.00%.

2.1.2.2 Generic Drug Product Development

On 8/1/2013, the Applicant submitted Bio-IND 118769 to the Office of Generic Drugs. The Bio-IND 118769 protocol was reviewed primarily for safety relative to the administration of a single dose (i.e. 3 inhalations equaling 750 mcg of fluticasone and 150 mcg of salmeterol) in the sponsor's proposed pharmacokinetic study (PK) that is higher than the highest approved orally inhaled dose of 500/50 mcg of fluticasone propionate and salmeterol xinafoate. DCR reviewed the study protocol and concluded that the dose to be used in the PK study is reasonably safe.

The Applicant submitted multiple controlled correspondences and had multiple meetings (Face-to-Face and teleconference) with the Agency during the development of their generic product. In Controlled Correspondence 12-0731, Mylan requested a Type C meeting to confirm their understanding of previous discussions with the Agency that two therapeutic equivalence method validation studies should be conducted to examine the dose-response for the fluticasone

propionate and salmeterol xinafoate components. A Type C meeting was held on 12/12/2012 in which the general development program was discussed and the meeting minutes from the Applicant were provided in Controlled Correspondence 12-0850.

In Controlled Correspondence 13-0422, Mylan requested a Type C meeting that was held on 9/27/2013 in which the pharmaceutical development program was discussed and an update on the clinical development program was provided by Mylan.³ In their response to the meeting request, the Agency noted that Mylan's plan to conduct a double-blind and double-dummy design study which may require placebo RLD product is acceptable. The FDA Draft Product Specific Guidance for Fluticasone Propionate; Salmeterol Xinafoate (Product Specific Guidance) does not recommend a double-blind, double-dummy study design due to concern of generic sponsor's ability to produce placebo RLD products. In Question 2 of the Agency's response, the Agency noted that the proposed minor variation in study inclusion criteria from that recommended in the Product Specific Guidance (only adult asthmatics ≥ 18 years, baseline FEV₁ 60-85% of predicted after having abstained from albuterol for at least 6 hours, and albuterol reversibility $\geq 12\%$) is acceptable. The Agency's response noted that Mylan was concerned about ethical issues with inclusion of severe asthmatics (with FEV₁ 40 to $< 60\%$ of predicted) into placebo controlled study and hence proposed a subject population with milder asthma (FEV₁ 60-85% of predicted). The Agency found Mylan's proposal of a four week placebo run-in period acceptable instead of having a two week placebo run-in period as recommended by the Product Specific Guidance. The Agency did not agree with Mylan's proposed statistical analyses for their clinical endpoint study. Specifically, the Agency did not agree that Test/Reference (T/R) ratio should be determined on the natural log scale and instead, the Agency recommended that the Applicant determine T/R ratio on the original scale (i.e., without log transformation).

The Agency found all of Mylan's proposed measures to minimize study endpoint assessment variability acceptable. The proposed measures include 1) excluding subjects who are showing signs of uncontrolled asthma at the time of the study or who have a history of recent exacerbation or seasonally unstable disease and withdrawing subjects who become uncontrolled during the study, 2) conducting spirometry in accordance with American Thoracic Society (ATS) guidance and using centralized spirometry with appropriate quality control for collection of all lung function data, 3) maintaining the same time of day (± 1 hour) for measurement of lung function endpoints at each visit, 4) collecting 2 measures of trough FEV₁, one at the run-in visit and the mean of 2 measures taken at least 30 minutes apart at the randomization visit with the mean of these measures forming the trough FEV₁ baseline (Day 29 endpoint baseline), and 5) collecting 2 measures of pre-dose FEV₁ (at least 30 minutes part) on both day 1, with their mean recorded as the baseline for the assessment of FEV₁ AUEC0-12 (Day 1 endpoint baseline), and on day 29 with their mean recorded as the trough FEV₁ at endpoint (Day 29 endpoint). With respect to the Applicant's proposal of collecting of 2 measures of trough FEV₁, one at the run-in visit and the mean of the 2 measures taken at least 30 minutes apart at the randomization visits with the mean of these measures forming the trough FEV₁ baseline (Day 29 endpoint baseline), the reviewer of the controlled correspondence noted that the Product Specific Guidance states "A

3

<http://mercado.fda.gov/search/resources/panorama/documentum/Panorama/090026f8806f745d?includeRequestSystem=false>

FEV₁ baseline is defined as the average of two pre-dose FEV₁ values of at least two time point measured in the morning of the first day of a 4 week treatment period.” It is explained that the Applicant’s proposal should be acceptable because all trough FEV₁ measurements forming the baseline trough FEV₁ for the Day 29 endpoint will be from the third and fourth week of the placebo run-in period giving sufficient time for washout of prior inhaled corticosteroid medications. The reviewer for Controlled Correspondence 13-0422 noted that the Applicant’s proposal includes using a different baseline for each of the two co-primary endpoints (FEV₁ AUEC₀₋₁₂ and trough FEV₁).

The Agency agreed with Mylan’s proposal for blinded sample size re-estimation and adjustment of subjects as long as such approach is pre-specified in the study protocol but also requested that Mylan justify their proposed sample size re-estimation approach with validation either from simulation studies or literature references. In reference to the Applicant’s question about handling and retention of bioequivalence testing samples in the clinical endpoint study, the Agency did not agree with the Applicant’s proposal and instead, recommended that at least 50 units for each batch of test and reference products including placebos with no less than 10 units per each batch per site be retained. The Applicant was also referred to Section 4 (B) of the product specific guidance for Budesonide Inhalation Suspension for further guidance. For proposed clinical studies, the Agency recommended that the same batches of the RLD and the test product be used in the clinical program and in vitro bioequivalence studies whenever feasible and that the drug product intended for marketing be used in the clinical studies. On 7/2/2015, Mylan submitted a meeting package and after a Face-to-Face meeting was held on 10/22/2015, OGD provided responses to the firm’s questions on their overall development program to date, manufacturing data, proposed labeling, suggested format for ANDA submission, and request for expedited review/priority review status for their ANDA submission.

On 8/4/2014, Mylan submitted Protocol 140014 to the Agency for review. This was a non-dosing inhaler development study designed to assess the use of the four key operational steps of CRC749 inhaler and the likelihood of orientation-related errors by representative users. On 8/27/2014, Mylan submitted a device orientation study protocol seeking the Agency’s concurrence with their proposed human factors study protocol. OGD provided responses to the firm’s questions on human factors study protocol for orientation of use of CRC749.

After OGD completed review of the Original ANDA submission, Mylan requested a Post Complete Response Scientific Meeting on 4/4/2017 to discuss deficiencies noted in the Complete Response Letter. This request was granted by the Agency and a Face-to-Face meeting was held on 7/13/2017. There were no issues discussed in the Preliminary Meeting Comments or Face-to-Face meeting between Mylan and the Agency held on 7/13/2017 that directly pertained to the clinical endpoint study (MGR001-3001).⁴⁵

Mylan requested a Face-to-Face meeting on 10/19/2017 as a “means to help facilitate and accelerate the review of this important generic product.” On 3/1/2018, a Face-to-Face meeting

⁴ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f8812d628b>

⁵ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f8813b9a80>

was held between Mylan and the Agency to discuss the progress of the review of ANDA 208891.

Reviewer's Comments:

(b) (4)

(b) (4)

In Controlled Correspondence 13-0422, the Agency found Mylan's proposal to collect two measures of pre-dose FEV₁ (at least 30 minutes apart) on Day 29 with their mean recorded as the trough FEV₁ to be used in the Day 29 endpoint analysis as acceptable.⁷ (b) (4)

(b) (4)

(b) (4) *Mylan in Controlled Correspondence 13-0422 appear similar, a key difference is that Mylan's proposal used the average of two pre-dose FEV₁ measurements on the same day*

(b) (4)

⁶ <http://panorama.fda.gov/task/view?ID=558ac76200c6612eb2b0a68812f9d37c>

⁷

<http://mercado.fda.gov/search/resources/panorama/documentum/Panorama/090026f8806f745d?includeRequestSystem=false>

(b) (4) Since Mylan's proposal used the average of two pre-dose FEV₁ measurements on Day 29 only in MGR001-3001, this is acceptable.

2.1.2.3 Relevant Communications with Other Generic Applicants

There are (b) (4) protocols, (b) (4) Bio-INDs, and seventy five controlled correspondences submitted to OGD for Fluticasone Propionate and Salmeterol Xinafoate (See Appendix, Table 4.1, Table 4.2, and Table 4.3). All controlled correspondences have been reviewed. There are two controlled correspondences (14-0298 & 14-0001) that are currently open.

2.1.2.4 Other ANDA submissions for same product

No generic version of Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder has been approved, and there is no other ANDA for Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder currently pending review.

There are no other ANDAs for this drug product filed prior to the current ANDA and therefore, this is a potential first generic for this drug product.

Table 2.2: ANDAs Submitted to Office of Generic Drugs for Fluticasone Propionate and Salmeterol Xinafoate (b) (4)

ANDA NUMBER	DRUG PRODUCT	APPLICANT	CURRENT STATUS
(b) (4)			
208891 (Current ANDA)	Fluticasone Propionate and Salmeterol Xinafoate	Mylan Pharmaceuticals Inc	Pending 08/28/2017
(b) (4)			

Source: Search of DAARTS and Orange Book on 3/15/2018

2.1.3 Other Relevant Information

On December 29, 2015, the Applicant submitted ANDA 208891 for Fluticasone Propionate and Salmeterol Inhalation Powder 100/50µg, 250/50µg, and 500/50µg as a generic version of the RLD, Advair Diskus® Fluticasone Propionate and Salmeterol Xinafoate 100/50µg, 250/50µg, and 500/50µg. The Division of Bioequivalence I (DB I) in the Office of Generic Drugs originally completed the primary review of the clinical endpoint study.⁸ During the first cycle review of the clinical endpoint study, DB I consulted the Division of Clinical Review for per protocol population recommendations and evaluation of the study design of the clinical endpoint study. DCR did not provide per protocol population recommendations to DB I in their consult response. In their response, DCR provided some minor deficiency comments for the Complete

⁸ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f88106a223>

Response letter based on the preliminary review of the clinical endpoint study.⁹ On March 28, 2017, the Agency issued a Complete Response (CR) letter to the Applicant for ANDA 208891. On April 4, 2017, Mylan requested a Post Complete Response Scientific Meeting to discuss issues related to the device orientation, in vitro bioequivalence studies at multiple flow rates, 4kPa study design, stability of fluticasone propionate, conditioning of active pharmaceutical ingredient (API), agency’s preliminary in vitro testing results, cascade impactor method sensitivity and mass balance, stability of salmeterol xinafoate, PK study for the 50/250 strength, and flow profile study. The FDA’s meeting minutes summarized the major discussion points of the Face-to-Face meeting held between Mylan and the Agency on July 13, 2017.¹⁰ The primary review responsibility of the clinical endpoint bioequivalence study and clinical review of the drug-device combination product after the Major Complete Response Amendment (Amendment 22) dated August 28, 2017 was transferred to DCR from DB I.

2.2 Description of Clinical Data and Sources

The applicant conducted one clinical endpoint bioequivalence study to compare the test product to the RLD.

Table 2.3: Source of Clinical Data

Protocol Number	MGR001-3001
Study Design	Randomized, multiple dose, double-blinded, placebo-controlled, parallel-group, multi-center
CRO	Pharmaceutical Product Development Inc. (PPD, Inc.)
Study Period	Start date: Oct 22 2014 End date: Jul 10 2015
Study Centers	101 sites in the United States (97 sites screened and enrolled subjects, 3 sites screened but did not enroll any subjects, and 1 site neither screened nor enrolled any subjects but received investigational product)
Enrollment	1871
NCT Number	NCT02245672

Reviewer’s Comments: *Clinical sites #3001048, #3001066, and #3001116 screened subjects but did not enroll any subjects as all subjects screened at these sites did not meet the inclusion/exclusion criteria for the study. Clinical site #3001079 did not enroll any subjects and screening was closed at the site prior to the site screening any subjects due to quality concerns identified during an FDA inspection at the site for another study. The study included a total of 101 clinical sites and all clinical sites were in the United States and this is acceptable.*

2.3 Clinical Review Methods

2.3.1 Overview of Materials Consulted in Review

ANDA Submissions	12/29/2015 (eCTD Sequence 0000): Original Submission

⁹ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f880f800a5>

¹⁰ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f8813b9a80>

4/3/2017 (eCTD Sequence 0016): Request for a Post Complete Response Scientific Meeting – Contains proposed meeting agenda and topics requesting clarification including device orientation study

4/4/2017 (eCTD Sequence 0017): Post Complete Response Clarification Request Written Responses Requested – Contains clarification request about Post Complete Response bioequivalence deficiency comment related to OSIS inspection findings for clinical endpoint study

8/7/2017 (eCTD Sequence 0019): Sponsor Minutes – Post Complete Response Scientific Meeting – Contains Applicant’s Meeting Minutes for Post Complete Response Scientific Meeting held with Agency on July 13, 2017

8/28/2017 (eCTD Sequence 0021): Resubmission – 1st Major Complete Response Amendment – Contains response to deficiency comments related to clinical endpoint study, OSIS inspection findings for clinical endpoint study, and device orientation study

12/18/2017 (eCTD Sequence 0023): Response to Division of Clinical Review Information Request – Contains submitted samples of study drug and to-be-marketed device inhalers

2/1/2018 (eCTD Sequence 0024): Response to Division of Clinical Review Information Request – Contains clarification and information regarding per protocol populations, formulation, inclusion/exclusion criteria, and protocol deviations

2/26/2018 (eCTD Sequence 0027): Response to Division of Clinical Review Information Request – Contains clarification and information regarding per protocol populations, formulation, inclusion/exclusion criteria, and protocol deviations

3/15/2018 (eCTD Sequence 0030): Clinical Amendment – Contains information regarding sealed blinding codes and Interactive Web Response System (IWRS)/Interactive Voice Response System (IVRS) in response to item 2a from Face-to-Face Meeting held on March 1, 2018

3/22/2018 (eCTD Sequence 0032): Response to Division of Clinical Review Information Request – Contains clarification and information regarding study design, per protocol populations, inclusion/exclusion criteria, protocol deviations and retention samples

4/26/2018 (eCTD Sequence 0036): Response to Division of Clinical Review Information Request – Contains clarification and information regarding subjects who received investigational product from first shipment and retention of reserve samples

5/25/2018 (eCTD Sequence 0038): Response to Division of Clinical Review Information Request – Contains clarification and information regarding retention of reserve samples

6/7/2018 (eCTD Sequence 0039): Response to Division of Clinical Review Information Request – Contains clarification and information regarding retention of reserve samples

This ANDA is submitted in eCTD format and entirely electronic. The ANDA submission is archived at the following location:

	\\cdseub1\evsprod\ANDA208891
FDA Statistical Reviews	• ANDA 208891 Statistical Primary Review (“A208891_Statistical.doc”) by Cynthia Liu, Ph.D., Completed on 8/12/2016¹¹ • ANDA 208891 Statistical Review and Evaluation (“A208891DBVIII-Review.docx”) by Youngsook Lee, Ph.D., Completed on 6/12/2018¹²
Division of Bioequivalence I Review	Division of Bioequivalence Review for Dry Powder Inhaler Products (“A208891N000DB_N12292015.pdf”) by Tian Ma, Ph.D., Completed on 3/22/2017 ¹³
Division of Clinical Review Clinical Consult Review	Clinical Consult Review (“A208891N000DCR_ANDAconsult.docx”) by Sunny Tse, Ph.D. and Sarah H. Seung, Pharm.D., Completed on 1/23/2017 ¹⁴
Post Complete Response Face-to-Face Preliminary Meeting Comments	FDA Face-to-Face Meeting Preliminary Comments for Post Complete Response Scientific Meeting (“A208891N000DPM-PreliminaryMeetingComments01.doc”) by Frank Giannandrea, Completed on 7/7/2017 ¹⁵
Post Complete Response Face-to-Face FDA Meeting Minutes	FDA Face-to-Face Meeting Minutes for Post Complete Response Scientific Meeting (“A208891N000DPM-MeetingMinutes01.pdf”), Meeting held on 7/13/2017 ¹⁶
Mid-Cycle Review Face-to-Face FDA Meeting Minutes	FDA Face-to-Face Meeting Minutes for Mid-Cycle Review Meeting (“A208891N000DPM-MeetingMinutes02.pdf”), Meeting held on 3/1/2018 ¹⁷
Reserve Sample Memorandum	Reserve Sample Memorandum (“A208891N000DCR_ReserveSampleMemorandum”) by Sarah Yin, M.D., Completed on 6/26/2018 ¹⁸
OSIS Consult Response	OSIS Consult Response (“OSIS_CResponse_ANDA 208891 04052018_signed.pdf”) by Xingfang Li, M.D., RAC, Completed on 4/5/2018 ¹⁹
Clinical Review of Drug-Device Combination Product	Clinical Review of Drug-Device Combination Product (“A208891N000DCR_ClinicalReviewofDrugDeviceCombinationProduct”) by Michael Spagnola, M.D., Completed on 6/26/2018 ²⁰

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<http://panorama.fda.gov/document/preview?versionID=57ae284d005cebfb2ab12c906a1a907&ID=57ae284d005cebfa43a708f76d26f10c>

12

<http://panorama.fda.gov/document/preview?versionID=5b200bb00093d15be69dd92ac52de445&ID=5b200bb00093d15a2765e0b80f7fce25>

¹³ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f88106a223>

¹⁴ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f880f800a5>

¹⁵ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f8812d628b>

¹⁶ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f8813b9a80>

¹⁷ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881a2883c>

¹⁸ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881b38bc7>

¹⁹ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881a42095>

²⁰ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881b37e29>

2.3.2 Overview of Methods Used to Evaluate Data Quality and Integrity

Blinding	See Applicant’s Study Report ²¹ , Section 3.6.5, Applicant’s Study Protocol, Section 7.1 ²² , and Applicant’s Statistical Analysis Plan, Section 4.2 ²³
Randomization	See Applicant’s Study Protocol, Sections 7.5 ²⁴ and Applicant’s Statistical Analysis Plan, Section 4.2 ²⁵
Retention of Reserve Samples	See Applicant’s Study Report ²⁶ , Section 7.4.1

Reviewer’s Comments: *This was a double-blind, double-dummy design study. In order to maintain the double-blind study design, a double-dummy dosing technique was utilized and subjects were required to make one inhalation twice a day from each of 2 inhalers (one CRC749 and one Diskus® inhaler, containing active or placebo) for each study treatment. See Table 2.6 of this review for a summary of the treatments used to maintain the blind. In Controlled Correspondence 13-0422, it was noted that to conduct a double-blind and double-dummy study, generic sponsors may require placebo Reference Listed Drug (RLD) product (i.e. Placebo Diskus® DPI devices containing lactose only) and that producing these placebo RLD products may be challenging for a generic sponsor. Therefore, the Office of Generic Drugs, in concurrence with Division of Pulmonary, Allergy, and Rheumatology Products (DPAAP), did not recommend a double-blind, double-dummy clinical endpoint bioequivalence study in the FDA Draft Product Specific Guidance for Fluticasone Propionate; Salmeterol Xinafoate. In the same controlled correspondence, the Agency stated that if an applicant wants to conduct a double-blind, double-dummy design clinical bioequivalence study for this product, it is acceptable.*

The Applicant’s method for blinding and randomization was not initially acceptable according to the OSIS Establishment Inspection Report dated October 25, 2016 as there was a failure to maintain a sealed randomization schedule including blinding codes at the clinical sites prior to the dosing of subjects. The OSIS inspection report stated that each clinical site was sent a blinding code envelope for the reserve samples only after the study has commenced. After the study was completed and the database was locked, the CRO provided the study sites with a CD of the full randomization schedule (listing of unblinded treatment assignments for all subjects enrolled in the study) to facilitate regulatory inspections. After the study was completed, the investigators were provided with an Excel file with randomization information about treatment

²¹ <\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-report-body.pdf>

²² <\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-protocol.pdf>

²³ <\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-statistical.pdf>

²⁴ <\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-protocol.pdf>

²⁵ <\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-statistical.pdf>

²⁶ <\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-protocol.pdf>

assignment, kit number, subject number, and other dosing information. The full randomization codes for Study MGR001-3001 were managed centrally by the CRO through their IVRS/IWRS and that a manual containing complete instructions for use of the IVRS/IWRS was provided to each study site prior to the study start. Clinical sites were not aware that it was necessary for a copy of the full randomization schedule to be held at the clinical site as the randomization schedule managed centrally by the CRO (PPD Inc.) covered the entire study and was in place. The investigators stated that a “mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding” was in place prior to randomization of the first subjects and emergency unblinding envelopes were not necessary. The investigators felt that the safety of the subjects was not impaired. On 8/29/2016, OSIS requested that an ORA investigator return to the Princeton Center for Clinical Research clinical site to attempt to identify treatments for each subject through IVRS/IWRS audit trails records. The ORA investigator visited the clinical site but could not examine the audit trail records from IVRS/IWRS to confirm the blinding codes since there was no access to audit trail from the clinical site. Since blinding codes were not held at each clinical site before dosing the first subject and the ORA investigator could not access the IVRS/IWRS audit trails to confirm the identity of drug products that were administered to each subject, OSIS concluded in their inspection report that they cannot be assured that the subjects received the treatments as intended or described in the study report.

On December 8, 2017, the Division of Clinical Review sent a consult to the Office of Study Integrity and Surveillance (OSIS) to review the Applicant’s response to the Complete Response deficiency comments related to randomization schedule and blinding codes and provide an updated recommendation on the acceptability of the data from MGR001-3001. During the face-to-face meeting between Mylan and the Agency on March 1, 2018, Mylan provided additional information for the original blinding codes and the IVRS/IWRS system²⁷. In OSIS’ consult response completed on April 5, 2018, the OSIS reviewer concluded that subjects were dosed with the products as reported based on additional information provided by Mylan.²⁸ The Applicant’s methods of blinding and randomization are acceptable.

According to the October 25, 2016 OSIS inspection report, the Applicant’s method for selection of reserve samples was initially not acceptable. All clinical sites were instructed to retain reserve samples from the first shipment only by the Contract Research Organization (PPD, Inc.) on behalf of the Applicant. OSIS concluded that study MGR001-3001 violated 21 CFR 320.38 and 21 CFR 320.63 because the clinical sites did not retain reserve samples representative of each shipment of drug product used in the clinical endpoint study. The clinical sites noted that during a September 2013 meeting between the Applicant and OGD, the Applicant was provided guidance on the quantities of reserve samples. However, OSIS noted that it is uncertain based on the meeting minutes if any discussion occurred on selection of reserve samples from multiple shipments. OSIS recommended that the data from Study MGR001-3001 not be accepted for further agency review and a deficiency comment (Bioequivalence Deficiency Comment 48) regarding the failure to retain reserve samples from subsequent shipments was included in the Complete Response letter sent to the Applicant. In the Applicant’s Complete Response

²⁷ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881a2883c>

²⁸ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881a42095>

Amendment, the Applicant explained that the total number of shipments of blinded treatment packs from the Applicant's Clinical Supplies CRO to the clinical sites was 953. The Applicant provided the number of shipments of drug products to each clinical site. The Applicant also asserted that the selection of retained samples for Study MGR001-3001 was conducted in line with the "FDA Guidance for Industry: Handling and Retention of BA and BE Testing Samples (May 2004)," the "Draft FDA Guidance for Budesonide Inhalation Suspension (2012)," and in accordance with feedback provided by the Agency to the Applicant at a Type C meeting held in September 2013. At the September 2013 meeting with the Agency, Mylan sought specific guidance from the Agency related to the retention samples from bioequivalence studies, in particular for the clinical endpoint bioequivalence study MGR001-3001, since this was a multi-center study with a large number of clinical sites. Mylan noted in their response that they sought the guidance of the Agency because they believed that the May 2004 FDA Guidance, Handling and Retention of BA and BE Testing Samples, is related more to the retention of samples in a single center pharmacokinetic bioequivalence study (randomized at the site) than a multi-site clinical endpoint bioequivalence study (randomized centrally). The Applicant also stated that they requested guidance on two important aspects, the number of retained samples of each batch of study product by each clinical site and that retained samples were selected only from the first shipment made to each site given the nature of randomization and study product distribution to the sites. In the Pre-Meeting Briefing Package, the Applicant asked if the Agency agreed with the Applicant's proposal for retention of study products for Study MGR001-3001 which included as follows: 1) one 60 dose inhaler from each batch of study product supplied for use in the study would be retained by each site, 2) initial consignment sent to the clinical site would contain sufficient study product to support sampling on receipt, 3) the clinical site would select one inhaler from a series of blinded kits in such a manner to allow random sampling of every batch of test and reference (active and placebo) product supplied and these inhalers would form the bioequivalence testing sample, and 4) the clinical site would be instructed to comply with the OGD guidance in terms of handling and storage of samples. The Agency did not agree with the Applicant's proposal for retention of reserve samples for Study MGR001-3001. In the response to the Applicant, the Agency recommended that at least 50 units for each batch of test and reference product including placebo products with no less than 10 units per each batch per clinical site be retained for the bioequivalence studies. The Applicant was referred to Section 4(B) of the FDA Draft Product Specific Guidance for Budesonide Inhalation/Suspension for further guidance. The Applicant stated in their April 26, 2018 Information Request response that the Product Specific Guidance for Budesonide Inhalation/Suspension provides guidance on retaining samples per batch but does not suggest that there are additional requirements for retaining samples from multiple shipments. The Applicant also stated that the Agency provided no comment at or following the September 2013 Type C Meeting regarding a requirement to retain samples from shipments after the first shipment. In the response to the Complete Response Deficiency Comment, the Applicant stated that a total of approximately 1000 units of each study treatment were retained across all of the clinical sites and this is 20 times the amount of each study treatment required for release testing according to Agency feedback. With exception of retaining reserve samples from the first shipment of study products only to the extent Mylan received no further comment from the Agency, Mylan asserted that all other aspects of selection of retention samples were consistent with the May 2004 FDA Guidance, Handling and Retention of BA and BE Testing Samples.

On December 8, 2017, the Division of Clinical Review sent a consult to the Office of Study Integrity and Surveillance (OSIS) to review the Applicant's response to the Complete Response

deficiency comments related to the retention of reserve samples and provide an updated recommendation on the acceptability of the data from MGR001-3001. In OSIS' consult response completed on April 5, 2018, the OSIS reviewer stated that if used or unused drug products from subsequent shipments were available, they might serve as substitutes for reserve samples.

On March 15, 2018, DCR sent an Information Request to the Applicant requesting that the Applicant clarify if any used or unused drug products from subsequent shipments were currently available or have been destroyed. According to the Applicant's response to the IR question that was submitted to the Agency on March 22, 2018, Mylan stated that none of the clinical sites had leftover drug products as all unused drug products were destroyed. OSIS concluded that the information submitted in the Applicant's CR response to Bioequivalence Deficiency Comment 48 and the IR response dated March 22, 2018 are consistent with OSIS' original understanding of the reserve samples as documented in the inspectional findings. OSIS recommended that the Division of Clinical Review assess the potential impact of the lack of reserve samples for each subsequent shipment from all clinical sites as the study sites retained reserve samples only from the first shipment of drug products to each clinical site.

The Division of Clinical Review had multiple internal meetings with other individuals within the Office of Generic Drugs and the Office of Study Integrity and Surveillance. During these meetings, a thorough review and discussion regarding Mylan's method for retaining reserve samples was conducted. Since additional information and clarification regarding the processes used to retain samples were necessary, three Information Requests were sent by DCR and the Applicant responded to these Information Requests on April 26, 2018, May 25, 2018 and June 7, 2018. On June 11, 2018, an internal meeting was held between the OGD and OSIS to discuss the additional information that Mylan submitted to determine whether the information provided could support that the retention samples from the first shipment are adequate to represent the study products used in their clinical endpoint bioequivalence study. The meeting minutes for the internal meeting between OGD and OSIS held on June 11, 2018 outlines the information that was presented and the discussion that occurred at the meeting. The internal memorandum to file dated 6/26/2018 completed by Sarah Yim describes the discussions and outcome of the June 11, 2018 meeting.²⁹

In summary, there were five separate batches of clinical supplies made by the manufacturers of the clinical supplies and these five batches were all shipped to (b) (4) by the manufacturers in their entirety in separate individual shipments. The five batches of clinical supplies were packaged and labeled into blinded kits in their entirety in a single run by (b) (4) and all of the blinded kits were packaged and labeled prior to start of the study and shipment to individual sites. During the packaging and labeling process at (b) (4), each individual inhaler was labeled with its blinded kit number before being placed in a pouch which was then sealed before being packed in a carton and labeled with the same blinded kit number. Mylan stated that the pouching of each labeled inhaler performed by (b) (4) essentially made the blinded kit "tamper evident" from the time they were packaged and labeled. Staff at (b) (4) were not blinded to the identity of the blinded kits as the staff needed to know the identity of the kits in order to place the correct clinical supply into each kit.

²⁹ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881b38bc7>

Staff at (b) (4) were blinded to the allocation of any blinded kit to a particular study subject and (b) (4) could not send blinded kits other than those specified by the IVRS/IWRS system. Mylan states that the contents of a blinded kit could not be intentionally influenced by (b) (4) staff regardless of whether they were unblinded because the content of any blinded kit could not be influenced after the packaging and labeling were complete due to the inhalers being placed in a sealed pouch and blinded kit numbers were specifically requested for shipment to each site by the IVRS/IWRS system.

Since the study was double-blind, double-dummy, at least 14 kits of each of the five batches were included in the first shipment to each site allowing 10 kits (inhalers) per batch per clinical site to be randomly selected by the clinical site for retention. The initial shipment to each clinical site contained 72 kits (inhalers) irrespective of the treatment group that the first subject enrolled at a clinical site was assigned to and the initial shipment was sent to each clinical site before the clinical sites could begin enrolling any subjects. Once the first shipment was received, each clinical site identified an independent staff member who selected the samples to be retained from the initial shipment. The independent staff member was not directly involved in the conduct of study MGR001-3001 and the identity of this person was not communicated to Mylan or (b) (4). The independent staff member used the IVRS/IWRS system to select 10 kits from each batch to be retained from the initial shipment in a blinded fashion. The independent staff member selected the 10 kits from each batch to be retained without any guidance or instruction from Mylan, (b) (4) or any other individual. When selecting the 10 kits from each batch, the independent staff member was presented with a list of kits all from the same batch and were instructed to select 10 of the kits. The independent staff member repeated this process for the remaining four batches. The identity of the kits in the five lists were not disclosed thus making the independent staff member blinded to the identity of the kits when selecting the kits to be retained for reserve samples. The independent staff member's only role in the IVRS/IWRS system was to access the five lists of blinded kit numbers that were used to select the samples to be retained. The retained kits were physically separated from the general study supply by the independent staff member and maintained under appropriate storage conditions according to the study drug label. Following this process, the independent staff member did not perform any other duties related to subjects for this study.

The study products that was shipped in all subsequent shipments to all clinical sites were from the same five batches as the initial shipments. The study products in all subsequent shipments were packaged and labeled by (b) (4) at the same time as the initial shipments. Therefore, kits in both the initial and all subsequent shipments to any particular site originated from any part of the product batch. In other words, reserve samples were derived from a single run that packaged all study product batch and all kits were identical at release except for the unique kit number. Thus, OGD and OSIS concluded that the retention samples selected from the first shipment to each site were fully representative of the total study products used in the study irrespective of whether the study product was delivered in the initial or subsequent shipments. Since the reserve samples were representative of the study products used in the clinical endpoint study, OGD and OSIS determined that Study MGR001-3001 met 21 CFR 320.38 and 21 CFR 320.63 despite not retaining reserve samples from every shipment to every clinical site as recommended in the FDA Guidance "Handling and Retention of BA and BE Testing Samples" (May 2004) (Retention Sample BE Guidance). To the extent Mylan's approach to retaining reserve samples is not consistent with the Retention Sample BE Guidance, a departure from the guidance is appropriate because Mylan has demonstrated that its approach satisfied the

applicable statutory and regulatory standards. Thus, the Applicant's methods for retention of reserve samples is acceptable.³⁰

2.3.3 Were Trials Conducted in Accordance with Accepted Ethical Standards

- The study appears to have been conducted in accordance with accepted ethical standards.
- The IRB approved the original protocol and the informed consent form prior to the start of the study.

2.3.4 Evaluation of Financial Disclosures

- Form FDA 3454 is submitted.
- The Principal Investigator and all sub-investigators are listed.
- The applicant had no financial arrangements with the investigators to disclose.

2.4 Review of a Clinical Endpoint Bioequivalence Study

2.4.1 Detailed Review of a Clinical Endpoint Bioequivalence Study

Applicant's Study #	MGR001-3001
Title	A Randomized, Double-Blind, Double-Dummy, Parallel Group Study to Determine the Local Equivalence of Multiple Doses of MGR001 to Advair® Diskus® Administered Via Oral Inhalation in Adult Asthma Patients
Objectives	To confirm the local bioequivalence of MGR001 100/50 (Test) versus Advair® Diskus® 100/50 (RLD) after oral inhalation of single and multiple doses (4 weeks, twice a day [BID]) using clinical endpoints

2.4.1.1 Protocol Review

Protocol Version	Protocol Date	IRB Approval Date
Original	11/25/2013 ³¹	2/4/2014 ³² (b) (4)
Amendment 1	1/26/2015 ³³	1/29/2015 ³⁴ (b) (4)

Reviewer's Comments: The original version of the study protocol was approved by an Institutional Review Board (IRB) prior to study initiation (study period: 10/22/2014 to

³⁰ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881b38bc7>

³¹ \\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-protocol.pdf , p.4-64

³² \\cdsesub1\evsprod\anda208891\0021\m5\53-clin-stud-rep\535-rep-effic-safety-stud\asthma-and-copd\5351-stud-rep-contr\mgr001-3001\mgr001-3001-iec-irb-1.pdf

³³ \\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-protocol.pdf p.65-149

³⁴ \\cdsesub1\evsprod\anda208891\0021\m5\53-clin-stud-rep\535-rep-effic-safety-stud\asthma-and-copd\5351-stud-rep-contr\mgr001-3001\mgr001-3001-iec-irb-2.pdf

7/10/2015). Amendment 1 to the study protocol was approved by an IRB while the study was being conducted but prior to study completion and subject unblinding. A summary of the changes made in Amendment 1 of the study protocol can be found in Section 13 of Amendment 1 of the study protocol. The changes made to the study protocol in Amendment 1 included the following: broadening the pre-bronchodilator pulmonary function range for randomization from 60-85% predicted FEV₁ to 50-85% predicted FEV₁, increasing the upper limit of the Body Mass Index from 40 kg/m² to 45 kg/m², changing the duration of the run-in period from 28 days ±2 days to 28 days -7/+2 days thereby permitting the run-in period to be reduced to a minimum of 3 weeks, removing the requirement to perform a FSH test for females who have been amenorrhoeic for at least 2 years, and increasing the flexibility in the timing of the blinded sample size assessment so that it may be performed after approximately 250-300 subjects (instead of approximately 300 subjects) have completed Visit 5.

In the Applicant's Original Study Protocol, Inclusion Criterion 5 required subject's predicted FEV₁ at Visit 1 to be 60-85% if the subject was previously maintained on a LABA or 60-95% if the subject was on an ICS medication prior to enrollment in the study while in Amendment 1 to the Study Protocol, a subject's predicted FEV₁ must have been between 50-85% if the subject was previously maintained on a LABA or 55-95% if on ICS medication prior to enrollment in the study. This change in the required percent predicted FEV₁ at Visit 1 is acceptable since the required predicted FEV₁ are still within the Product Specific Guidance recommendation of 40-85% for the percent predicted FEV₁ during screening. The required percent predicted FEV₁ for Visit 2 and Visit 3 for Inclusion Criterion 5 was 60-85% in the Applicant's Original Study Protocol and changed to 50-85% in Amendment 1. This change is acceptable since the required predicted FEV₁ are still within the product specific guidance recommendation of 40-85% for the percent predicted FEV₁ during screening and on the first day of treatment. Additionally, it was determined that 505 subjects (out of the 2726 subjects who were screened and enrolled) had pre-bronchodilator percent predicted FEV₁ of 50-59.9% at Visit 1, 2, or 3 and that the distribution of these subjects was balanced based on the assignment ratio used in this study (145 subjects in test group, 146 subjects in reference group, 31 subjects in placebo group, 183 subjects were not randomized).

The change in the duration of the placebo run-in period from 28 ± 2 days to 28 -7/+2 days is acceptable since both meet the Product Specific Guidance recommended run-in period of 2 weeks. This change did not affect the washout period for any of the prohibited concomitant medications that could affect the analysis and results of this study. All washout periods for prohibited concomitant medications were acceptable based on the Product Specific Guidance recommendations.

According to the FDA Statistical review, the change in the timing of the blinded sample size re-estimation (BSSR) in the study protocol is acceptable.

The definition of potentially uncontrolled asthma requiring assessment by the Investigator was changed from FEV₁ below 60% of predicted value according to NHANES III predicted values in the Original Study Protocol to FEV₁ below 50% of predicted value according to NHANES III predicted values. This change is acceptable since the Study Protocol included other similar parameters (albuterol use, nighttime awakenings, peak expiratory flow rate) to those used in the pivotal studies (SFCA 3002 and SFCA 3003) of the NDA 021077. Both versions of the study

protocol allowed for sufficient safety measures to protect subjects and allowed for Investigators to evaluate and potentially remove subjects with worsening asthma during the study.

The conditions that if protocol specified spirometry inclusion criteria (FEV₁ and FVC) were not achieved during Visit 1, it could be repeated once at a rescheduled visit prior to Visit 2 and if FEV₁ reversibility was not achieved at Visit 1, then FEV₁ reversibility can be repeated at Visit 2 or at a rescheduled visit prior to Visit 3 were added to Section 8.1.1 of Amendment 1 of the study protocol. In Amendment 1 of the study protocol, the requirement that the spirometry was to be completed between 04:30 and 11:00 was added. Additionally, the conditions that if protocol specified spirometry inclusion criteria were not achieved, the FEV₁ spirometry could be repeated once at a rescheduled visit prior to Visit 3 and subjects were permitted two attempts to demonstrate reversibility during the run-in period (either at the scheduled visit or at rescheduled visits prior to Visit 3) were added to Section 8.2 of Amendment 1 of the study protocol. These changes in the study protocol are acceptable since subjects were required to meet spirometry inclusion criteria and reversibility prior to continuing into the double-blind treatment period.

The Original Study Protocol stated that spirometry measurements would be performed in accordance with the American Thoracic Society guidelines (1995) using standardized equipment to ensure quality, reproducibility, and repeatability. In Amendment 1 of the Study Protocol, an additional paragraph was added to Section 8.8 stating that spirometry data was assessed for quality by a vendor, independent of the Investigator, to ensure that the data was of sufficient quality for use in the study analyses. At Visit 1, if the FEV₁ acceptability criteria had not been fully met, either as determined by the investigator or according to vendor review (“Best Test Review”), then the subject was to be rescheduled to repeat the spirometry as soon as possible prior to Visit 2. Subjects who were unable to provide spirometry data which fully met the acceptability criteria at Visit 1 or at the repeat visit were screen-failed. At other visits, every effort was made to provide three technically acceptable and flow-volume loops. However, if the flow-volume loops were technically acceptable but the repeatability criterion was not met (i.e. “borderline acceptable”), then data from those flow-volume loops were valid and were included in the analyses. Subjects with “borderline acceptable” data at Visits 2 to 5 were allowed to continue in the study.

On March 15, 2018, DCR sent an Information Request to the Applicant requesting clarification and information about Pulmonary Function Test grading performed in the study. In their IR response, the Applicant explained that according to ATS guidelines, up to 8 spirometry measures (flow-volume loops) were made by each subject at each timepoint. Initial quality assessment was completed concurrently with the completion of each individual spirometry measurement at the site with the (b) (4) CT spirometer making a computerized evaluation which provided real time automatic identification of any measures that had major quality issues. Subsequently, a centralized over-read quality assessment was made by a Clinical Specialist and the purpose of the assessment was to ensure measures were of appropriate technical quality and that the appropriate loop had been selected from the valid measures performed. Every individual spirometry loop was assessed for quality and given a “Pulmonary Function Test Grade” by the Clinical Specialist. The “Pulmonary Function Test Grades” that could be assigned to FEV₁ measures collected at each timepoint were 1) “Acceptable” Grade – meets ATS and study specific criteria for acceptability and repeatability, 2) “Borderline Acceptable” Grade – meets ATS and study specific criteria for acceptability but not repeatability, and 3) “Unacceptable” Grade – does not meet ATS and study specific criteria for acceptability or repeatability.

Following the initial assessment of quality of each measure by the Clinical Specialist, an evaluation was made to determine whether the appropriate measure had been selected as the best (highest) FEV₁ as required by the Study Protocol. This process was termed “Best Test Review (BTR)” and was intended to identify any unacceptable measures that had been used to provide the best value for a particular timepoint. This process was required as the (b) (4) CT spirometer would report the highest value for FEV₁ as the best value, irrespective of the technical quality of the flow-volume loop from which it was derived. Any spirometry assessment that was graded as “Unacceptable” which means that the spirometry measure did not meet ATS guidelines for acceptability or repeatability was considered to be of poor technical quality and was not used in calculation of an endpoint for a subject. Spirometry assessments that were graded as “Acceptable” or “Borderline Acceptable” which means that the spirometry measure at least met the ATS guidelines for acceptability were suitable for use in the Applicant’s statistical analysis and was used in calculation of an endpoint for a subject. It is reasonable that if the investigators deemed a spirometry value “Unacceptable”, this spirometry value should not be included in the calculation of any endpoint since the criteria used during “Best Test Review (BTR)” was pre-specified and made at the time of testing. Since there is a component of acceptability that can be considered subjective, it is important that the determination was not subjectively based after seeing the result or knowing the treatment group that a subject was assigned to.

The Applicant used some spirometry assessments that were graded as “Unacceptable” in determining if subjects met all required inclusion criteria. This is not acceptable as spirometry assessments that were graded as “Unacceptable” did not meet ATS and study specific criteria for acceptability or repeatability. Several subjects were found to not meet Inclusion Criterion 6 (post-bronchodilator reversibility of at least 12%) after excluding spirometry assessments with an “Unacceptable” grade and these subjects were recommended to be excluded from the FDA PP populations.

The addition to the study protocol to include additional quality assessments including “Best Test Review” and Pulmonary Function Test grading is acceptable because it was added prior to subject unblinding and pre-specified criteria was used to determine the Pulmonary Function Test grade for all spirometry values.

The definition of the Full Analysis Set was changed in the different versions of the study protocol. In the Original Study Protocol, the Full Analysis Set was defined as “all randomized subjects who have taken study medication and have provided data for at least the FEV₁ AUEC₀₋₁₂ primary endpoint measured on Day 1” and in Amendment 1, the Full Analysis Set was defined as “all randomized subjects who have taken at least one dose of the study medication and have provided data for either the FEV₁ AUEC₀₋₁₂ primary endpoint measured on Day 1 (Visit 3), or the trough FEV₁ on Day 29 endpoint, including the corresponding baseline FEV₁ values.” Since the Full Analysis Set was used to detect sensitivity of the study by testing superiority, this population is analogous to the FDA’s mITT population. The FDA mITT population definition includes all randomized subjects who applied or used at least one dose of assigned drug product and was used in the FDA superiority analysis.

All other changes to the study protocol have been reviewed and are acceptable.

2.4.1.2 Study Design

2.4.1.2.1 Study Visits and Procedures

Table 2.4 outlines the study visits and procedures during each visit.

Table 2.4: Study Schedule

	Visit 1 Screening Visit (28 [-7/+2] ^a Days Pre-Visit 3)	Visit 2 Run-In Visit (3 to 7 Days Pre-Visit 3)	Visit 3 Day 1											Visit 4 Day 15 (±2 Days)	Visit 5 Day 29 (±2 Days) EOT and Follow-Up			
			-30 min	0 h	0.5 h	1 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h		-30 min	0 h	Post Spirometry	
Informed consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IVRS/IWRS registration/entry	X	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Medical history (including asthma/atopy) and demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Concomitant medication	X	X	X	-	-	-	-	-	-	-	-	-	-	X	X	-	-	-
Full physical examination (including height and weight at Screening)	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Inclusion/exclusion criteria	X	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Confirm no SABA for 6 hours and other background medications that day	X	X	X	-	-	-	-	-	-	-	-	-	-	X	X	-	-	X
12-Lead ECG/BP/PR	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Spirometry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
FEV ₁ reversibility	X	X ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Laboratory safety tests (blood and urine) including FSH ^c	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Urine pregnancy test (if applicable)	X	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Inhaler training	X	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Dispense PEFR meter and diary and rescue medication	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PEFR and complete daily diary	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Diary data review	-	X	X	-	-	-	-	-	-	-	-	-	-	X	X	-	-	-
Placebo run-in	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Compliance/accountability	-	X	X	-	-	-	-	-	-	-	-	-	-	X	X	-	-	-
Randomization	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Subject takes study drug in clinic	X	X	-	X	-	-	-	-	-	-	-	-	X ^d	X	-	-	-	-
Device questionnaire	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-
Review adverse events	-	X	X	-	-	-	-	-	-	-	-	-	-	X	X	-	-	X

Abbreviations: BP, blood pressure; ECG, electrocardiogram; EOT, end of treatment; FEV₁, forced expiratory volume in 1 second; FSH, follicle stimulating hormone; h, hour; IVRS/IWRS, Interactive Voice Response/Web Response system; min, minutes; PEFR, peak expiratory flow rate; PR, pulse rate; SABA, short-acting β₂-agonists.

^a Screening can start 21 days up to 30 days prior to randomization.

^b Only if not assessed or <12% reversible at screening visit.

^c Screening only.

^d Evening dose may have been taken in clinic after completion of 12-hour spirometry.

Source: Applicant’s Study Report, Section 3.7.1, Table 3-4

Reviewer’s Comments: *The study design is mostly consistent with the recommendations in the FDA Draft Product Specific Guidance for Fluticasone Propionate and Salmeterol Xinafoate. There is a minimum three week run-in period followed by a four week treatment period and this is acceptable as the Product Specific Guidance only recommends at least a two week run-in period followed by a four week treatment period.*

In the Original Study Protocol, the visit window for the Screening Visit was defined as Day -28 ± 2 days while the visit window for the Screening Visit according to Amendment 1 was Day -28

-7/+2 days. According to the Applicant's response to IR question 6 that was submitted on 2/1/2018, forty seven subjects in the Applicant's Per Protocol Set completed their Visit 1 (Screening Visit) outside of the pre-specified visit window for Visit 1 (Day -28 ± 2 days in the Original Protocol and Day -28 -7/+2 days in Amendment 1). The Applicant stated in their IR response that since the run-in period was used to confirm eligibility of subjects for the study and to provide the necessary baseline data for the primary endpoint data, it is the length of the run-in period and not the date of Visit 1 (Screening Visit) that was critical to consider. The Applicant stated that the length of the run-in period was set around a 28 day target based on the contents of the placebo inhaler although it was clear that the intended purpose of the run-in period could be achieved over a shorter duration. A wider window was used by the Applicant in considering whether to exclude a subject from the Per Protocol Set based on the date of the Screening Visit or duration of the run-in period. The Applicant decided that fourteen days was the minimum period for the run-in period as this was the minimum recommended duration for the run-in period according to the Product Specific Guidance. The Applicant excluded one subject (Subject (b) (6)) from their Per Protocol Set because this subject had a run-in period of only 10 days. Both of the Applicant's definition for the visit window for the Screening Visit are acceptable since the Product Specific Guidance does not recommend a specific visit window for the Screening Visit and the study had a minimum three week run-in period which is longer than the recommended two week duration of the run-in period according to the Product Specific Guidance. Additionally, both versions of the Study Protocol included acceptable washout periods for all prohibited concomitant medications. It is acceptable that the Applicant excluded Subject (b) (6) from their Per Protocol Set since this subject had a run-in period that was less than the recommended length in the Product Specific Guidance. No additional subjects were recommended to be excluded from the FDA Per Protocol Population based on out of window Screening Visit.

According to Table 3-4 from Section 3.7.1 of the Study Report, Visit 5 is listed as occurring on Day 29 with a visit window of ± 2 days. Several subjects who were included in the Applicant's PPS were noted to have their Visit 5 outside of the Day 27 to Day 31 visit window specified in the Applicant's study protocol. As a result, multiple Information Requests were sent to the Applicant requesting clarification from the Applicant about out of window study visits for the Visit 5. In the Applicant's response to Question 7 sent to the Agency on 2/1/2018, the Applicant explained that "The protocol set a window of ±2 days for the scheduling of Day 29 in order to focus investigators into scheduling their subjects into as narrowly-defined window as possible. However, when considering whether to class subjects as major protocol violators resulting in exclusion of their data from sensitivity analyses, wider windows were applied for deviations, especially those above the 29+2 days limit." The Applicant later explained that out of window study visit for Visit 5 cases were documented as protocol deviations and the significance of each deviation was decided on a treatment blinded case-by case review. Since protocol deviations for out of window study visit for Visit 5 affected only the Day 29 endpoint and the Applicant's definition of the PPS required protocol deviations to affect both co-primary endpoints to exclude a subject from the PPS, the subjects with out of window study visit for Visit 5 were included in the Applicant's PPS. The Applicant's justification why subjects with out of window study visits for Visit 5 were included in their PPS is not acceptable. The Applicant's definition for their PPS is not acceptable as protocol deviations that affected either co-primary endpoint should have resulted in a subject being excluded from the Applicant's PPS. Additionally, the Applicant's explanation that the study protocol set a visit window of ±2 days for Visit 5 but a different visit window was used when determining protocol deviations is unacceptable. The

Applicant did not document any different visit window for Visit 5 when determining protocol deviations. Subjects whose Visit 5 occurred outside of the pre-specified visit window for Day 27 to Day 31 were recommended to be excluded from the FDA PP and FDA Day 29 PP populations.

Spirometry data (trough FEV₁) was collected during Visit 4 (Day 15 ± 2 days) of the study. Visit 4 took place in the middle of the double-blind treatment period. According to Section 4.1.4.2.4 of the Study Report, if both the 30 minute predose and 0 hour predose FEV₁ measurements for Visit 5 were missing, then the non-missing predose FEV₁ measurements measured at Day 15 (Visit 4) were carried forward for the co-primary endpoint of “Change from baseline in trough FEV₁ at Week 4” for both the bioequivalence and superiority analysis. According to the Applicant’s response to IR question 8 that was submitted on 2/26/2018, fifteen subjects had spirometry data carried forward from Day 15 (Visit 4) or an Early Termination Visit for the Day 29 endpoint. The Applicant stated that spirometry data was only carried forward to provide the Day 29 trough FEV₁ assessment if the Day 29 trough FEV₁ measurement was not performed due to subject discontinuation. In the Applicant’s response to IR question 7 that was submitted on 2/1/2018, the Applicant stated that it is evident from visual inspection of the data in this study that the trough FEV₁ at Day 15 is not dissimilar from that at Day 29 suggesting that the effect of the study treatments has plateaued already between Day 15 and Day 29. It is not acceptable to carry forward spirometry data for the Day 29 trough FEV₁ assessment for the per protocol population if the Day 29 trough FEV₁ measurement was not performed because a subject discontinued from the study unless the reason that the subject discontinued from the study was due to a lack of efficacy from the study drug. By carrying forward spirometry data for the Day 29 endpoint from the Day 15 visit, the bioequivalence evaluation would not be conducted in a relevant and consistent manner as there would be a significant difference in the time of co-primary endpoint evaluation and number of doses of study drug received during the treatment period. Subjects who had trough FEV₁ measurements carried forward from the Day 15 visit could have received as few as 21 doses (75% treatment compliance for the first 14 days of treatment period). It is felt that 21 received doses are not enough doses to accurately reflect the effect of the study drug. Additionally, subjects who had 125% treatment compliance with the study drug at Day 29 would have received 70 doses of the study drug and the endpoint evaluation for the Day 29 endpoint would not have been conducted in a consistent manner if some subjects received almost three times the number of doses of study drug as other subjects received (70 doses of study drug received vs 21 doses of study drug received). Therefore, subjects who had spirometry data carried forward from Day 15 (Visit 4) were recommended to be excluded from the FDA PP and FDA Day 29 PP populations.

According to the Study Protocol and the Study Report, the visit window for Visit 5 was Day 29 ± 2 days. In the Applicant’s Study Protocol and Statistical Analysis Plan, it was not prespecified whether out of window study visit for Visit 5 were considered major protocol deviations. However, several subjects in the Applicant’s Per Protocol Set were identified to have completed their Visit 5 out of the pre-specified visit window of Day 27 to Day 31. The Applicant explained in one of their IR responses that since they defined the Per Protocol Set as all subjects in the Full Analysis Set who had not violated or deviated from the protocol in such a way that could have affected the outcome of the FEV₁ assessment for both primary endpoints, subjects who completed their Visit 5 out of the pre-specified visit window for Visit 5 were included in the Applicant’s Per Protocol Set since this protocol deviation could only affect the Day 29 endpoint and could not affect the Day 1 endpoint. The Applicant stated that the study protocol set a window of ± 2 days

for scheduling of the Day 29 to focus the investigators into scheduling their subjects into as narrowly defined window as possible but wider windows were applied when considering whether to classify subjects as major protocol deviations resulting in exclusion of data for sensitivity analyses. The Applicant explained in their IR response that wider windows were used for visit windows for sensitivity analyses because “the effect of active treatments on FEV₁ has plateaued within that time and so modestly longer exposures to the study drugs were not anticipated to have a significant impact on the trough FEV₁ beyond Day 29.” Although the Applicant stated that wider windows were used in determining whether subjects should be included in sensitivity analyses, the use of wider windows including the definition of the wider visit window used was not documented in the Study Protocol or Statistical Analysis Plan. The Product Specific Guidance does not recommend a specific visit window for the Week 4 endpoint. The Division of Clinical Review has historically and consistently considered out of window study visits that contribute to primary endpoint evaluation as major protocol deviations. The Division of Clinical Review has historically excluded subjects from the FDA Per Protocol Population that do not meet the study protocol’s pre-specified visit windows that are appropriate and contribute to primary endpoint evaluation as a measure to ensure that the bioequivalence evaluation is being conducted in a relevant and consistent manner when there could be a potentially significant difference in the timing of the primary endpoint evaluation. Therefore, the Applicant’s justification for why subjects with out of window study visits for Visit 5 or use of wider windows that were not pre-specified in the Study Protocol or Statistical Analysis Plan is not acceptable. Based on the Applicant’s responses to IR question 7 that was submitted on 2/1/2018 and IR question 6 (2/26/2018), eighty five subjects who were included in the Applicant’s Per Protocol Set were recommended to be excluded from the FDA Per Protocol Population and FDA Day 29 Per Protocol populations. These subjects were recommended to be included in the FDA Day 1 Per Protocol population since the major protocol deviation of out of window Visit 5 would not affect evaluation of the Day 1 endpoint.

According to the Study Report, subjects were not supposed to take the study medication the morning of the Visit 5 (last day of double-blind treatment period). The subject’s last dose of study medication should have occurred on the evening of the day prior to Visit 5 (one calendar day difference between day of last dose of study medication and Visit 5). During review of the study, several subjects were discovered to have more than one calendar day between their last dose of study medication and Visit 5. An IR was sent to the Applicant seeking clarification and details on why some subject’s last dose of the study medication did not occur the evening before the Last Day Clinic Visit as outlined in the Study Protocol and Study Report. In the Applicant’s response to Question 1 sent to the Agency on 2/26/2018, the Applicant provided a list of 10 subjects who had greater than 4 days between the last dose of the study medication and final lung function assessment at Visit 5. In the same IR response, the Applicant explained that the study compliance requirement of 75% to 125% with the study drug in the double-blind treatment period was used to define significant deviations from the protocol designated investigational drug treatment plan rather than a time window between the last dose of study medication and spirometry assessments. This is reasonable because there was no pre-specified limit on the time between the last dose of study medication and Visit 5 in the Study Protocol and the Applicant used study compliance instead to ensure subjects had received the appropriate number of days of study medication to be included in their Per Protocol Set.

According to Section 4.2.1.6.1 “Treatment Compliance” of the Study Report, the expected last dose in the double-blind treatment period for subjects who completed Visit 5 was the day prior to

Visit 5. It is acceptable that the subject's last dose of study medication in double-blind treatment period occurred on the evening on the day before Visit 5. Thus, the expected number of doses of the double-blind treatment medication based on the Applicant's study design is 56 doses since there are 28 days of expected dosing as the last dose of the study medication occurred on the evening prior to Visit 5 and the double-blind treatment medication was taken twice a day. Several subjects were identified to have more than one calendar day between their last dose of study medication and Visit 5 which is when co-primary endpoint evaluation occurred. An IR was sent to the Applicant seeking clarification and details why some subject's last dose of the study medication did not occur the evening before Visit 5 as outlined in the Study Report. In the Applicant's response to Question 1 sent to the Agency on 2/26/2018, the Applicant acknowledged that a prolonged period between the date of the last dose of study medication and date of Visit 5 may have an impact on trough FEV₁. However, the Applicant explained that for the purpose of identifying protocol deviations that warrant exclusion of subjects from the Per Protocol Set, the Applicant used treatment compliance limits that were pre-specified in the study protocol (e.g. 75-125% compliance with the study medication during the double-blind treatment period) to ensure that subjects had received an appropriate number of doses of the study medication. The Applicant also remarked that significant deviations based on either the compliance criteria or number of days between the last dose of the study medication and primary endpoint evaluation would not have excluded subjects from the Applicant's Per Protocol Set. The Applicant's Per Protocol Set was defined such that only protocol deviations that could have affected both primary endpoints would lead to subject's exclusion from the Per Protocol Set. The Applicant identified and provided a list of ten subjects who had ≥ 4 days between the last dose of the study medication during the double-blind treatment period and when the primary endpoint of trough FEV₁ was measured at Visit 5. Of the ten subjects identified by the Applicant in their IR response, seven subjects were in the reference group, one subject was in the test group, and two subjects were in the placebo group. All ten subjects were included in the Applicant's Per Protocol Set. Although it is unusual to have subjects with greater than four days between the last dose of study medication and primary endpoint evaluation according to the study design, this is acceptable and no subject adjustments were recommended to the FDA Per Protocol populations based on this issue because there was no pre-specified limit on the time between the last dose of study medication and Visit 5 in the Study Protocol or in the Product Specific Guidance. The Applicant's justification to use study compliance to ensure that subjects received roughly the same number of doses of double-blind treatment medication in each treatment group and to ensure the bioequivalence analysis was conducted in a relevant and consistent manner is acceptable.

According to Applicant's response to IR question 12 that was submitted on 2/26/2018, the Applicant does not believe that spirometry performed outside of a ±1 hour window for the Day 29 trough FEV₁ endpoint as stated in the Study Protocol is a valid reason to exclude subjects from the Day 29 Per Protocol Set.³⁵ Instead, the Applicant stated that a ±2 hour window for the Day 29 trough FEV₁ endpoint as pre-specified in the "Out-of-window (OOW) Sensitivity Analyses" section of the Statistical Analysis Plan was used in the Applicant's relevant sensitivity analyses submitted in the Applicant's response to IR question 12 and would allow for the

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predictable situation that some patients would attend the clinic earlier or later than stated in the protocol.³⁶ The Applicant’s justification to use a ±2 hour window for the Day 29 trough FEV₁ endpoint as pre-specified in the “Out-of-window (OOW) Sensitivity Analyses” section of the Statistical Analysis Plan instead of ±1 hour time window for the Day 29 trough FEV₁ endpoint as stated in the Study Protocol is acceptable. The Product Specific Guidance does not recommend that spirometry assessments be performed in certain time windows and it is not likely that use of a wider ±2 hour window for the Day 29 trough FEV₁ endpoint will bias the statistical results despite diurnal variations in lung function. According to the Applicant’s response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018, several subjects had Day 29 out of window spirometry assessments in which their Day 29 (Visit 5) average pre-dose assessments are not within ±2 hours of Day 1 (Visit 3) average pre-dose time-points and/or their pre-dose assessments were completed after 12 noon on Day 29 (Visit 5) and these subjects were recommended to be excluded from the FDA PP and FDA Day 29 PP populations.

All other procedures and their timing outlined in the study schedule are acceptable.

2.4.1.2.2 Treatment Arms

Subjects were randomized to receive one of three treatments: MGR001 100/50 containing 100 mcg Fluticasone Propionate and 50 mcg Salmeterol Xinafoate in the CRC749 inhaler (Test product), Advair® Diskus® 100/50 containing 100 mcg Fluticasone Propionate and 50 mcg Salmeterol Xinafoate in the Diskus® inhaler, or Placebo containing lactose only in placebo inhalers that matched the CRC749 inhaler or Diskus® inhaler (Placebo). Details of each treatment arm are provided in the table below.

Table 2.5: Treatment Arms

Treatment Arms	Test	Reference	Placebo
Product Name	MGR001 100/50	Advair® Diskus® 100/50	A) Placebo (lactose only) for CRC749 B) Placebo (lactose only) for Diskus®
Manufacturer	MGR Dublin	GSK	A) MGR Dublin (b) (4)
Lot No.	Batch 1: 631-001 Batch 2: 631-002	4ZP4083	A) 605-039 B) E113247-003I002
Manufacture Date	Batch 1: 08May2014 Batch 2: 25Jun2014	Not available	A) 20Dec2013 B) 19Jul2013
Expiration Date	Batch 1: 07Nov2015 Batch 2: 24Dec2015	30Sep2015	A) 19Dec2015 B) 19Jul2016
Strength	100/50 mcg	100/50 mcg	Not applicable
Dosage Form	Dry powder inhaler	Dry power inhaler	Dry powder inhaler
Route of	Oral inhalation	Oral inhalation	Oral inhalation

³⁶ <\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-statistical.pdf>

administration			
Inhaler	CRC749	Diskus®	A) CRC749 B) Diskus®
Dose administered	One inhalation	One inhalation	One inhalation
Dosing regimen	BID	BID	BID
Dosing time	Morning and Evening	Morning and Evening	Morning and Evening
Dosing duration	28 (±2) days	28 (±2) days	28 (±2) days
Assignment ratio	5	5	1

Source: Applicant’s Summary of Clinical Efficacy – Tables – Appendix 1, Module 2.7.3, Table 7

In order to maintain the double-blind study design, a double-dummy dosing technique was utilized and subjects were required to take one inhalation twice a day from both of the Diskus® inhaler and CRC749 inhaler for each study treatment. Subjects were to use the inhalers in the same order each time. The following table provides details of the study treatments used to maintain the double-blind in the study.

Table 2.6: Study Treatments to Maintain the Blind

Treatment Identifier	Treatment Description	Diskus® inhaler 1 inhalation	CRC749 inhaler 1 inhalation
A	MGR001	Placebo	Active
B	Advair® Diskus®	Active	Placebo
C	Placebo	Placebo	Placebo

Source: Applicant’s Study Report, Section 9.5.1, Table 9.1

Reviewer’s Comments: *The treatment application and dosing regimen are consistent with the recommendations in the approved labeling of the RLD (Advair Diskus®). Subjects were instructed not to take the study medication on the morning of Visit 5 so the dosing duration was 28 (±2) days and the dosing duration of 26 to 30 days is acceptable. Two batches of the test product were used in the study and all batches of test, reference, and placebo product had not expired prior to the last date that all subjects completed the study (July 10, 2015).*

As detailed in the Agency’s response to Question 1 in Controlled Correspondence 13-0422, the Applicant’s proposal for the clinical endpoint study in Controlled Correspondence 13-0422 included double blinding in their study design. In order to conduct a double-blind and double-dummy clinical endpoint study, the generic sponsor would be required to obtain placebo RLD product (e.g. Diskus® DPI inhalers containing lactose only) and OGD felt that producing these placebo RLD product may be challenging for a generic sponsor. Therefore, OGD (in concurrence with the Division of Pulmonary, Allergy, and Rheumatology Products) did not recommend a double-blind, double-dummy clinical endpoint study in the Product Specific Guidance for Fluticasone Propionate and Salmeterol Xinafoate. The Applicant’s proposal for a double-blind, double-dummy clinical endpoint study was found acceptable in Controlled Correspondence 13-0422 and this difference in the study design from that recommended in the Product Specific Guidance is acceptable.

2.4.1.2.3 Study Population Selection

This study enrolled 1871 male and non-pregnant female patients ≥ 18 years of age with a clinical diagnosis of asthma. Subjects must have had a physician-diagnosed history of asthma for at least 12 weeks prior to screening and had $\geq 12\%$ reversibility of FEV₁ within 30 minutes following 360 mcg of albuterol. According to the Original Study Protocol, subjects must have had screening visit (Visit 1) pre-bronchodilator FEV₁ of 60% to 85% (60% to 95% for subjects taking inhaled corticosteroid or long-acting β_2 -agonist prior to screening) of the predicted value, run-in visit (Visit 2) pre-bronchodilator FEV₁ of 60% to 85% of the predicted value, and mean of pre-dose Day 1 (Visit 3) FEV₁ of 60 to 85% of the predicted value according to NHANES III reference values. In Amendment 1 to the Study Protocol, subjects must have had screening visit (Visit 1) pre-bronchodilator FEV₁ of 50% to 85% (55% to 95% for subjects taking inhaled corticosteroid or long-acting β_2 -agonist prior to screening) of the predicted value, run-in visit (Visit 2) pre-bronchodilator FEV₁ of 50% to 85% of the predicted value, and mean of pre-dose Day 1 (Visit 3) FEV₁ of 50 to 85% of the predicted value according to NHANES III reference values. See Applicant's Original Study Protocol and Study Protocol Amendment 1, Section 6.3 for the full list of the Applicant's inclusion and exclusion criteria for all versions of the study protocol.³⁷

Reviewer's Comments: *The Applicant's inclusion and exclusion criteria are similar to the inclusion and exclusion criteria in the FDA Draft Product Specific Guidance for Fluticasone Propionate and Salmeterol Xinafoate.*

The study included subjects ≥ 18 years old while the Product Specific Guidance recommends including subjects ≥ 12 years of age. Mylan believed that recruitment of subjects who are minors (< 18 years old) is not required to fulfill the objectives of the study and may cause ethical issues with some IRBs due to issues of consent. In Controlled Correspondence 13-0422, the Office of Generic Drugs told Mylan Pharmaceuticals that their proposed differences in inclusion criteria enrolling subjects 18 years and older instead of the product specific recommended of 12 years and older is acceptable. This difference in the minimum age of subjects enrolled in the study is acceptable.

In the Applicant's Original Study Protocol, Inclusion Criterion 5 required a subject's predicted FEV₁ at Visit 1 to be 60-85% if the subject was previously maintained on a LABA or 60-95% if on an ICS medication while in Amendment 1 to the Study Protocol, subject's predicted FEV₁ must have been between 50-85% or 55-95% if the subject was previously maintained on a LABA or an ICS medication. The required percent predicted FEV₁ for Visit 2 and Visit 3 for Inclusion Criterion 5 was 60-85% in the Applicant's Original Study Protocol and changed to 50-85% in Amendment 1. Mylan was concerned about ethical issues with the inclusion of severe asthmatics with FEV₁ 40% to $< 50\%$ of predicted) into a placebo controlled study and hence proposed a patient population with less severe asthma. The FDA Draft Product Specific Guidance for Fluticasone Propionate and Salmeterol Xinafoate recommends that subjects have a pre-bronchodilator FEV₁ of $\geq 40\%$ and $\leq 85\%$ of the predicted value during the screening visit and

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on the first day of treatment. This difference in the required predicted FEV₁ is acceptable as the distribution of subjects based on severity of FEV₁ was balanced based on the assignment ratio used in this study and it is unlikely that not including subjects with more severe asthma (40% to <50% of predicted FEV₁) would bias or affect the results.

The Study Protocol stated that standardized, centralized spirometry equipment was provided to the clinical sites and the formulas (NHANES III) used to calculate predicted FEV₁ were pre-loaded into the spirometry equipment. As explained in Section 3.4 of the FDA Statistical Review completed by Youngsook Lee, Ph.D. on June 12, 2018, the FDA statistician independently calculated the percent predicted FEV₁ values using the demographic information (age, height, race, and sex) and the formulas from NHANES III. The FDA statistician compared their percent predicted FEV₁ values for each subject with the percent predicted FEV₁ values provided by the Applicant in their submitted materials. Several discrepancies were noted and in their IR response submitted to the Agency on February 26, 2018, the Applicant explained that all discrepancies in percent predicted FEV₁ value was due to incorrectly entered demographic information. The Applicant provided updated correct demographic information for those subjects with discrepancies in percent predicted FEV₁ value. The FDA statistician then verified that the same and correct formulas from NHANES III were used at each clinical site and the FDA statistician used the updated correct demographic information to whether each subject met Inclusion Criterion 5.

Since there were different predicted FEV₁ requirements for Inclusion Criterion 5 based on the version of the study protocol, the FDA statistician used the predicted FEV₁ requirements to determine a subject's status for Inclusion Criterion 5 based on the version of the study protocol that each subject was enrolled under. For example, if a subject was enrolled in the study under the Original Study Protocol, then that subject must have met the predicted FEV₁ requirements specified in the Original Study Protocol and if a subject was enrolled in the study under the Amendment 1 to the Study Protocol, then that subject must have met the predicted FEV₁ requirements specified in Amendment 1 to the Study Protocol.

Both versions of the study protocol required subjects to meet a predicted FEV₁ twice during the screening period (Visit 1 and Visit 2) and on the first day of the treatment period (Visit 3) while the Product Specific Guidance only recommends that subjects meet the predicted FEV₁ once during the screening period and on the first day of the treatment period. Since the Product Specific Guidance recommended that subjects only must meet the predicted FEV₁ once during the screening period, subjects were included in the FDA PP populations if they met the predicted FEV₁ requirements for Inclusion Criterion 5 for the version of the study protocol that they were enrolled under at Visit 1 or Visit 2 (once during screening period) and at Visit 3 (first day of treatment period). If a subject did not meet the predicted FEV₁ requirements for Inclusion Criterion 5 at Visit 1 or Visit 2 but met the predicted FEV₁ requirements at the other visit during the screening period, that subject was recommended to be included in the FDA PP populations. Several subjects were recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations since they did not meet Inclusion Criterion 5 according to the FDA statistician's calculations.

The inclusion criteria for the study required subjects to have a post-bronchodilator reversibility of at least 12% within 30 minutes of 360 mcg of albuterol while the Product Specific Guidance recommended an inclusion criterion of $\geq 15\%$ reversibility of FEV₁ within 30 minutes following

360 mcg of albuterol inhalation. The difference is the percentage reversibility that is needed to be included in the study is acceptable as the definition of a bronchodilator response to diagnose asthma is not standardized. In clinical practice, patients with asthma will be diagnosed with asthma if they have an increase in FEV₁ of 12% or more, accompanied by an absolute increase in FEV₁ of at least 200 mL after receiving a bronchodilator.

Exclusion Criterion 17 of the study protocol states that a subject should not be enrolled in the study if they have other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results and, in the judgment of the study investigator, would have made the subject inappropriate for entry into the study. According to Listing 16.2.2-1.2 “Subjected Excluded from Analysis Sets – Randomized Set”, six subjects were excluded from the Applicant’s Per Protocol Set because the subject had a severe acute or chronic medical condition that in the judgment of the study investigator, would make the subject inappropriate for entry into the study. All six subjects completed double-blind treatment period. In the Applicant’s response to Question 10 of the Complete Response Amendment sent to the Agency on 8/28/2017, the Applicant explained that these six subjects were excluded from the Applicant’s Per Protocol Set due to Exclusion Criterion 17. These subjects had the presence of reported adverse events of an allergic nature affecting the upper airways that were symptomatic at the time of screening or baseline which were not present for the whole study. It was felt that these adverse events may have an impact on the screening and/or baseline spirometry and therefore, could have affected a subject’s eligibility for the study or both primary endpoints. The adverse events reported by these six subjects that lead to their exclusion from the Applicant’s Per Protocol Set include: upper-airway cough syndrome, rhinorrhea, nasal congestion, upper respiratory tract congestion, allergy to animal, and rhinitis allergic. Several other subjects were identified in the ae.xpt data set with the same adverse events and were included in the Applicant’s Per Protocol Set. The decision to exclude these six subjects from the Applicant’s Per Protocol Set was made prior to unblinding of the study and this minimizes the chances for bias. The number of subjected excluded due to Exclusion Criterion 17 was relatively balanced between the test group (two subjects) and the reference group (four subjects). The Applicant’s decision to exclude six subjects because of Exclusion Criterion 17 is acceptable. No additional subject adjustments were recommended to the FDA Per Protocol populations because of Exclusion Criterion 17.

The Applicant added several inclusion criteria and exclusion criteria which are not recommended in the Product Specific Guidance, all of which are acceptable. All of the Applicant’s inclusion and exclusion criteria are acceptable.

Criteria for removal from the study	☒ Acceptable See Applicant’s Study Report, Sections 3.5.2.4, 3.5.2.5, and 3.5.4.3 ³⁸ ☐ Not Acceptable and Applicant’s Study Protocol, Sections 6.3.4, 6.3.5, and 8.6 ³⁹

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³⁹ <\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-protocol.pdf>

Restrictions during the study	☒ Acceptable See Applicant's Study Report, Sections 3.5.1 to 3.5.3, 3.5.4.2, and ☐ Not Acceptable 3.6.6 ⁴⁰ and Applicant's Study Protocol, Sections 6.4, 6.5, 7.6, and 8.10 ⁴¹
Treatment compliance	☒ Acceptable See Applicant's Study Report, Sections 3.6.7, and 4.2.1.6 ⁴² ☐ Not Acceptable

Reviewer's Comments: During the study, each subject's asthma control was assessed at each study visit. If during the study including the placebo run-in period, a subject's peak expiratory flow rate (PEFR) decreased by 20% or more from their baseline PEFR on 2 consecutive days, the subject had persistent worsening of their asthma symptoms, or found their asthma symptoms unacceptable, subjects were instructed to call the clinical site. If a subject called the clinical site for any of the reasons listed previously, the Investigator (or medically qualified designee) was to speak with and assess the subject. If required (e.g. in subjects with worsening asthma control), the clinical site arranged for subjects to be evaluated by the Investigator in the clinic as soon as possible. Potentially uncontrolled asthma that required assessment by the Investigator was defined as any subject who met any of the following criteria: 1) FEV₁ below 50% of predicted values according to age, height, race, and sex using NHANES III predicted values, 2) fall in either morning or evening PEFR on 2 consecutive days to less than or equal to 80% of their mean baseline PEFR, 3) albuterol use (except for prevention of exercise-induced asthma) on more than 3 occasions/day for at least 3 consecutive days, 4) at least 2 night-time awakenings/week due to asthma requiring treatment with albuterol, 5) unacceptable respiratory symptoms or clinical worsening leading to the need for any new asthma maintenance or emergency medication beyond that allowed in the study, or 6) hospitalization or emergency room visit for asthma-related symptoms. Subjects displaying potentially uncontrolled asthma at any time during the placebo run-in period or during the double-blind treatment period visited the clinic site for assessment by the Investigator. The Applicant's criteria for removal of subjects due to worsening asthma listed in their study protocol is different than in the pivotal studies (SFCA 3002 and SFCA 3003) of the NDA 021077.

In the pivotal studies of the NDA, a subject would be discontinued from the study if during the placebo run-in period, the subject had more than 3 days in which they used greater than 12 puffs per day of rescue medication use (Ventolin inhaler) if the subject previously used inhaled corticosteroids, had more than 3 days with 6 puffs per day of rescue medication use if the subject previously used salmeterol, or had more than 3 nights with awakenings due to asthma requiring treatment with the Ventolin inhaler. During the treatment period, subjects in the two pivotal studies were discontinued from the study for lack of efficacy if they met any of the following criteria in the 7 days immediately preceding each clinic visit: 1) no more than 2 days in which $\geq$ 12 puffs per day of Ventolin use, 2) no more than 2 nights in which awakenings due to asthma that required treatment with Ventolin, 3) no more than 3 days in which the subject was below the peak expiratory flow rate (PEFR) stability limit calculated at the clinic visit on the first day of

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⁴¹ [\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-protocol.pdf](#)

⁴² [\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-report-body.pdf](#)

treatment with study medication, and 4) FEV₁ at each visit $\geq$ the FEV₁ Stability Limit calculated at clinic visit on first day of treatment with study medication. Although Study MGR001-3001 used different criteria for removal of subjects due to worsening asthma compared to the pivotal studies of the NDA, the withdrawal criteria due to asthma control used in Study MGR001-3001 is acceptable as it has a similar level of safety protection for the subjects and comparable set of criteria to that which was used in the two pivotal studies in the NDA.

All other criteria for withdrawal from the study is acceptable.

In the Applicant's IR response to Question 1 submitted to the Agency on February 1, 2018, the Applicant explained that rescue medication (short acting beta agonist) use or awakenings was not captured during the study. Lack of efficacy ("treatment failure") was not captured as a reason for discontinuation and there was no definition of "treatment failure" based on albuterol use. Instead, rescue medication use was prohibited from being used within 6 hours of lung function testing during a clinic visit according to the study protocol. The Applicant reported that one subject (Subject (b) (6)) used a short-acting beta agonist within six hour prior to spirometry at Visit 2 and contrary to the Study Protocol, the visit was not re-scheduled. The FDA statistician verified that when the spirometry data from Visit 2 for Subject (b) (6) was set to missing, the subject met all requirements of the Study Protocol and still could provide sufficient spirometry data to calculate both co-primary endpoints. Therefore, Subject (b) (6) was appropriately included in the Applicant's PPS and recommended to be included in the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.

The Applicant reported that 18 additional subjects were identified as having taken a short-acting beta agonist (albuterol rescue medication) during the 12-hour serial spirometry assessment performed during their Visit 3 (Day 1) visit. Mylan reported that no subjects were excluded from either Per Protocol Set for using rescue medication within 6 hours of lung function testing. The FDA statistician and FDA clinical reviewer reviewed each subject who used a short-acting beta agonist during Visit 3 (Day 1). All spirometry data collected within six hours are short-acting beta agonist use was set to missing and subject adjustments were recommended based on the Applicant's pre-specified method of handling missing co-primary endpoint data as specified in Section 4.5.4 of their Statistical Analysis Plan. Thus, several subjects were recommended to be excluded from the FDA PP and FDA Day 1 PP populations due to short-acting beta agonist use within 6 hours of lung function testing during Visit 3.

Since the Applicant did not explicitly define subjects with lack of efficacy ("treatment failure"), they did not describe which populations these subjects were to be included or excluded from the bioequivalence analysis or how these subjects would be handled statistically. In the Applicant's IR response to Question 1 submitted to the Agency on February 1, 2018, the Applicant stated that four subjects discontinued from the study for adverse events related to worsening asthma and these cases could be considered "treatment failures" although the etiology of these cases would most likely be clinically indistinguishable to worsening of the subject's asthma which may occur spontaneously as part of the natural course of a disease of variable airflow obstruction.

(b) (4) the following group of subjects were considered to have lack of efficacy from the study drug ("treatment failures"): 1) subjects whose reason for

discontinuation from the study was asthma exacerbation or lack of efficacy and 2) subjects who discontinued from the study due to an adverse event of asthma exacerbation or worsening of asthma as long as both of these groups of subjects received a sufficient number of doses (e.g. greater than 42 doses) of the study drug to see the treatment effect of the study drug. Subjects who discontinued from the study due to an adverse event of wheezing, worsening of dyspnea, shortness of breath, respiratory tract infection, cough, and acute chronic bronchitis were not considered “treatment failures.” Zero subjects discontinued from the study due to an asthma exacerbation or lack of efficacy and four subjects discontinued from the study due to an adverse event of asthma exacerbation or worsening of asthma during Study MGR001-3001. Of the four subjects who discontinued from the study due to an adverse event of asthma exacerbation or worsening of asthma, three subjects (Subject (b) (6)) first experienced the adverse event of asthma exacerbation or worsening of asthma on Day 1 (first day of double-blind treatment period). Subject (b) (6) discontinued from the study due to an adverse event of asthma exacerbation that began on Day 16 and it was determined that this subject did not receive sufficient doses of the study drug to be considered a “treatment failure.” All four subjects were appropriately excluded from the Applicant’s Per Protocol Set as they were not considered “treatment failures” due to not receiving sufficient doses of the study drug. No subject adjustments were recommended and all four subjects were not included in the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.

The Applicant’s list of prohibited concomitant medications is consistent with the FDA Draft Product Specific Guidance for Fluticasone Propionate and Salmeterol Xinafoate. Several subjects were identified as having taken prohibited concomitant medications during the study and were included in the Applicant’s Per Protocol Set. In the Applicant’s IR response to Question 4 submitted to the Agency on February 26, 2018, Mylan responded that subjects who had not deviated from the protocol in such a way that could have affected the outcome of the FEV₁ assessments for both primary endpoints were included in the Per Protocol Set. Since the Applicant’s definition for the Per Protocol Set is not acceptable, the Applicant incorrectly included subjects who took a prohibited concomitant medication during the study in their Per Protocol Set. According to Applicant’s response to IR question 12a (Table 9) that was submitted on 2/1/2018, several subjects used a prohibited concomitant medication of oral or parenteral corticosteroid during the double-blind treatment period and were included in the Applicant’s PPS. The subjects who used a prohibited concomitant medication during the study were recommended to be excluded from the FDA PP population and the FDA Day 1 PP and/or FDA Day 29 PP depending on the timing of the prohibited concomitant medication use.

The Applicant’s treatment compliance range of 75% to 125% for the double-blind treatment period is acceptable and consistent with the recommendation in the Product Specific Guidance. However, the Applicant incorrectly defined and calculated the number of expected doses in the treatment period. As explained in Section 5.3 of the FDA Statistical Review completed by Youngsook Lee, Ph.D. on June 12, 2018, the formula provided by the Applicant for determining the total expected dose was “total expected dose = 2 (date of expected last dose – date of first dose + 1)” where the date of expected first dose is the date the dose was first administered in clinic on Day 1 (Visit 3) and the date of expected last dose is Day 28 for those subjects who completed Day 29 and the actual date of last dose for the subjects who terminated from the study early. Specifically, the date of expected last dose for those subjects who terminated from the study before Day 29 is determined incorrectly based on the Applicant’s method. Historically for clinical endpoint studies, the number of expected doses in the study should be a constant number*

for all subjects in a study and based on the study design. The number of expected doses in the study should not be determined by the dates of a subject's visits. Because of incorrectly calculating the number of expected doses in the double-blind treatment period, the Applicant's calculation for the treatment compliance for the double-blind treatment period was incorrect. The FDA statistician used 56 as the total expected doses for all subjects regardless of when the subject terminated from the study in calculating the double-blind treatment period study drug compliance for every subject.

Treatment compliance for the double-blind treatment period was verified using inhaler dose counter numbers that were collected at each study visit. If a subject was unable to provide their inhaler at a clinic visit due to loss, damage, or forgetting to bring the inhaler to the visit, the (b) (4) data from the (b) (4) device was used to assess compliance by the Investigator. In the Applicant's IR response to Question 11 submitted to the Agency on February 1, 2018, the Applicant explained that the (b) (4) device is a combined electronic PEFr recorder and daily (b) (4). The (b) (4) through the (b) (4) records the dosing time, rescue medication usage, and asthma symptoms. The Applicant's method for verifying compliance is acceptable.

Since the Product Specific Guidance does not recommend a required treatment compliance for subjects in the placebo run-in period, the treatment compliance for subjects in the placebo run-in period was not verified by FDA. As a result, no subject adjustments were recommended to be made to the FDA PP populations based on subject's treatment compliance in the placebo run-in period and this approach is consistent with how treatment compliance for the placebo run-in period for (b) (4)

(b) (4).

2.4.1.2.4 Assessments

Assessments	Description
Efficacy Measures	• FEV₁ reversibility • Spirometry (flow volume loop assessments, FEV₁, Forced Vital Capacity - FVC, FEV₁ reversibility) ▪ PEFR and daily diary See Applicant's Study Protocol, Sections 3, 8.1-8.6, and 8.8⁴³ and Applicant's Study Report, Sections 3.1 and 3.7⁴⁴
Safety Measures	• Full physical examination • 12-lead electrocardiogram (ECG)/Blood pressure/Pulse rate • Urine pregnancy test (females) and serum FSH test for any female ≥45 years who has been amenorrhoeic for at least 2 years • Clinical laboratory tests (hematology, chemistry, urinalysis, and other) • Collection and assessment of adverse events • Concomitant medication review ▪ Medical history review ▪ Daily home Asthma monitoring See Applicant's Study Protocol, Sections 3, 6.6, 7.6, 8.1-8.6, 8.7.1, 8.9, and 11.1⁴⁵ and Applicant's Study Report, Sections 3.1, 3.6.6, 3.7, and 4.2.4⁴⁶
Device Inhaler Measures	• Device Questionnaire See Applicant's Study Protocol, Sections 3 and 8.1-8.6⁴⁷ and Applicant's Study Report, Section 3.7.4⁴⁸

Reviewer's Comments: According to the Study Report, subjects completed a questionnaire at Visit 5 or an Early Termination Visit to assess the subject's use of inhaler devices that were administered during the study. A copy of the Device Usability Questionnaire was provided in Appendix IV of the Study Protocol.⁴⁹ Section 8 of the Study Report provides the results of the

⁴³ <\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-protocol.pdf>

⁴⁴ <\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-report-body.pdf>

⁴⁵ <\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-protocol.pdf>

⁴⁶ <\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-report-body.pdf>

⁴⁷ <\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-protocol.pdf>

⁴⁸ <\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-report-body.pdf>

⁴⁹ <\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-protocol.pdf>, p. 59-61

*Device Usability Questionnaire.*⁵⁰ As mentioned in the Division of Bioequivalence Review for Dry Powder Inhaler Products completed by Tian Ma, Ph.D. on 3/22/2017, the CRC 749 inhaler (test product) used in this clinical endpoint study was different from the proposed commercial device inhaler (b) (4). Thus, interpretation of the results of the Device Questionnaire must take into consideration that the proposed commercial device inhaler was not used by the subjects when completing the questionnaire.

All efficacy and safety measures are acceptable.

2.4.1.2.5 Endpoints

Co-Primary Endpoints	1. Change from baseline in FEV₁ area under the effect curve over 12 hours post (FEV₁AUEC₀₋₁₂) on Day 1 2. Change from baseline in trough FEV₁ at Week 4 For the change from baseline in FEV₁ area under the effect curve over 12 hours post (FEV₁AUEC₀₋₁₂) on Day 1 endpoint, (FEV₁AUEC₀₋₁₂) was calculated as the area under the FEV₁ effect curve over 12 hours post dose on Day 1 estimated by the linear trapezoidal rule (corrected for the appropriate baseline FEV₁ value). The baseline for this endpoint was calculated by taking the mean of the 2 predose FEV₁ measures taken at Day 1 (Visit 3)]. For the change from baseline in trough FEV₁ at Week 4 endpoint, trough FEV₁ on Day 29 (±2 days) was calculated as the mean of the 2 FEV₁ values obtained (±1 hour of the trough spirometry assessments made at Day 1 [Visit 3]) at that visit. The baseline for this endpoint was calculated by taking the mean of [prebronchodilator FEV₁ measured at run-in (Visit 2) and the mean of the 2 predose FEV₁ measures taken at Day 1 (Visit 3)].

Reviewer's Comments: *The Applicant's co-primary endpoints are mostly consistent with the FDA Draft Product Specific Guidance for Fluticasone Propionate and Salmeterol Xinafoate with the major difference being how the baseline value for each co-primary endpoint was calculated.*

According to the study protocol, the baseline for the Day 1 endpoint (FEV₁AUEC₀₋₁₂) was defined as the mean of 2 pre-dose FEV₁ measurements on Day 1. This is consistent with recommended definition of the baseline in the Product Specific Guidance. However, the baseline for the Day 29 endpoint was defined as the mean of prebronchodilator FEV₁ measurement at the run-in visit (Visit 2) and mean of 2 pre-dose FEV₁ measurements on Day 1. The baseline for the Day 29 endpoint is inconsistent with the recommended definition of the baseline in the Product Specific Guidance which is "the average of pre-dose FEV₁ values of at least two time points measured in the morning of the first day of a 4 week treatment period." In Controlled Correspondence 13-0422, OGD found Mylan's proposal to use the mean of

⁵⁰ [\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-report-body.pdf](#) , p. 165-167

prebronchodilator FEV₁ measurement at the run-in visit (Visit 2) and mean of 2 pre-dose FEV₁ measurements on Day 1 for the baseline for the Day 29 endpoint as acceptable. The Applicant's baseline definition for the Day 29 endpoint is acceptable because all pre-dose FEV₁ measurements forming the baseline will be at least two weeks after Visit 1 giving sufficient time for wash out of prior inhaled corticosteroid medications and other prohibited concomitant medications. Since the Day 29 baseline was calculated using the same method in all treatment groups, the effect on the bioequivalence determination is minimal. Thus, the use of a different baseline for each of the two primary endpoints (FEV₁ AUEC₀₋₁₂ and trough FEV₁) is acceptable since the two co-primary endpoints evaluate the two different components of the study drug: the Day 1 endpoint evaluates the salmeterol component of the study drug and the Day 29 endpoint evaluates the fluticasone component of the study drug.

2.4.1.2.6 Statistical Analysis Plan

See Applicant's Study Report, Section 4.1.3⁵¹ and FDA Statistical Review⁵², Section 3.1 for details of the statistical analysis plan (SAP). The Applicant's population definitions are provided below.

Screened Set

The Screened Set was defined as all subjects who signed the Informed Consent Form. Screen failures were defined as subjects who never received the placebo study drug during the single-blind placebo run-in period.

Enrolled Set

The Enrolled Set was defined as all subjects who took at least one dose of single-blind placebo run-in study drug during the placebo run-in period. Run-in failures were defined as subjects who received the placebo study drug during the single-blind placebo run-in period but were not randomly assigned in the study.

Randomized Set

The Randomized Set was defined as all subjects randomly assigned to receive double-blind study treatment regardless of whether or not they received a dose of double-blind study drug.

Full Analysis Set

The Full Analysis Set was defined as all randomly assigned subjects who had taken at least one dose of study drug and had provided data for either the FEV₁ AUEC₀₋₁₂ co-primary endpoint measured on Day 1 (Visit 3), the trough FEV₁ measured on Day 15 (Visit 4), or the trough FEV₁ co-primary endpoint measured on Day 29 (Visit 5), including a corresponding baseline FEV₁ value. Subjects in this set were analyzed and summarized according to their assigned treatment at randomization.

⁵¹ <\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-report-body.pdf>

⁵²

<http://panorama.fda.gov/document/preview?versionID=57ae284d005cebfb2ab12c906a1a907&ID=57ae284d005cebfa43a708f76d26f10c>

Per Protocol Set

The Per Protocol Set was defined as all subjects in the Full Analysis Set who had not violated, or deviated from, the protocol in such a way that could have affected the outcome of the FEV1 assessments for both primary endpoints. A complete list of protocol deviations along with severity codes that excluded a subject from the Per Protocol Set are included in the Deviation Guidance document (b) (4). Subjects in this set were analyzed and summarized according to the actual treatment received. The actual treatment received would only differ from the assigned treatment at randomization if the subject took the incorrect study drug for the entire double-blind treatment period.

Safety Set

The Safety Set was defined as all randomly assigned subjects who had taken at least one dose of study drug and for whom postdose safety data were available. Subjects in this set were analyzed and summarized according to their actual treatment received.

Reviewer's Comments: *The FDA Draft Product Specific Guidance for Fluticasone Propionate; Salmeterol Xinafoate does not provide a recommended definition for the safety, modified intent-to-treat population (mITT), and per protocol populations.*

The FDA Draft Product Specific Guidance for Fluticasone Propionate; Salmeterol Xinafoate Inhalation Powder does not recommend a definition for the Per Protocol population but the Applicant's Per Protocol Set (PPS) definition is not acceptable. The FDA accepted PP population used for bioequivalence evaluation includes all randomized subjects who meet all inclusion/exclusion criteria, are dosed a pre-specified proportion of the scheduled doses (generally at least 75% and no more than 125%) of the assigned product for the specified duration of the study, and complete the evaluation within the designated visit window with no protocol violations that would affect any primary endpoint treatment evaluations. The Applicant's PPS does not require subjects to meet all inclusion and not meet any exclusion criteria and complete the evaluation within the designated visit window and this is not acceptable. The Applicant's PPS definition is not acceptable as it is important that all subjects included in the per protocol population have met all inclusion criteria and not met any exclusion criteria to ensure that subjects have the disease of interest (e.g. predicted FEV1, diagnosis of asthma, post bronchodilator percent reversibility, etc.) and to allow for a consistent and relevant comparison in the statistical analysis. Subjects must complete the evaluation (Visit 5 – Day 29) within the designated visit window to be included in the per protocol population to avoid potential bias and unequal comparison of the test group to the reference group. The currently accepted FDA Per Protocol population definition was used in the FDA Statistical Analysis for the single per protocol population (FDA PP population). Six subjects and fifty one subjects were excluded from the FDA PP population for not meeting inclusion criterion 5 and inclusion criterion 6, respectively.

The FDA Draft Product Specific Guidance for Fluticasone Propionate and Salmeterol Xinafoate does not make any recommendations on the use of a single per protocol population (FDA PP population) versus two separate per protocol populations (FDA Day 1 and FDA Day 29 PP populations) for the two co-primary endpoints. Since the co-primary endpoints evaluate the two separate and different components of the drug products: the co-primary endpoint of change from baseline in FEV1 AUEC0-12 measured on Day 1 evaluates the salmeterol component of the drug product and the co-primary endpoint of change in baseline in trough FEV1 measured on Day 29

evaluates the fluticasone component of the drug product, it is clinically and statistically acceptable to use two separate per protocol populations.

(b) (4)

(b) (4)

(b) (4)

(b) (4).⁵³ Thus, the FDA statistician was provided with three separate per protocol populations recommendations by DCR: 1) FDA PP population (single per protocol population) recommendations to be used for both co-primary endpoints and 2) FDA Day 1 PP population and FDA Day 29 PP population (two separate per protocol populations) recommendations to be used separately for each co-primary endpoint.

Since the Applicant's Full Analysis Set (FAS) was considered definitive while testing superiority according to their study protocol, this population is analogous to the FDA's mITT population. In the Original Study Protocol, the Full Analysis Set was defined as "all randomized subjects who have taken study medication and have provided data for at least the FEV₁ AUEC₀₋₁₂ primary endpoint measured on Day 1" and in Amendment 1, the Full Analysis Set was defined as "all randomized subjects who have taken at least one dose of the study medication and have provided data for either the FEV₁ AUEC₀₋₁₂ primary endpoint measured on Day 1 (Visit 3), or the trough FEV₁ on Day 29 endpoint, including the corresponding baseline FEV₁ values." Both Applicant's definitions for the Full Analysis Set are not consistent with the current FDA Modified Intent-to-Treat population definition and are not acceptable. The FDA mITT population includes all randomized subjects who applied or used at least one dose of assigned drug product while the Applicant's Full Analysis Set has the extra requirement that subjects must have provided data for either of the co-primary endpoints including baseline values. According to the FDA statistician, zero subjects were excluded from the Applicant's FAS due to not providing data for either of the co-primary endpoints and had to be adjusted and included in the FDA's mITT population. The FDA mITT population was used in superiority analysis for the FDA Statistical Review.

The Applicant's Safety Set definition is consistent with the historically accepted FDA Safety population definition and safety population definition recommended in other product specific guidances.

2.4.1.3 Study Subjects

2.4.1.3.1 Subjects Analyzed

Of the 1128 subjects randomized into the study, 1122 subjects were included in the Applicant's Full Analysis Set and 1105 subjects in the Applicant's Per Protocol Set. There were 1122 subjects in the FDA modified intent-to-treat population, 1028 subjects in the FDA Day 1 Per Protocol population, 775 subjects in the FDA Day 29 Per Protocol population, and 765 subjects in the FDA Per Protocol population. The following table provides details of the Applicant's Full Analysis Set and Per Protocol Set, FDA's modified intent-to-treat, Day 1 Per Protocol, Day 29 Per Protocol, and Per Protocol populations and the reasons for exclusion from each study population.

⁵³ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f8818b3ce5>

Table 2.7: Number of Subjects in Applicant’s Study Sets and FDA’s Study Populations

	Applicant				FDA			
	Test	RLD	Placebo	Total	Test	RLD	Placebo	Total
Randomized	512	513	103	1128	512	513	103	1128
Safety population	512	512	103	1127	512	512	103	1127
Total exclusion	0	1	0	1	0	1	0	1
Reasons for exclusion								
Did not take any study medication	0	1	0	1	0	1	0	1
Applicant FAS/FDA mITT population	509	511	102	1122	509	511	102	1122
Total exclusion	3	2	1	6	3	2	1	6
Reason for exclusion								
Did not take any study medication	0	1	0	1	0	1	0	1
Entered into study twice	3	1	1	5	3	1	1	5
FDA Day 1 PP population					475	463	90	1028
Total exclusion					37	50	13	100
Reason for exclusion								
Excluded from the mITT Population					3	2	1	6
Subject has at least one significant protocol deviation impacting both endpoints					7	9	1	17
Did not meet inclusion criterion 5					2	4	0	6
Did not meet inclusion criterion 6					20	27	4	51
Missing Baseline					0	1	0	1
Insufficient Data for Day 1 Endpoint					5	7	7	19
FDA Day 29 PP population					357	350	68	775
Total exclusion					155	163	35	353
Reason for exclusion								
Excluded from the mITT Population					3	2	1	6
Subject has at least one significant protocol deviation impacting both endpoints					7	9	1	17
Did not meet inclusion criterion 5					2	4	0	6
Did not meet inclusion criterion 6					20	27	4	51
Missing Baseline					0	1	0	1
Concomitant medication after Day 1					4	3	2	9
Not compliant					22	21	4	47
Day 29/Visit 5 out of visit window					22	24	6	52
Day 29 out of time window spirometry assessments					74	71	17	162
Dosed before completion of pre-dose spirometry assessments at Visit 5					1	1	0	2
Applicant PPS/FDA PP population	502	502	101	1105¹⁾	354	348	63	765
Total exclusion	10	11	2	23	158	165	40	363
Reason for exclusion								
Excluded from the mITT Population	3	2	1	6	3	2	1	6
Subject has at least one significant	7	9	1	17	7	9	1	17

protocol deviation impacting both endpoints								
Did not meet inclusion criterion 5					2	4	0	6
Did not meet inclusion criterion 6					20	27	4	51
Missing Baseline					0	1	0	1
Concomitant medication after Day 1					4	3	2	9
Not compliant					22	21	4	47
Day 29/Visit 5 out of visit window					22	24	6	52
Day 29 out of time window spirometry assessments					74	71	17	162
Dosed before completion of pre-dose spirometry assessments at Visit 5					1	1	0	2
Insufficient Data for Day 1 Endpoint					3	2	5	10

¹⁾ Applicant’s PPS contained 1105 subjects. Applicant’s equivalence analysis for Day 1 endpoint contained 1085 subjects and applicant’s equivalence analysis for Day 29 endpoint contained 1094 subjects. See below Reviewer’s Comments for more details.

Source: FDA Statistical Review, Table 3, p. 20-21

Reviewer’s Comments: After a review of the submitted study information including the study protocol, study report, data sets, and listings, many subject adjustments were made to the Applicant’s Per Protocol Set. The most common reasons for subject adjustments included Day 29 out of time window spirometry assessments, Day 29 (Visit 5) out of window study visit, Inclusion Criterion 6 (post bronchodilator percent reversibility), and double-blind study treatment period study drug compliance. Details of all subject adjustments and Per Protocol recommendations can be found in Tables 4.4, 4.5, and 4.6 in the Appendix of this review and Section 3 of the FDA Statistical Review.⁵⁴

According to the FDA Statistical Review, no adjustments were made to the Applicant’s mITT population.

2.4.1.3.2 Demographics & Baseline Characteristics

The following table provides the demographic and baseline characteristics for the Applicant’s Safety population.

Table 2.8: Demographic and Baseline Characteristics in the Applicant’s Safety Population

⁵⁴ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881b292c4>

Variable	MGR001 100/50 N = 512	Advair® Diskus® 100/50 N = 512	Placebo N = 103	Total N = 1127
Age (years)				
n	512	512	103	1127
Mean (SD)	42.6 (14.08)	42.5 (14.21)	43.5 (13.85)	42.6 (14.11)
Min, Max	18, 84	18, 81	18, 77	18, 84
Sex, n (%)				
Male	206 (40.2)	203 (39.6)	39 (37.9)	448 (39.8)
Female	306 (59.8)	309 (60.4)	64 (62.1)	679 (60.2)
Race, n (%)				
White	378 (73.8)	372 (72.7)	73 (70.9)	823 (73.0)
Black or African American	92 (18.0)	98 (19.1)	22 (21.4)	212 (18.8)
Asian	11 (2.1)	11 (2.1)	1 (1.0)	23 (2.0)
American Indian or Alaska native	0	0	0	0
Native Hawaiian or other Pacific Islander	1 (0.2)	0	1 (1.0)	2 (0.2)
Other	30 (5.9)	31 (6.1)	6 (5.8)	67 (5.9)
Ethnicity, n (%)				
Hispanic or Latino	102 (19.9)	92 (18.0)	24 (23.3)	218 (19.3)
Not Hispanic or Latino	410 (80.1)	420 (82.0)	79 (76.7)	909 (80.7)
Body mass index (kg/m²)				
n	512	512	103	1127
Mean (SD)	29.38 (6.026)	29.12 (5.886)	29.37 (5.890)	29.26 (5.947)
Min, Max	18.0, 44.9	17.8, 45.0	18.6, 44.7	17.8, 45.0

Abbreviations: Max, maximum; Min, minimum.

Note: Age was calculated as the difference between the date of informed consent and subject birth date.

Percentages are based on the number of subjects in each treatment group in the Safety Set. Demographics were collected at Screening Visit 1. Body mass index was calculated as (body weight in kilograms)/(height in meters)².

Source: Applicant's Study Report, Section 5.3.1, Table 5-4

Reviewer's Comments: *Demographics were similar between the three treatment groups in the Applicant's Safety, Randomized, Full Analysis, and Per Protocol Populations. The age range is consistent with the study protocol and distribution of ages affected by asthma. The majority of the subjects were female. The majority of subjects were White. The next largest race was Black or African American. According to Table 5-5 and Table 5-7 of the Applicant's Study Report, the duration and severity of asthma including baseline spirometry data were similar between the three treatment groups in the Applicant's Safety Population. According to the FDA statistical reviewer, the treatment groups appear to be comparable regarding demographic and baseline characteristics.*

2.4.1.4 Results

2.4.1.4.1 Bioequivalence and Superiority Analysis Results

The Applicant’s bioequivalence and superiority analysis results for the co-primary endpoints of change from baseline in FEV₁ AUEC₀₋₁₂ measured on Day 1 and change from baseline in Trough FEV₁ measured on Day 29 are provided in Table 2.9 and Table 2.10.

Table 2.9: Applicant’s Bioequivalence and Superiority Analysis for the Co-Primary Endpoint of Change from Baseline in FEV₁ AUEC₀₋₁₂ Measured on Day 1

	Treatment		
	Test	RLD	Placebo
Equivalence Analysis			
PPS Population (n)	497	494	94
LS Mean (SE)	3.9734 (0.1704)	3.5411 (0.1593)	
90% CI for LS Mean Ratio of Test/RLD	(101.6% , 123.7%)		
Superiority Analysis			
FAS Population (n)	508	511	102
LS Mean difference from placebo (SE)	3.1343 (0.3760)	2.6773 (0.3769)	
P-value for difference from placebo	<0.0001	<0.0001	

LS Mean = Least Square Mean; SE = Standard Error; CI = Confidence Interval

Source: Applicant’s Table 6-1 and Table 6-2 in Clinical Study Report (page 133 and 135 of 811) and FDA Statistical Review, Table 5

Table 2.10: Applicant’s Bioequivalence and Superiority Analysis for the Co-Primary Endpoint of Change from Baseline in Trough FEV₁ Measured on Day 29

	Treatment		
	Test	RLD	Placebo
Equivalence Analysis			
PPS Population (n)	498	497	99
LS Mean (SE)	0.2911 (0.0163)	0.2728 (0.0162)	
90% CI for Test/RLD LS Mean Ratio	(93.8% , 122.0%)		
Superiority Analysis			
FAS Population (n)	504	505	102
LS Mean difference from Placebo (SE)	0.2352 (0.0380)	0.2145 (0.0381)	
P-value for difference from Placebo	<0.0001	<0.0001	

LS Mean = Least Square Mean; SE = Standard Error; CI = Confidence Interval

*Source: Applicant’s Table 6-3 and Table 6-4 in Clinical Study Report (page 142 and 144 of 811) and FDA Statistical Review, Table 6

The FDA’s bioequivalence and superiority analysis results for the co-primary endpoints of change from baseline in FEV₁ AUEC₀₋₁₂ measured on Day 1 and change from baseline in Trough FEV₁ measured on Day 29 are provided in Table 2.11 and 2.12.

Table 2.11: FDA’s Bioequivalence and Superiority Analysis for the Co-Primary Endpoint of Change from Baseline in FEV₁ AUEC₀₋₁₂ Measured on Day 1

	Treatment		
	Test	RLD	Placebo
Equivalence Analysis			
FDA Day 1 PP Population (n)	475	463	90
LS Mean (SE)	3.9315 (0.1610)	3.5459 (0.1619)	
90% CI for LS Mean ratio of Test/RLD	(100.7% , 122.2%)		
FDA PP Population (n)	354	348	63
LS Mean (SE)	3.810 (0.1797)	3.3690 (0.1801)	
90% CI for LS Mean ratio of Test/RLD	(101.1% , 126.8%)		
Superiority Analysis			
FDA mITT Population (n)	509 ¹⁾	511 ²⁾	102
LS Mean difference from placebo (SE)	3.1325 (0.3826)	2.6758 (0.3657)	
P-value for difference from placebo	<0.0001	<0.0001	

LS Mean = Least Square Mean; SE = Standard Error; CI = Confidence Interval

¹⁾ 1 subject (b) (6) is not included because of a missing baseline.

²⁾ 2 subjects (b) (6) are not included because of missing data.

Source: FDA Statistical Review, Table 7

Table 2.12: FDA’s Bioequivalence and Superiority Analysis for the Co-Primary Endpoint of Change from Baseline in Trough FEV₁ Measured on Day 29

	Treatment		
	Test	RLD	Placebo
Equivalence Analysis			
FDA Day 29 PP Population (n)	357	350	68
LS Mean (SE)	0.2912 (0.0179)	0.2746 (0.0180)	
90% CI for LS Mean ratio of Test/RLD	(92.0% , 122.4%)		
FDA PP Population (n)	354	348	63
LS Mean (SE)	0.2905 (0.0181)	0.2750 (0.0181)	
90% CI for LS Mean ratio of Test/RLD	(91.5% , 122.1%)		

Superiority Analysis			
FDA mITT Population (n)	509 ¹⁾	511	102
LS Mean difference from placebo (SE)	0.2346 (0.0381)	0.2143 (0.0366)	
P-value for difference from placebo	<0.0001	<0.0001	

LS Mean = Least Square Mean; SE = Standard Error; CI = Confidence Interval

¹⁾ 1 subject (b) (6) is not included because of a missing baseline.

Source: FDA Statistical Review, Table 8

Reviewer’s Comments: According to the Applicant’s statistical analyses, the test product is shown to be bioequivalent to the reference product for both co-primary endpoints and both the test and reference products are statistically superior to the placebo for both co-primary endpoints.

According to the FDA statistical analyses, the test product is shown to be bioequivalent to the reference product using two separate per protocol populations, the FDA Day 1 and FDA Day 29 Per Protocol populations, for both co-primary endpoints. The test product fails to show bioequivalence to the reference product using a single FDA Per Protocol population for the endpoint of change from baseline in FEV₁ AUEC₀₋₁₂ measured on Day 1 but the test product is shown to be bioequivalent to the reference product for the endpoint of change in baseline in trough FEV₁ measured on Day 29.

In understanding the divergent results of FDA’s single combined Per Protocol population analysis compared to the Applicant’s single combined PPS analysis, it is notable that FDA’s approach to the single Per Protocol population results in a per protocol population that is very consistent with the separate Day 29 FDA Per Protocol population. This is because FDA’s approach to a single combined Per Protocol population analysis would be to exclude subjects with potential confounders for **either** endpoint, which would naturally result in a Per Protocol population most consistent with the single Per Protocol population that contains the most exclusions/protocol violations, which would ordinarily be the Day 29 Per Protocol population. This contrasts with the Applicant’s pre-specified definition for the single combined PPS, which includes subjects unless they have potential confounders for **both** endpoints. The resulting Per Protocol Set of the Applicant’s would be most consistent with a Full Analysis Set since few subjects would be likely to have an exclusion/protocol violation that would impact both the Day 1 and Day 29 endpoints.

The numeric results of the study are consistent with these PPS analysis approaches. Because the Applicant’s single combined PPS results in a PPS that is like a FAS, as shown in Table 2.9 and 2.10, the numbers of patients in the Applicant’s PPS are similar for Day 1 and Day 29 endpoints, and few patients have been excluded compared to the FAS. As discussed previously, the Applicant’s definition is not conservative and could potentially obscure the assessment of bioequivalence because the Applicant’s PPS could include subjects who violated or deviated from the protocol in a way that could have affected the outcome of **one** of the endpoints, and additionally does not require subjects to meet all inclusion and not meet any exclusion criteria and complete the evaluation within designated visit windows, which can also obscure the bioequivalence assessment, e.g., by including groups who are prone to appear equivalent not

from the effects of treatment but from other confounding factors. Therefore, the Applicant's results appearing to demonstrate bioequivalence required additional analyses.

In FDA's additional analyses, shown in Table 2.11 and Table 2.12, it is reassuring that when a rigorous per protocol selection approach is utilized, analyses using separate Day 1 and Day 29 FDA Per Protocol populations are consistent with the Applicant's pre-specified analysis in supporting a conclusion of bioequivalence. As mentioned above, using separate Per Protocol populations for the Day 1 and Day 29 endpoints would be a clinically and scientifically justifiable approach for this fixed dose combination product of two different drugs with two different effects that may have different confounding factors. When FDA's per protocol selection approach was utilized for a single combined Per Protocol population, the Day 1 endpoint failed to meet BE criteria (90% CI for LS Mean ratio of Test/RLD was slightly high at 101.1%,126.8%), whereas the Day 29 endpoint continued to meet BE criteria. Notably, the FDA single combined Per Protocol population included 354 subjects in the Test group and 348 subjects in the RLD group. This is very consistent with the FDA single Per Protocol population for the Day 29 population, which passed, so the fact that Day 29 passed is expected. The single combined FDA Per Protocol population (FDA PP) resulted in a drop of 121 subjects in the Test group and a drop of 115 subjects in the RLD group, at Day 1, compared to the FDA Day 1 single combined Per Protocol population analysis (See Table 2.11). Although trends between the Test and RLD group are numerically consistent, the reduction in patients resulted in a larger Standard Error, or more variability in the estimate. Given that the Day 1 endpoint is change from baseline in FEV₁ area-under-the-effect-curve over 12 hours post dose, which was derived from eight spirometry assessments, this inherently could include more variability than the Day 29 endpoint, which is a trough FEV₁ assessment, and was an average of two pre-dose spirometry assessments. Therefore it is not unexpected that the Day 1 endpoint might be more sensitive to subject variability.

The FDA Draft Product Specific Guidance for Fluticasone Propionate and Salmeterol Xinafoate does not make any recommendations on the use of a single per protocol population (FDA PP population) versus two separate per protocol populations (FDA Day 1 and FDA Day 29 PP populations) for the two co-primary endpoints. Since the co-primary endpoints evaluate the two separate and different components of the drug products: the co-primary endpoint of change from baseline in FEV₁ AUEC₀₋₁₂ measured on Day 1 evaluates the salmeterol component of the drug product and the co-primary endpoint of change in baseline in trough FEV₁ measured on Day 29 evaluates the fluticasone component of the drug product, it is clinically and scientifically justifiable and statistically acceptable to use two separate per protocol populations to evaluate the two co-primary endpoints that evaluate different components of the drug product and which may be subject to different confounders.

(b) (4)

⁵⁵ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f8818b3ce5>

In addition, (b) (4) products are statistically superior to the placebo for both co-primary endpoints in the FDA statistical analyses, demonstrating that the study is sensitive enough to detect a difference between products.

2.5 Comparative Review of Safety

2.5.1 Description of Adverse Events

A total of 1127 subjects in the Safety Population were randomized and used the study medication during the double-blind treatment period on at least one occasion. Subjects orally inhaled one puff of the study drug twice a day (morning and evening) for 4 weeks (28 ± 2 days). Mean exposure in the safety population was 27.7 days for subjects who received the test product, 27.5 days for subjects who received the reference product, and 27.1 days for subjects who received the placebo product. A total of 209 adverse events (AEs) were reported by 162 subjects (14.4%). The number of subjects who experienced an AE during the study was comparable between the test group (n=72; 14.1%) and the reference group (n=75; 14.6%). The proportion of mild, moderate, and severe AEs reported were similar between the test group and the reference group. There were no deaths or serious adverse events in the study.

During screening and the single-blind placebo run-in period, two subjects (b) (6) (b) (6). Both these subjects were withdrawn from the study and neither subject entered the double-blind treatment or received any doses of the study medication. Subject (b) (6) did not take a single dose of the placebo treatment during the placebo run-in period. Subject (b) (6) began taking the placebo treatment during the placebo run-in period on (b) (6). According to the Applicant, Subject (b) (6) was found to be ineligible for the study on (b) (6) at Visit 2 due to not meeting Inclusion Criterion 2 (“Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and all other study procedures”) although the Case Report Form documents the reason for discontinuation as “Adverse Event.” The only adverse event documented was pleuritic chest pain (b) (6) (b) (6). Other documentation from the study site shows that the subject decided she would like to take a different approach for her asthma treatment and declined further treatment in the study. The subject discontinued from the study on (b) (6) after taking 31 doses of the placebo medication. (b) (6) (b) (6)

Mylan Product Safety and Risk Management reviewed the subject’s case and since the subject did not take any investigational product (test or reference product) and only received placebo treatment and rescue medication albuterol, no follow-up of the case was completed. (b) (6)

The tables below provide a summary of AEs.

Table 2.13: Summary of Adverse Events in the Safety Population

Description	Test N(%)	Reference N(%)	Placebo N(%)	Total N(%)
Patients Randomized	512	512*	103	
Patients with at least one AEs	72 (14.1%)	75 (14.6%)	15 (14.6%)	162 (14.4%)
Discontinued study drug due to above AE	4 (0.8%)	4 (0.8%)	4 (3.9%)	12 (1.1%)
AEs reported	92	99	18	209
Mild	57	62	10	129
Moderate	35	37	8	80
Severe	0	0	0	0
Definite Related	2	2	0	4
Probably Related	3	6	0	9
Possibly Related	9	7	2	18
Unlikely Related	12	11	4	27
Not Related	66	73	12	151
Death	0	0	0	0
Serious AE	0	0	0	0

*513 subjects were randomized but 512 received at least one dose of double-blind study drug.

Source: Applicant's Summary of Clinical Efficacy – Tables – Appendix 1, Module 2.7.3, Table 20

Table 2.14: Most Frequent Treatment-Emergent Adverse Events Occurring in At Least 3 Subjects Across Treatments Groups

System Organ Class	MGR001 100/50 N = 512	Advair® Diskus® 100/50 N = 512	Placebo N = 103	Total N = 1127
Preferred Term	n (%) [E]	n (%) [E]	n (%) [E]	n (%) [E]
Number of subjects with at least 1 TEAE ^a	72 (14.1) [92]	75 (14.6) [99]	15 (14.6) [18]	162 (14.4) [209]
Infections and infestations	34 (6.6) [34]	38 (7.4) [39]	5 (4.9) [5]	77 (6.8) [78]
Upper respiratory tract infection	7 (1.4) [7]	11 (2.1) [11]	0	18 (1.6) [18]
Nasopharyngitis	3 (0.6) [3]	7 (1.4) [7]	2 (1.9) [2]	12 (1.1) [12]
Sinusitis	3 (0.6) [3]	3 (0.6) [3]	1 (1.0) [1]	7 (0.6) [7]
Oral candidiasis	4 (0.8) [4]	2 (0.4) [2]	0	6 (0.5) [6]
Urinary tract infection	2 (0.4) [2]	2 (0.4) [2]	0	4 (0.4) [4]
Viral upper respiratory tract	1 (0.2) [1]	3 (0.6) [3]	0	4 (0.4) [4]
Bronchitis	2 (0.4) [2]	0	1 (1.0) [1]	3 (0.3) [3]
Gastroenteritis	0	3 (0.6) [3]	0	3 (0.3) [3]
Viral infection	1 (0.2) [1]	2 (0.4) [2]	0	3 (0.3) [3]
Respiratory, thoracic and mediastinal disorders	15 (2.9) [20]	25 (4.9) [29]	7 (6.8) [7]	47 (4.2) [56]
Asthma	7 (1.4) [9]	10 (2.0) [13]	5 (4.9) [5]	22 (2.0) [27]
Oropharyngeal pain	3 (0.6) [3]	5 (1.0) [5]	1 (1.0) [1]	9 (0.8) [9]
Dysphonia	1 (0.2) [1]	3 (0.6) [3]	0	4 (0.4) [4]
Cough	1 (0.2) [1]	2 (0.4) [2]	0	3 (0.3) [3]
Gastrointestinal disorders	6 (1.2) [9]	5 (1.0) [6]	1 (1.0) [1]	12 (1.1) [16]
Dyspepsia	1 (0.2) [1]	2 (0.4) [2]	0	3 (0.3) [3]
Nervous system disorders	6 (1.2) [6]	6 (1.2) [6]	0	12 (1.1) [12]
Headache	3 (0.6) [3]	5 (1.0) [5]	0	8 (0.7) [8]
Musculoskeletal and connective tissue disorders	4 (0.8) [4]	4 (0.8) [4]	1 (1.0) [1]	9 (0.8) [9]
Injury, poisoning and procedural complications	2 (0.4) [2]	3 (0.6) [4]	1 (1.0) [1]	6 (0.5) [7]
Investigations	3 (0.6) [4]	2 (0.4) [2]	0	5 (0.4) [6]
Cardiac disorders	3 (0.6) [3]	0	1 (1.0) [1]	4 (0.4) [4]
General disorders and administration site conditions	2 (0.4) [3]	2 (0.4) [2]	0	4 (0.4) [5]
Skin and subcutaneous tissue disorders	2 (0.4) [2]	1 (0.2) [1]	0	3 (0.3) [3]

Abbreviations: AE, adverse event; E, the number of events at each level of summarization; n, the number of subjects at each level of summarization; TEAE, treatment-emergent adverse event.

Note: Treatment-emergent adverse events were reported. The total number of AEs counts all TEAEs for subjects.

^a At each level of subject summarization, a subject was counted once if the subject reported one or more events. The preferred terms were presented by decreasing frequency of incidence for all treatment groups combined.

Source: Applicant’s Study Report, Section 7.1.2, Table 7-2

Reviewer’s Comments: *The percentage of subjects who experienced at least one AE was similar in the test group (14.1%) compared to the reference group (14.6%) and the placebo group (14.6%). The percentage of subjects who discontinued the test product due to an AE (0.8%) is similar to the percentage of subjects who discontinued the reference product due to an AE (0.8%) and lower than the percentage of subjects who discontinued the placebo product due to an AE (3.9%). Regarding the severity of AEs, the proportion of mild, moderate and severe AEs reported are similar between the test and reference group. The AE rates in the test group were similar to the AE rates in the reference group for most types of adverse events. The incidence and types of adverse events reported in the test group are similar to that expected for the Reference Listed Drug. Ten subjects (2.0%) in the reference group, seven subjects (1.4%) in the test group, and five subjects (4.9%) in the placebo group had an adverse event of asthma exacerbation or asthma crisis during the double-blinded treatment period. There were four subjects in the test group and two subjects in the reference group who experienced an adverse*

event of oral candidiasis during the study. No significant safety concerns were identified in Study MGR001-3001.

2.6 Relevant Findings from Other Consultant Reviews

2.6.1 Office of Study Integrity and Surveillance

On 1/25/2016, OSIS selected 16 clinical sites for inspection. The final classification for seven of the inspected clinical sites was voluntary action indicated (VAI) and no action indicated (NAI) for nine of inspected clinical sites. Form 483 was issued to 7 of the 16 inspected clinical sites. Form 483 at 6 of the 7 sites cited that the clinical sites retained reserve samples from only the first shipment of drug products and not from subsequent shipments of drug products used for dosing study subjects. The remaining site (Princeton Center for Clinical Research) which received a Form 483 was cited for informed consent document that lacked a description of foreseeable risks to the subjects, failure to assure that an IRB complying with applicable regulatory requirements was responsible for the review and approval of the study, and failure to prepare or maintain adequate case histories.⁵⁶

OSIS initially recommended that data from Study MGR001-3001 not be accepted for further agency review. Two significant findings detailed in the OSIS inspection report include failure of clinical sites to retain reserve samples from subsequent shipments of the drug product and failure to maintain a sealed randomization schedule including blinding codes in possession of the clinical site prior to the dosing of subjects. In the OSIS inspection report, it is noted that the clinical sites were instructed to retain reserve samples from the first shipment only by the Contract Research Organization (PPD, Inc.) on behalf of the Applicant. The clinical sites included a portion of minutes from a meeting between the Applicant and Office of Generic Drugs in support of their positions and in response to the Form 483. According to OSIS, the minutes of the September 2013 meeting between Mylan and OGD reveal that OGD provided guidance for quantities of reserve samples, however, OSIS cannot ascertain based on the meeting minutes whether there was a further discussion at the meeting on selection of reserve samples from multiple shipments. OSIS concluded that study MRG001-3001 violated 21 CFR 320.38 and 21 CFR 320.63 because the clinical sites did not retain reserve samples representative of each shipment of drug product used in the clinical endpoint study. Since the study design and instructions from the Applicant and CRO did not call for clinical sites to retain reserve samples from each shipment, OSIS concluded that failure to retain reserve samples from all drug shipments is likely to be common to all study sites. The inspections were classified VAI or NAI because 1) each site retained reserve samples according to the Applicant's instructions and plan which the Applicant claimed to have discussed during the Sponsor-FDA Type C meeting in September 2013, 2) the study design using Interactive Voice Response System/Interactive Web Response System (IVRS-IWRS) permitted the clinical sites to select reserve samples from only one shipment, and 3) the clinical sites stored the reserve samples according to the requirements of 21 CFR 320.38 and 21 CFR 320.63. The OSIS inspection report stated that the study was conducted from 10/22/2014 to 7/10/2015 and in May 2015, each site was sent a sealed blinding code envelope for the reserve samples only. In November 2015, after the study was completed and the database was locked, the CRO provided the study sites with a CD of the full

⁵⁶ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f880df431c>

randomization schedule (listing of unblinded treatment assignments for all subjects enrolled in the study) to facilitate regulatory inspections. The investigators were provided with an Excel file with randomization information about treatment assignment, kit number, subject number, and other dosing information after the study was completed. In response to a Form 483 issued for this reason, an investigator stated that full randomization codes for Study MGR001-3001 was managed centrally by the CRO through their IVRS/IWRS and that a manual containing complete instructions for use of the IVRS/IWRS was provided to each study site prior to the study start. The investigator at the site were not aware that it was necessary for a copy of the full randomization schedule to be held at the clinical site as the randomization schedule managed centrally by the CRO (PPD Inc.) covered the entire study and was in place. The investigators stated thus a “mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding” was in place prior to randomization of the first subjects and emergency unblinding envelopes were not necessary. The investigators felt that the safety of the subjects was not impaired. On 8/29/2016, OSIS requested that an ORA investigator return to the Princeton Center for Clinical Research clinical site to attempt to identify treatments for each subject through IVRS/IWRS audit trails records. The ORA investigator visited the clinical site but could not examine the audit trail records from IVRS/IWRS to confirm the blinding codes since there was no access to audit trail from the clinical site. Since blinding codes were not held at each clinical site before dosing the first subject and the ORA investigator could not access the IVRS/IWRS audit trails to confirm the identity of drug products that were administered to each subject, OSIS cannot be assured that the subjects received the treatments as intended or described in the study report. OSIS felt that this observation was likely common to all clinical sites that participated in the study.

Table 2.15: Clinical Site Inspection Findings

Study	Clinical Site	OSIS Findings	Final Classification
MGR001-3001	Prestige Clinical Research Center Miami, FL	Observation 1 Failure to retain representative reserve samples specific to an in vivo bioequivalence study. According to a presentation from PPD, the site was to collect a retention samples “from the first shipment.” The site collected 50 kits from the first shipment but failed to retain reserve samples representative of all the shipments received. Observation 2 Failure to retain sealed randomization schedule prior to commencement of subject enrollment. Specifically, a sealed randomization scheme, including blinding codes, was not maintained in the possession of the clinical site prior to the dosing of the initial subjects (Run-in placebo on 06 November 2014 and Randomized dosing on 5 December 2014). The site completed the study and was closed by the IRB on 01 September 2015; however, the randomization scheme, which was not sealed, was sent to the site from PPD on 06 November 2015.	VAI
MGR001-3001	Princeton Center for Clinical Research	Observation 1 The informed consent document lacked a description of	VAI

Study	Clinical Site	OSIS Findings	Final Classification
	Skillman, NJ	reasonably foreseeable risks or discomforts to the subject. Specifically, the informed consent form failed to include: a. the following potential adverse events the subjects may encounter: nausea, vomiting, thrush, and tremors b. the volume of blood collected may range from 50 mL to 500 mL during their participation in the study c. the frequency of blood samples to be collected during the study d. what the blood samples collected would be analyzed for Observation 2 Failure to assure that an IRB complying with applicable regulatory requirements was responsible for the initial and continuing review and approval of a clinical study. Specifically, there is no documentation the clinical investigator assured the composition of the IRB met the regulatory requirement for the initial and continuing review of this clinical study nor was the clinical investigator aware of which panel met to review and approve this study. Furthermore, none of the panel members or alternate members were identified as having specialization in asthma or respiratory disease nor was there documentation the IRB consulted or invited an expert in the area of asthma or respiratory disease in reviewing this study. Observation 3 Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation. Specific observations include: a. For 7 out of 7 subjects reviewed, there is no documentation that the study subjects met exclusion criteria #15 which states that the subject should not be enrolled if they have been treated with "an investigational drug within 1 month or at least 5 half-lives (whichever is longer) preceding the first dose of the trial medication." b. Clinical investigator failed to retain the results for all Forced Spirometry results for four out of seven subjects reviewed.	
MGR001-3001	The Clinical Research Center, LLC Saint Louis, MO	None	NAI
MGR001-3001	Allergy and Asthma Consultants of the Ozarks (Clinical Research of the Ozarks) Columbia, MO	None	NAI
MGR001-3001	AAPRI Research Institute (FKA Kent Surgical Associates, Inc.)	Observation 1 Samples of the test article and reference standard used in a bioequivalence study were not retained. Specifically, the	VAI

Study	Clinical Site	OSIS Findings	Final Classification
	Warwick, RI	reserve samples were not representative of each sample of the test article and reference standard provided by the applicant. A total of 50 retention samples were chosen from the first shipment of 72 inhalers. The study site received a total of 63 inhalers in subsequent shipments, of which none were retained for reserve samples.	
MGR001-3001	Timber Lane Allergy & Asthma Associates South Burlington, VT	Observation 1 Samples of the test article and reference standard used in a bioequivalence study were not retained. The 50 reserve samples retained by Timber Lane Allergy & Asthma Research, LLC were not representative of each sample of the test article and reference standard provided by the applicant for the testing. The reserve samples were selected only from the initial shipment of 72 test kits. An additional 70 kits were received at the clinical site in subsequent shipments which were not sampled; therefore the reserve samples were not representative of these kits. The Study Drug Retention System Module of the Interactive Web Response System (IWRS) was designed by the Contract Research Organization (CRO) in such a way that exactly 50 reserve samples had to be selected from the initial shipment. Fifty reserve samples were the total amount to be collected from each clinical site and there was no option to collect additional samples from subsequent shipments. Observation 2 The general requirements for informed consent were not met in that the investigator did not seek consent under circumstances that minimized the possibility of coercion or undue influence. Specifically, Advertising for clinical subjects placed on Craigslist.org as a part-time employment posting was not approved by the IRB. The Craigslist.org posting was based on advertising approved by the IRB, with the exception that the amount of the compensation was not included on the IRB approved advertising. The Craigslist.org posting emphasized the amount of the compensation by using a bold print, enclosing it in a separate text box, and being placed under the job postings as part time employment. Observation 3 An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. Specifically, Section 8.1 Screening Procedures of the protocol states, "The Principal Investigator or Medical Sub-Investigator will review the inclusion and exclusion criteria to confirm eligibility of each subject prior to enrollment." <i>Section 8.1.1 Screening Visit (Visit 1)</i> states "Subjects will be screened approximately 28 days (+2 days) prior to administration of the study medication to confirm that they meet the subject selection criteria for the study." and "The following	VAI

Study	Clinical Site	OSIS Findings	Final Classification
		procedures will be completed:"..."Full physical examination"... "Standard 12-lead electrocardiogram ECG)"... and "Inclusion/Exclusion criteria." The inclusion/exclusion criteria checklists for seven subjects and ECGs for five subjects were reviewed after the date the subjects received run-in medication. Additionally, the physical examination was performed after one subject received run-in medication.	
MGR001-3001	Pharmaceutical Research and Consulting, Inc. Dallas, TX	None	NAI
MGR001-3001	Allergy and Asthma Research Group Eugene, OR	Observation 1 Samples of the test article and reference standard used in a bioequivalence study were not retained. Specifically, reserve samples were not retained from each shipment of study drug received. The site received 15 shipments totaling 143 individual blinded kits each containing test article, reference standard, or placebo. The site retained 50 kits as reserve samples from the initial shipments of 72 kits received on 10/21/2014, but did not retain samples from any of the subsequent shipments received.	VAI
MGR001-3001	Providence Clinical Research North Hollywood, CA	Observation 1 Samples of the test article and reference standard used in a bioequivalence study were not retained. Specifically, the 50 reserve samples retained by Teresa S. Sligh, MD and (b) (4) Providence Clinical Research were not representative of test kits provided by the applicant for testing. The reserve samples were selected only from the initial shipment of 72 test kits. An additional 134 kits were received at the clinical site in subsequent shipments which were not sampled. The Study Drug Retention System Module of the Interactive Web Response System was designed by the Contract Research Organization that exactly 50 reserve samples had to be selected from the initial shipment. Fifty reserve samples were the total amount to be collected from each clinical site and there was no option to collect additional samples from subsequent shipments.	VAI
MGR001-3001	Pediatric Care Medical Group, Inc. Huntington Beach, CA	None	NAI
MGR001-3001	Linfriz Research Center Coral Gables, FL	Observation 1 Regarding the clinical endpoint bioequivalence study MGR001-3001, reserve samples of the test article and reference standard representing each sample/shipment received at the test site were not retained as required. Specifically, the reserve sample of the test article and reference standard was only collected from the initial shipment received at the clinical site on 10/21/2014. Subsequent shipments of the test article and reference standard	VAI

Study	Clinical Site	OSIS Findings	Final Classification
		were received at the clinical site on 12/10/14, 3/10/2015, 3/19/2015, 04/02/2015, 04/07/2015, 04/24/2015, 04/25/2015, 05/05/2015, 05/13/2015, 05/14/2015, 05/19/2015, 05/22/2015, 06/05/2015, however no reserve sample was collected and retained from these shipments.	
MGR001-3001	Asthma and Allergy Center of Chicago River Forest, IL	None	NAI
MGR001-3001	Northeast Medical Research Associates North Dartmouth, MA	None	NAI
MGR001-3001	Montgomery Medical Smithfield, PA	None	NAI
MGR001-3001	Analab Clinical Research, Inc. Lenexa, KS	None	NAI

Reviewer's Comments: DCR sent a consult to OSIS to review the Applicant's response to the Complete Response deficiency comments related to randomization schedule and blinding codes. During the face-to-face meeting between Mylan and the Agency on March 1, 2018, Mylan provided additional information about the original blinding codes and the IVRS/TWRS system.⁵⁷ In OSIS' consult response to DCR completed on April 5, 2018, the OSIS reviewer concluded that the documents are adequate to show that subjects were dosed with the products as reported.⁵⁸ Thus, the Applicant's methods of blinding and randomization are acceptable.

On December 8, 2017, the Division of Clinical Review sent a consult to the Office of Study Integrity and Surveillance (OSIS) to review the Applicant's response to the Complete Response deficiency comments related to the retention of reserve samples and provide an updated recommendation on the acceptability of the data from MGR001-3001. In OSIS' consult response completed on April 5, 2018, the OSIS reviewer stated if used or unused drug products from subsequent shipments were available, they might serve as substitutes for reserve samples. On March 15, 2018, DCR sent an Information Request to the Applicant requesting that the Applicant clarify if any used or unused drug products from subsequent shipments were currently available or have been destroyed.

OSIS concluded that the information submitted in the Applicant's CR response to Bioequivalence Deficiency Comment 48 and the IR response dated March 22, 2018 are consistent with OSIS' original understanding of the reserve samples as documented in the inspectional findings. OSIS recommended that the Division of Clinical Review assess the potential impact of the lack of reserve samples for each subsequent shipment from all clinical sites as the study sites retained reserve samples only from the first shipment of drug products to each clinical site.

⁵⁷ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881a2883c>

⁵⁸ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881a42095>

The Division of Clinical Review had multiple internal meetings with other individuals within the Office of Generic Drugs and the Office of Study Integrity and Surveillance. During these meetings, a thorough review and discussion regarding Mylan's method for retaining reserve samples was conducted. Since additional information and clarification regarding the processes used to retain samples was necessary, three Information Requests were sent by DCR and the Applicant responded to these Information Requests on April 26, 2018, May 25, 2018 and June 7, 2018. On June 11, 2018, an internal meeting was held between the OGD and OSIS to determine whether the information provided by Mylan could support that the retention samples from the first shipment are adequate to represent the study products used in their clinical endpoint bioequivalence study. The internal memorandum to file dated 6/26/2018 completed by Sarah Yim describes the discussions and outcome of the June 11, 2018 meeting.⁵⁹

In summary, there were five separate batches of clinical supplies made by the manufacturers of the clinical supplies and these five batches were all shipped to (b) (4) (b) (4) by the manufacturers in their entirety in separate individual shipments. The five batches of clinical supplies were packaged and labeled into blinded kits in their entirety in a single run by (b) (4) and all of the blinded kits were packaged and labeled prior to start of the study and shipment to individual sites. During the packaging and labeling process at (b) (4) each individual inhaler was labeled with its blinded kit number before being placed in a pouch which was then sealed before being packed in a carton and labeled with the same blinded kit number. Mylan stated that the pouching of each labeled inhaler performed by (b) (4) essentially made the blinded kit "tamper evident" from the time they were packaged and labeled. Staff at (b) (4) were not blinded to the identity of the blinded kits as the staff needed to know the identity of the kits in order to place the correct clinical supply into each kit. Staff at (b) (4) were blinded to the allocation of any blinded kit to a particular study subject and (b) (4) could not send blinded kits other than those specified by the IVRS/IWRS system. Mylan states that the contents of a blinded kit could not be intentionally influenced by (b) (4) staff regardless of whether they were unblinded because the content of any blinded kit could not be influenced after the packaging and labeling was complete due to the inhalers being placed in a sealed pouch and blinded kit numbers were specifically requested for shipment to each site by the IVRS/IWRS system.

Since the study was double-blind, double-dummy, at least 14 kits of each of the five batches were included in the first shipment to each site allowing 10 kits (inhalers) per batch per clinical site to be randomly selected by the clinical site for retention. The initial shipment to each clinical site contained 72 kits (inhalers) irrespective of the treatment group that the first subject enrolled at a clinical site was assigned to and the initial shipment was sent to each clinical site before the clinical sites could begin enrolling any subjects. Once the first shipment was received, each clinical site identified an independent staff member who selected the samples to be retained from the initial shipment. The independent staff member was not directly involved in the conduct of study MGR001-3001 and the identity of this person was not communicated to Mylan or (b) (4). The independent staff member used the IVRS/IWRS system to select 10 kits from each batch to be retained from the initial shipment in a blinded fashion. The independent staff member selected the 10 kits from each batch to be retained without any guidance or instruction from Mylan,

⁵⁹ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881b38bc7>

(b) (4), or any other individual. When selecting the 10 kits from each batch, the independent staff member was presented with a list of kits all from the same batch and were instructed to select 10 of the kits. The independent staff member repeated this process for the remaining four batches. The identity of the kits in the five lists were not disclosed thus making the independent staff member blinded to the identity of the kits when selecting the kits to be retained for reserve samples. The independent staff member's only role in the IVRS/IWRS system was to access the five lists of blinded kit numbers that were used to select the samples to be retained. The retained kits were physically separated from the general study supply by the independent staff member and maintained under appropriate storage conditions according to the study drug label. Following this process, the independent staff member did not perform any other duties related to subjects for this study.

The study products that was shipped in all subsequent shipments to all clinical sites were from the same five batches as the initial shipments. The study products in all subsequent shipments were packaged and labeled by (b) (4) at the same time as the initial shipments. Therefore, kits in both the initial and all subsequent shipments to any particular site could have originated from any part of the product batch. In other words, reserve samples were derived from a single run that packaged all study product batch and all kits were identical at release except for the unique kit number. Thus, OGD and OSIS concluded that the retention samples selected from the first shipment to each site were fully representative of the total study products used in the study irrespective of whether the study product was delivered in the initial or subsequent shipments. Since the reserve samples were representative of the study products used in the clinical endpoint study, OGD and OSIS determined that Study MGR001-3001 met 21 CFR 320.38 and 21 CFR 320.63 despite not retaining reserve samples from every shipment to every clinical site as recommended in the FDA Guidance "Handling and Retention of BA and BE Testing Samples" (May 2004) (Retention Sample BE Guidance). To the extent Mylan's approach to retaining reserve samples is not consistent with the Retention Sample BE Guidance, a departure from the guidance is appropriate because Mylan has demonstrated that its approach satisfied the applicable statutory and regulatory standards. OSIS and OGD concluded that the data from Study MGR001-3001 be accepted for further agency review.

Finally, no subject adjustments to the FDA study populations were recommended and no additional statistical analysis was recommended based on the final conclusions of OSIS and OGD.

2.7 Formulation

2.7.1 Formulation of Reference Product

The formulation for the Reference Product (Advair Diskus® Fluticasone Propionate and Salmeterol Xinafoate 100/50µg) is presented in Table 2.16.

Table 2.16: Reference Product Formulation

Components	100/50 mcg	250/50 mcg	500/50 mcg
	per blister	per blister	per blister
Salmeterol xinafoate, (micronized)	72.5 mcg ¹	72.5 mcg ¹	72.5 mcg ¹
Fluticasone propionate (micronized)	100 mcg ²	250 mcg ²	500 mcg ²
Lactose monohydrate ³	to 12.5 mg	to 12.5 mg	to 12.5 mg

¹72.5 mcg salmeterol xinafoate is equivalent to 50 mcg

(b) (4)

Source: NDA 021077, Module 3.2.P.2 Pharmaceutical Development

2.7.2 Formulation of Test Product and Placebo

The formulation for the Test product (MGR001 100/50) is presented in Table 2.17.

Table 2.17: Test Product Formulation

Ingredients	Function	Test Amount (mg, %)	
		mg	%w/w
Salmeterol xinafoate	Active		(b) (4)
Fluticasone propionate	Active		
Lactose monohydrate	Excipient		

(b) (4)

Reviewer's Comments: *The test product is qualitatively the same but quantitatively different compared to the RLD. The test product contains lower amount of Lactose monohydrate (b) (4) (b) (4) The final acceptability of the active ingredients is deferred to the Office of Pharmaceutical Quality.*

There is more Lactose monohydrate in the placebo product compared to the test product. This difference is likely to allow the placebo product to have the same total weight as the test product and this is acceptable. A visual and tactile examination of the test and placebo CRC749 device

⁶⁰ [\\cdsesub1\evsprod\anda208891\0024\m1\us\12-cover-letters\cover-letter-0024-information-request-response-20180201.pdf](#) , Comment 2, Table 2

inhaler used in the clinical endpoint study showed no apparent clinically significant differences. The study results show no apparent effect of the formulation differences on product performance or safety.

2.7.3 To-Be-Marketed Product and Related Information

According to their certificates of analysis (COAs), the batches used in the clinical endpoint study (MGR001-3001), pharmacokinetic studies, and in vitro studies for the 100/50 mcg and 500/50 mcg strengths had a different device configuration (b) (4) than the device configuration in the proposed to-be-marketed (commercial) device (b) (4). The batches used in the clinical endpoint study and pharmacokinetic studies were manufactured (b) (4).

(b) (4) –
(b) (4)⁶¹ The Applicant submitted in vitro BE study data conducted using test products manufactured (b) (4) and the corresponding strength of the RLD products to support the Applicant's proposal (b) (4) used in the batches in the clinical endpoint study (b) (4) as proposed to be used in the to-be-marketed (commercial) batch. Mylan stated that there were no differences between the formulation of the batch used in the clinical endpoint study and the formulation of the to-be-marketed (commercial) batch (b) (4).

Reviewer's Comments: *In the Applicant's response to Bioequivalence Deficiency 1 in their Complete Response Amendment, Mylan states that the changes in (b) (4)*

(b) (4). *According to the Drug Product Review completed by Fang Yuan, Ph.D., the revision from the device used in the clinical endpoint study to the to-be-marketed (commercial) device is not expected to affect the product performance as evidenced by comparable airflow resistance from the Applicant's data and FDA lab testing results.⁶⁴ Mylan provided in vitro bridging studies at 60 L/min flow rate for the (b) (4) (b) (4) change. According to the Bioequivalence Review completed by Tian Ma, Ph.D., the in vitro bridging studies at 60 L/min flow rate are adequate to support the change (b) (4) (b) (4) (b) (4) between the strengths was*

⁶¹ [\\cdsesub1\evsprod\anda208891\0000\m2\23-qos\drug-product-fluticasone-propionate-and-salmeterol-mdr-1.pdf](#) , p.97

⁶² [\\cdsesub1\evsprod\anda208891\0000\m3\32-body-data\32p-drug-prod\fluticasone-propionate-and-salmeterol-inhalation-pwdr-mdr\32p3-manuf\batch-formula.pdf](#)

⁶³ [\\cdsesub1\evsprod\anda208891\0000\m3\32-body-data\32p-drug-prod\fluticasone-propionate-and-salmeterol-inhalation-pwdr-mdr\32p2-pharm-dev\pharmaceutical-development-1.pdf](#) , p. 571

⁶⁴ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881b1f9a8> , p. 51

determined to be acceptable in the Bioequivalence Review (b) (4)

(b) (4). The Applicant has provided sufficient information to bridge the drug product and device used in the clinical endpoint study to the drug product and device used in the other studies submitted to support approval of ANDA 208891 and to the to-be-marketed (commercial) drug product and device.

During the clinical endpoint study (MGR001-3001), two subjects had to return an inhaler during the double-blind treatment period. The Applicant explained that a root cause analysis on the returned inhaler was conducted through external visual inspection, device disassembly, and in-depth, internal visual inspection. Subject (b) (6) returned a placebo MGR001 inhaler and root cause analysis revealed that the device was assembled correctly and functioning as expected with no evidence of device malfunction. Subject (b) (6) also returned an Active Diskus® Inhaler and root cause analysis concluded that the Diskus inhaler was functioning correctly. Subject (b) (6) returned a Placebo Diskus® inhaler and root cause analysis showed that the device was not providing the correct dose. (b) (4)

. A device robustness study (MGR001-1010) to evaluate the pharmaceutical and performance robustness of the proposed to-be-marketed device inhaler was submitted by the Applicant and reviewed by the Office of Pharmaceutical Quality (OPQ). The OPQ review team found the device robustness study adequate.

In the “Clinical Review of Drug-Device Combination Product” completed by Michael Spagnola, M.D. on June 26, 2018, it was concluded that there are acceptable differences between the Wixela Inhub (CRC749) inhaler and the RLD, Advair Diskus® inhaler and that the data submitted supports that the Wixela Inhub (CRC749) inhaler will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling.⁶⁵

2.8 Conclusion and Recommendation

2.8.1 Conclusion

The clinical data submitted to ANDA 208891 are adequate to demonstrate bioequivalence of the Applicant’s Fluticasone Propionate and Salmeterol Inhalation Powder 100/50µg with the reference listed drug (RLD), Advair Diskus® Fluticasone Propionate and Salmeterol Xinafoate 100/50µg.

2.8.2 Recommendations

Study MGR001-3001 is adequate to support an approval recommendation contingent on approval recommendations from the other disciplines on the review team.

⁶⁵ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881b37e29>

3 CLINICAL BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

The Clinical Discipline has completed its review and concluded that Study MGR001-3001 is adequate to demonstrate that the test product is bioequivalent to the reference product.

The Division of Clinical Review has the following additional comments:

We note that clinical sites did not retain reserve samples from subsequent shipments after the first shipment of investigational drug products (IDPs). As is recommended in the “*FDA Guidance for Industry: Handling and Retention of BA and BE Testing Samples (May 2004)*” (Retention Sample BE Guidance), each clinical site should retain a sufficient quantity of reserve samples from subsequent shipments if additional supplies of IDPs will be used by the clinical site. We maintain that this guidance can and should be fully applied to clinical endpoint BE studies, and that it is possible to retain reserve samples from every shipment to each site even for studies with complex study designs and products such as Study MGR001-3001 (See Mylan’s Response to FDA Comment 2 to the Division of Clinical Review Information Request dated April 20, 2018). We disagree that the Agency and Mylan had an explicit and prospective agreement that selection of reserve samples from the first shipment only was acceptable during the Type C meeting in September 2013.

Although we concluded that your approach to retaining reserve samples met the relevant statutory and regulatory requirements, we note that our review required us to request a significant amount of additional information from Mylan and expend additional resources. For future BE studies, we recommend that you adopt a method for retaining reserve samples that more closely adheres to the recommendations described in FDA’s Retention Sample BE Guidance. We also recommend that sealed copies (paper or electronic) of the codes for blinding the IDPs be provided to all clinical sites before they select reserve samples and begin the study, to allow the clinical sites to preserve independent copies of the codes. Lastly, if you would like to propose an alternative method to retaining reserve samples, we recommend that you provide detailed background information on the alternative methods during pre-ANDA communications to avoid any future misunderstandings.

4 Appendix

Table 4.1: Protocols Submitted to the Office of Generic Drugs for Fluticasone Propionate and Salmeterol Xinafoate

Protocol No	Drug Name	Firm	Reviewer	Letter Date	Completed Date	Comments
140014	Fluticasone Propionate and Salmeterol Xinafoate	Mylan	ORS (Science Staff)	8/4/2014		Special Protocol Assessment. A non-dosing inhaler development study to assess the use of the 4 key operational steps of CRC749 and the likelihood of orientation-related errors by representative users, including Advair® Diskus® patients.

(b) (4)

Source: Search of OGD DBE Tracking System/Protocol Database and Mercado on 12/13/2017

Table 4.2: Bio-INDs Submitted to the Office of Generic Drugs for Fluticasone Propionate and Salmeterol Xinafoate

Bio-IND Number	Application SubType	Product Name	Submitter	Current Status	Status Date	Indication/ Subject/Issue
IND-118769	Commercial	Fluticasone Propionate and Salmeterol Xinafoate	Mylan Global Respiratory Group	Active	9/13/2013	Treatment of asthma & treatment of chronic obstructive pulmonary disease (COPD)

(b) (4)

Source: Search of DAARTS on 12/13/2017

Table 4.3: Controlled Correspondences Submitted to the Office of Generic Drugs for Fluticasone Propionate and Salmeterol Xinafoate (n=75; 3 open [14-0298 and 14-0001])

Control Number	Title	Description	Status	Document Date	From
04-458	Fluticasone Propionate/Salmeterol Xinfoate Oral Inhalation Powder				
04-469	Fluticasone Propionate/Salmeterol Xinafoate DPI				
04-031	Fluticasone Propionate and Salmeterol Inhalation Powder				
05-1551	Fluticasone Propionate/Salmeterol Xinafoate DPI				
06-0694	Fluticasone/Salmeterol Inhalation Powder				
06-0660	Fluticasone/Salmeterol Inhalation Powder				
06-0627	Fluticasone Propionate/Salmeterol Xinafoate DPI				
07-0587	Fluticasone Propionate/Salmeterol Xinafoate DPI				
08-0341	Fluticasone and Salmeterol Dry Powder Inhaler				

(b) (4)

08-0366	Fluticasone/Salmeterol Inhalation Powder	(b) (4)			
07-0627	Fluticasone Propionate/Salmeterol Xinafoate DPI				
07-1049	Fluticasone propionate; Salmeterol xinafoate HFA MDI				
09-0638	Fluticasone and Fluticasone/Salmeterol DPI				
10-0020	Fluticasone Propionate and/or Salmeterol Xinafoate DPI/MDI				
09-0271	Fluticasone Propionate and/or Salmeterol Xinafoate DPI/MDI				
10-0533	Fluticasone Propionate/Salmeterol Xinafoate DPI				
11-0888	Fluticasone/Salmeterol inhalation device				
12-0316	Fluticasone Propionate/Salmeterol Xinafoate DPI				
14-0298	Fluticasone Propionate/Salmeterol Xinafoate DPI				
12-0387	Fluticasone Propionate/Salmeterol Xinafoate DPI				
12-0555	Fluticasone/Salmeterol Inhalation Powder				
12-0731	Fluticasone Propionate/Salmeterol Xinafoate DPI				
12-0850	Fluticasone Propionate plus Salmeterol Xinafoate Inhalation Powder	Pre-meeting information package for control 12-0731. Fluticasone Propionate plus Salmeterol Xinafoate Inhalation Powder in CRC749 inhaler - Type C	Closed 9/14/2012	9/14/2012	Mylan Global Respiratory Group
12-1009	Fluticasone Propionate/Salmeterol Xinafoate DPI - meeting request	(b) (4)			
13-0147	Fluticasone Propionate/Salmeterol Xinafoate DPI				

		(b) (4)			
13-0422	Fluticasone Propionate/Salmeterol Xinafoate DPI - meeting request	Fluticasone Propionate plus Salmeterol Xinafoate Inhalation Powder in CRC749 inhaler - Type C meeting request to discuss MGR001	Closed 1/2/2014	5/22/2013	Mylan Global Respiratory Group
13-0576	Fluticasone propionate; Salmeterol xinafoate DPI Meeting Request	(b) (4)			
13-0422A	Fluticasone Propionate/Salmeterol Xinafoate DPI - meeting request	Fluticasone Propionate plus Salmeterol Xinafoate Inhalation Powder in CRC749 inhaler - Type C meeting request to discuss MGR001	Closed 1/2/2014	6/26/2013	Mylan Global Respiratory Group
13-0804	Fluticasone Propionate 100 mcg and Salmeterol 50 mcg, Inh Powder	(b) (4)			
13-0952	Fluticasone propionate; Salmeterol xinafoate DPI Meeting Request	(b) (4)			
13-0977	Fluticasone Propionate/Salmeterol Xinafoate DPI	(b) (4)			
14-0001	Fluticasone propionate; Salmeterol xinafoate DPI	(b) (4)			
14-0029	Fluticasone Propionate; Salmeterol Xinafoate mDPI, 100/50mcg	(b) (4)			
14-0081 (CC# 25059, 26314)	Fluticasone propionate; Salmeterol xinafoate DPI	(b) (4)			
14-0233 (CC# 25065)	Fluticasone Propionate/Salmeterol Xinafoate DPI	(b) (4)			
14-0236	Fluticasone Propionate/Salmeterol Xinafoate DPI, 100mcg/50mcg	(b) (4)			
14-0237	Fluticasone Propionate/Salmeterol Xinafoate DPI, 250mcg/50mcg	(b) (4)			

14-0238	Fluticasone Propionate/Salmeterol Xinafoate DPI, 500mcg/50mcg
14-0207	Fluticasone propionate; Salmeterol xinafoate DPI
25984	Fluticasone propionate; Salmeterol xinafoate DPI
46224	Fluticasone propionate; Salmeterol xinafoate DPI
1833232	Fluticasone propionate; Salmeterol xinafoate DPI
2126997	Fluticasone propionate; Salmeterol xinafoate DPI
2127319	Fluticasone propionate; Salmeterol xinafoate DPI
3195079	Fluticasone propionate; Salmeterol xinafoate DPI
327635	Fluticasone propionate; Salmeterol xinafoate
327636	Fluticasone propionate; Salmeterol xinafoate
1703167	Fluticasone propionate and Salmeterol 100/50 mcg inhalation powder
3128883	Fluticasone-Salmeterol Inhalation Powder
773768	Fluticasone Propionate/salmeterol xinafoate DPI
327639	Fluticasone propionate; Salmeterol xinafoate
1703165	Fluticasone propionate and Salmeterol 100/50 mcg inhalation powder
1703166	Fluticasone propionate and Salmeterol 100/50 mcg inhalation powder
14723117	Fluticasone Propionate; Salmeterol Xinafoate Aerosol ADVAIR HFDA 021254

2936755	Fluticasone propionate and Salmeterol DPI
8082902	Fluticasone Propionate and Salmeterol Inhalation Powder
48173	Fluticasone Propionate 100 mcg and Salmeterol 50 mcg Inhalation Powder
819050	Fluticasone Propionate and Salmeterol Inhalation Powder
41739	Fluticasone Propionate & Salmeterol Inhalation
41490	Fluticasone Propionate & Salmeterol Inhalation
50960	Fluticasone Propionate and Salmeterol Inhalation Powder
45747	Fluticasone Propionate and Salmeterol Inhalation Powder
8914698	Fluticasone Propionate/ Salmeterol Xinafoate Inhalation Powder
8914529	Fluticasone Propionate/ Salmeterol Xinafoate Inhalation Powder
8914552	Fluticasone Propionate/ Salmeterol Xinafoate Inhalation Powder
399105	Fluticasone Propionate/ Salmeterol Xinafoate Inhalation Powder
7827793	Advair Diskus 100/50, 250/50, 500/50
25987	Fluticasone Propionate/ Salmeterol Xinafoate Inhalation Powder
25986	Fluticasone Propionate/ Salmeterol Xinafoate Inhalation Powder
25988	Fluticasone Propionate/ Salmeterol Xinafoate Inhalation Powder

844398	Fluticasone Propionate/ Salmeterol Xinafoate	(b) (4)
17261499	Fluticasone Propionate/ Salmeterol Xinafoate Inhalation Powder	
17261603	Fluticasone Propionate/ Salmeterol Xinafoate Inhalation Powder	
17261580	Fluticasone Propionate/ Salmeterol Xinafoate Inhalation Powder	
18514316	Fluticasone Propionate/ Salmeterol Xinafoate Inhalation Powder	

Source: Search of OGD Tracking System/Internal Document Tracking and Mercado on 12/19/2017

Tables 4.4, 4.5, and 4.6: PP Population Recommendations from DCR to Statistician for ANDA 208891 (6/12/2018)

Per Protocol Population Recommendations for FDA Population

Study #	Subject number	Applicant included/ excluded	FDA PP Include/ Exclude	Reason
MGR001-3001	(b) (6)	Included	Exclude	Short-acting beta agonist use within 6 hours of lung function testing (Visit 3) According to the Applicant’s response to IR question 3 that was submitted on 2/1/2018, these subjects used a short-acting beta agonist (albuterol) during or within six hours prior to spirometry measurements and these spirometry measurements were used in calculation of Day 1 FEV₁ AUEC₀₋₁₂ endpoint during Visit 3 (Day 1 Visit). As described in Section 4.1.4.2.4 in the Clinical Study Report, if a subject took albuterol during the 0 to 12-hour post dose spirometry assessments on Day 1, then for the Per Protocol Analysis of the Day 1 FEV₁ AUEC₀₋₁₂ endpoint, all serial spirometry assessments collected after the albuterol use were set to missing. Based on the missing spirometry assessments during 0 to 12-hour post dose spirometry assessments, these subjects are recommended to be excluded from the FDA PP and FDA Day 1 PP based on Section 4.1.4.2.4 of the Clinical Study Report. These subjects are recommended to be included in the FDA Day 29 PP since the short-acting beta agonist (albuterol) use occurred after the two Visit 3 pre-dose FEV₁ spirometry measurements were collected that form part of the baseline for the Day 29 trough FEV₁ endpoint.
MGR001-3001		Included	Exclude	Short-acting beta agonist use within 6 hours of lung function testing (Visit 3) and Visit 5 completed out of pre-specified study visit window (Day 29 ±2 days) According to the Applicant’s response to IR question 3 that was submitted on 2/1/2018, these subjects used a short-acting beta agonist (albuterol) during or within six hours prior to spirometry measurements and these spirometry measurements were used in calculation of Day 1 FEV₁ AUEC₀₋₁₂ endpoint during Visit 3 (Day 1 Visit). As described in Section 4.1.4.2.4 in the Clinical Study Report, if a subject took albuterol during the 0 to 12-hour post dose spirometry assessments on Day 1, then for the Per Protocol

				Analysis of the Day 1 FEV₁ AUEC₀₋₁₂ endpoint, all serial spirometry assessments collected after the albuterol use were set to missing. Based on the missing spirometry assessments during 0 to 12-hour post dose spirometry assessments, these subjects are recommended to be excluded from the FDA PP and FDA Day 1 PP based on Section 4.1.4.2.4 of the Clinical Study Report. Based on the Applicant's response to IR question 7 that submitted on 2/1/2018 and IR question 6 submitted on 2/26/2018, it was determined by the FDA Statistician that these subjects were included in the Applicant's Per Protocol Set and completed their Visit 5 outside the Applicant's pre-specified visit window of Day 29 ±2 days. As a result, these subjects should be excluded from FDA PP and FDA Day 29 endpoint PP population. Therefore, these subjects are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP population.
MGR001-3001		Included	Exclude	Short-acting beta agonist use within 6 hours of lung function testing (Visit 3), Visit 5 completed out of pre-specified study visit window (Day 29 ±2 days), and Did not meet required 75-125% compliance for double-blind study treatment period According to the Applicant's response to IR question 3 that was submitted on 2/1/2018, these subjects used a short-acting beta agonist (albuterol) during or within six hours prior to spirometry measurements and these spirometry measurements were used in calculation of Day 1 FEV₁ AUEC₀₋₁₂ endpoint during Visit 3 (Day 1 Visit). As described in Section 4.1.4.2.4 in the Clinical Study Report, if a subject took albuterol during the 0 to 12-hour post dose spirometry assessments on Day 1, then for the Per Protocol Analysis of the Day 1 FEV₁ AUEC₀₋₁₂ endpoint, all serial spirometry assessments collected after the albuterol use were set to missing. Based on the missing spirometry assessments during 0 to 12-hour post dose spirometry assessments, this subject is recommended to be excluded from the FDA PP and FDA Day 1 PP based on Section 4.1.4.2.4 of the Clinical Study Report. Based on the Applicant's response to IR question 7 that submitted on 2/1/2018 and IR question 6 submitted on 2/26/2018, it was determined by the FDA Statistician that this subject was included in the Applicant's Per Protocol Set and completed their Visit 5 outside the Applicant's pre-specified visit window of Day 29 ±2 days. According to the FDA Statistician's calculation and verification, this subject was

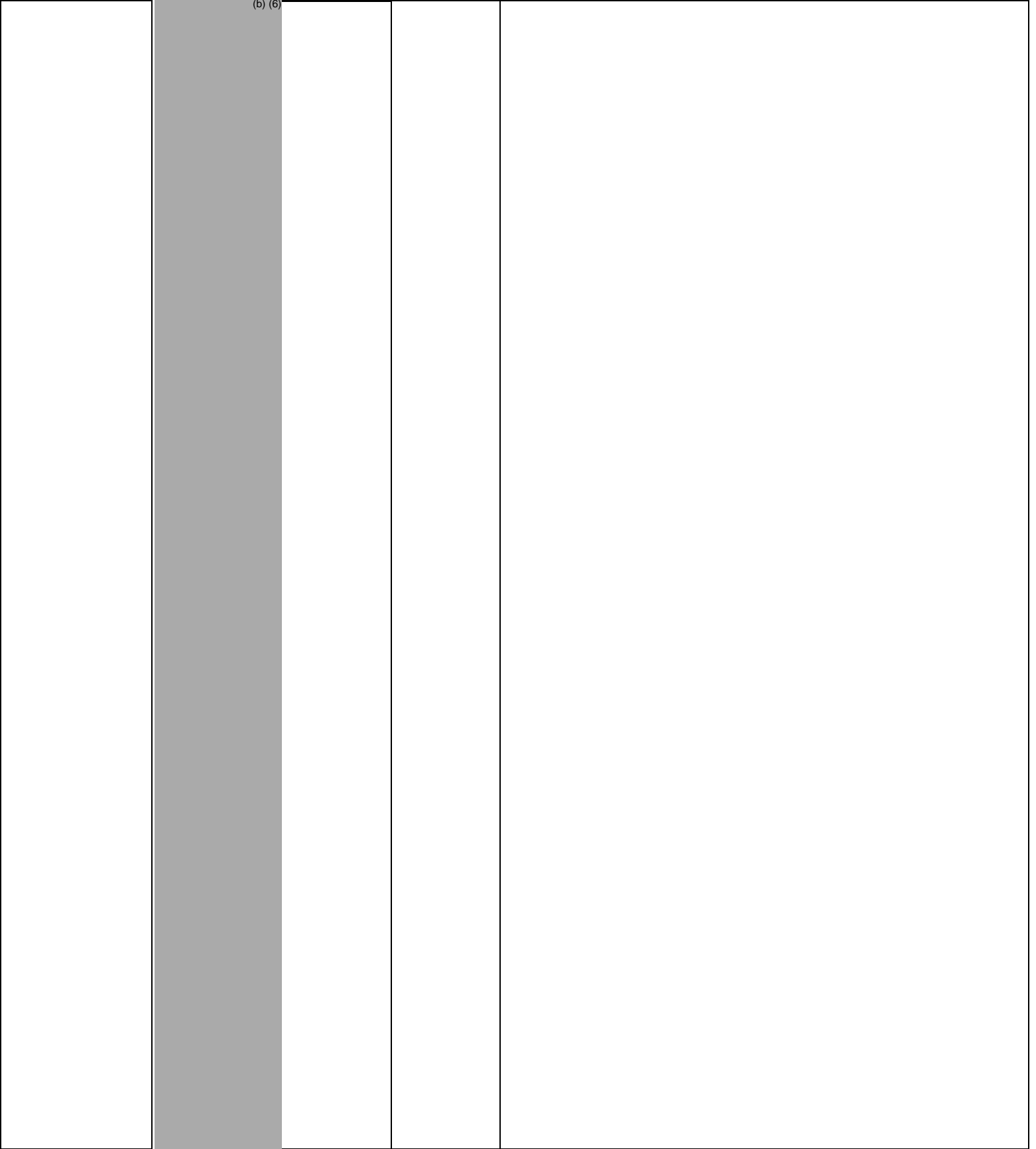
				included in the Applicant’s Per Protocol Set and did not meet the required 75-125% compliance with the study treatment during the double-blind study treatment period. The Applicant was noted to have incorrectly calculated the expected number of doses (denominator) based on the study design. As a result, this subject is recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP population.
MGR001-3001	(b) (6)	Included	Exclude	Missing data for 2 hours to 6 hours post-dose time for Day 1 endpoint According to Table 2 of Appendix 16.1.9.3.4.6, Subject (b) (6) is missing data for the 2 hours to 6 hours post-dose time points on Day 1. According to Section 4.5.4 of the Statistical Analysis Plan (“Handling Missing Co-primary Endpoint Data”), Subject (b) (6) Day 1 endpoint should be set to missing since data for 2 hour to 6 hours post-dose time point on Day 1 is missing. As a result, this subject is recommended to be excluded from the FDA PP and FDA Day 1 PP population but to be included in the FDA Day 29 PP population as the missing data for 2 hours to 6 hours post-dose time point does not affect the Day 29 endpoint.
MGR001-3001	(b) (6)	Included	Exclude	Used prohibited concomitant medication (corticosteroid) – Did not meet Inclusion Criterion 9, Did not meet required Double-blind Study drug compliance of 75-125%, and Early Termination Visit data improperly carried forward for Day 29 endpoint (Visit 5 completed out of pre-specified study visit window - Day 29 ±2 days) Subject (b) (6) experienced an adverse event of “asthma exacerbation” from (b) (6) (Day 1) to (b) (6) (Day 6). According to Applicant’s response to IR question 2 that was submitted on 2/26/2018, the adverse event started between hour 4 and hour 6 serial spirometry measurements on Day 1 and all serial spirometry measurements on Day 1 after hour 6 were set to missing. Subject took Prednisone 40mg oral QD from (b) (6) to Ongoing (Day 2 to Ongoing). Subject included in Applicant’s PPS with Day 1 endpoint set to missing. Applicant improperly carried forward data from Early Termination Visit on Day 15 (b) (6) for Day 29 endpoint.

				Subject (b) (6) should be excluded from FDA PP and FDA Day 1 endpoint PP population since there is insufficient FEV1 data to calculate a Day 1 AUEC0-12 value and excluded from FDA PP and FDA Day 29 endpoint PP population since data from ET visit was improperly carried forward (prohibited concomitant medication and double-blind study drug compliance).
MGR001-3001	(b) (6)	Included	Exclude	Used prohibited concomitant medication (inhaled corticosteroid) – Did not meet Inclusion Criterion 9, Short-acting beta agonist use within 6 hours of lung function testing (Visit 3), Did not meet required Double-blind Study drug compliance of 75-125%, and Early Termination Visit data improperly carried forward for Day 29 endpoint Subject (b) (6) experienced an adverse event of “asthma exacerbation” from 6/10/2015 (Day 1) to 6/10/2015 (Day 1). According to Applicant’s response to IR question 2 that was submitted on 2/26/2018, the adverse event started between hour 3 and hour 4 serial spirometry measurements on Day 1 and all serial spirometry measurements on Day 1 after hour 4 were set to missing. Subject took Flovent inhaler 1 puff BID from (b) (6) to Ongoing (Day 1 to Ongoing). Subject included in Applicant’s PPS with Day 1 endpoint set to missing. Applicant improperly carried forward data from Early Termination Visit on Day 8 (b) (6) for Day 29 endpoint. Subject (b) (6) should be excluded from FDA PP and FDA Day 1 endpoint PP population since there is insufficient FEV1 data to calculate a Day 1 AUEC0-12 value and excluded from FDA PP and FDA Day 29 endpoint PP population since data from ET visit was improperly carried forward (prohibited concomitant medication and double-blind study drug compliance).
MGR001-3001	(b) (6)	Included	Exclude	Visit 4 data (FEV1) improperly carried forward for Day 29 endpoint and subject did not meet required 75-125% compliance with study treatment for double-blind study treatment period According to the Applicant’s response to IR question 8 that was submitted on 2/26/2018, Subject (b) (6) discontinued from the study on (b) (6) (Day 29) due to “withdrawal by subject.” According to adef22.xpt data set, the subject’s last day of exposure to the study medication (double-blind treatment) was Day 28 and FEV1 spirometry data from Visit 4 collected on Day 15

				(b) (6) was carried forward and used in the primary bioequivalence analysis for the Day 29 endpoint. According to the FDA Statistician's calculation and verification, this subject was included in the Applicant's Per Protocol Set and did not meet the required 75-125% compliance with the study treatment during the double-blind study treatment period. The Applicant was noted to have incorrectly calculated the expected number of doses (denominator) used in calculation of double-blind study treatment period compliance based on the study design. Subject (b) (6) should be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in FDA Day 1 endpoint PP population since the Day 1 endpoint is not affected by FEV1 spirometry data from Visit 4 improperly carried forward for Day 29 endpoint and since the Day 1 endpoint is not affected by compliance with the study treatment during the double-blind treatment period.
MGR001-3001	(b) (6)	Included	Exclude	Used prohibited concomitant medication (corticosteroid) According to Applicant's response to IR question 12a (Table 9) that was submitted on 2/1/2018, these subjects used a prohibited concomitant medication of oral or parenteral corticosteroid during the double-blind treatment period and were included in the Applicant's PPS. Subject (b) (6) used Prednisone 30mg PO QD from (b) (6) (Day 20) to (b) (6) (Day 24) and Singulair 10mg PO QD from (b) (6) (Day 20) to Ongoing. Subject (b) (6) used Prednisone 40mg PO QD from (b) (6) (Day 7) to (b) (6) (Day 10). Subject (b) (6) used Prednisone 20mg PO BID from (b) (6) (Day 3) to (b) (6) (Day 6). Subject (b) (6) used Methylprednisolone Acetate 80mg IV once on (b) (6) (Day 18). Subject (b) (6) used Dexamethasone 10mg IV once on (b) (6) (Day 3). These subjects should be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in FDA Day 1 endpoint PP population since the Day 1 endpoint is not affected since all prohibited concomitant medications were first taken after Day 1.
MGR001-3001	(b) (6)	Included	Exclude	Used prohibited concomitant medication (inhaled corticosteroid) during double-blind treatment period

				According to the Applicant's response to IR question 4 submitted on 2/26/2018 and Concomitant Medication data set (cm.xpt), Subject (b) (6) used Qvar (Beclomethasone Dipropionate) 80µg inhaled BID on (b) (6) (Day 32). Visit 5 for this subject occurred on (b) (6) (Day 33). This subject was included in the Applicant's PPS and used a prohibited concomitant medication (inhaled corticosteroid) during the double-blind treatment period that would affect the Day 29 endpoint. Subject (b) (6) should be excluded from FDA PP and FDA Day 29 endpoint PP population and included in the FDA Day 1 PP as the Day 1 endpoint is not affected since the prohibited concomitant medication use occurred after Day 1.
MGR001-3001	(b) (6)	Included	Exclude	Used prohibited concomitant medication (inhaled short acting anti-muscarinic) during double-blind treatment period According to the Applicant's response to IR question 4 submitted on 2/26/2018 and Concomitant Medication data set (cm.xpt), Subject (b) (6) used Ipratropium Bromide and Albuterol Sulfate 0.5mg/3mg per 3mL (Combivent) 1 nebulizer inhaled on (b) (6) (Day 17). This subject was included in the Applicant's PPS and used a prohibited concomitant medication (inhaled short acting anti-muscarinic) during the double-blind treatment period that would affect the Day 29 endpoint. Subject (b) (6) should be excluded from FDA PP and FDA Day 29 endpoint PP population and included in the FDA Day 1 PP as the Day 1 endpoint is not affected since the prohibited concomitant medication use occurred after Day 1.
MGR001-3001	(b) (6)	Included	Exclude	Visit 5 completed out of pre-specified study visit window (Day 29 ±2 days) Based on the Applicant's response to IR question 7 that submitted on 2/1/2018 and IR question 6 submitted on 2/26/2018, it was determined by the FDA Statistician that these subjects were included in the Applicant's Per Protocol Set and completed their Visit 5 outside the Applicant's pre-specified visit window of Day 29 ±2 days. These subjects' inclusion into the Day 1 PP population is not affected by this protocol deviation since the Day 1 endpoint is not affected by Visit 5 being out of the visit window.

(b) (6)



	(b) (6)			
MGR001-3001		Included	Exclude	Product Specific Guidance and Study Protocol required FEV₁ Percent Predicted not met on First Day of Study Treatment - Did not meet Inclusion Criterion 5 According to Applicant's response to IR question 12A that was submitted on 2/1/2018, Subject (b) (6) had a mean FEV₁ Percent Predicted of 93.1% at Visit 3. Since this subject was enrolled under the Original version of the Study Protocol and was taking an ICS and/or LABA prior to screening, the pre-specified study protocol for Inclusion Criterion 5 required the mean FEV₁ Percent Predicted at Visit 3 to be between 50% to 85% of FEV₁ Percent Predicted. The Applicant's justification in IR Comment 12A stated that although the mean FEV₁ Percent Predicted at Visit 3 did not meet Inclusion Criterion 5, the mean of FEV₁ Percent Predicted at Visit 2 (71.1%) and mean FEV₁ Percent Predicted at Visit 3 (93.1%) were within the range of 50-85% that this subject was not excluded from the Per Protocol Set. This rationale is not acceptable since this is different than what is pre-specified in the Applicant's Study Protocol and the requirement in the Product Specific Guidance. This subject is recommended to be excluded from the FDA PP, FDA Day 1, and FDA Day 29 PP populations.
MGR001-3001		Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved - Did not meet Inclusion Criterion 6 According to Applicant's response to IR question 13a that was submitted on 2/1/2018, Subjects (b) (6) (b) (6) did not meet Study Protocol's requirement of demonstration of 12% reversibility after bronchodilator and subjects were entered

				into the double-blind treatment phase in error. Since these subjects did not meet Inclusion Criterion 6, they are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.
MGR001-3001	(b) (6)	Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved - Did not meet Inclusion Criterion 6 According to the Applicant's response to IR question 10b that was submitted on 2/26/2018, these subjects did not meet Study Protocol's requirement of demonstration of 12% reversibility after bronchodilator and subjects were entered into the double-blind treatment phase in error. Since these subjects did not meet Inclusion Criterion 6, they are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations. Several subjects had additional protocol deviations. Subject (b) (6) did not meet required 75-125% compliance with study treatment for double-blind study treatment period. Subject (b) (6) had Visit 5 completed out of pre-specified study visit window (Day 29 ±2 days) and did not meet required 75-125% compliance with study treatment for double-blind study treatment period. Subject (b) (6) had Visit 5 completed out of pre-specified study visit window (Day 29 ±2 days). Subject (b) (6) did not meet required 75-125% compliance with study treatment for double-blind study treatment period. Subject (b) (6) did not meet required 75-125% compliance with study treatment for double-blind study treatment period.
MGR001-3001		Included	Exclude	Did not meet required 75-125% compliance with study treatment for double-blind study treatment period According to the FDA Statistician's calculation and verification, these subjects were included in the Applicant's Per Protocol Set and did not meet the required 75-125% compliance with the study treatment during the double-blind study treatment period. The Applicant was noted to have incorrectly calculated the expected number of doses (denominator) used in calculation of double-blind study treatment period compliance based on the study design.

	(b) (6)			These subjects should be excluded from FDA PP and FDA Day 29 endpoint PP population and included in FDA Day 1 endpoint PP population since the Day 1 endpoint is not affected by compliance with the study treatment during the double-blind treatment period.
MGR001-3001		Included	Exclude	Did not meet required percent predicted FEV1 during the screening period and on first day of double-blind treatment period - Did not meet Inclusion Criterion 5 According to the FDA Statistician's calculation and verification, these subjects were included in the Applicant's Per Protocol Set and did not meet the required percent predicted FEV1 during the screening period and on first day of double-blind treatment period (Violation of Inclusion Criterion 5). The Study Protocol required subjects to meet percent predicted FEV1 at Visit 1

				(Screening Visit), Visit 2 (Run-in Visit), and Visit 3 (First day of double-blind treatment period) while the Product Specific Guidance recommends pre-bronchodilator percent predicted FEV1 be met during the screening visit and on the first day of treatment. As a result, subjects were recommended to be excluded from the FDA PP populations if they did not meet percent predicted FEV1 at Visit 1 or Visit 2 (once during placebo run-in period) and at Visit 3 (first day of double-blind treatment period). Subject (b) (6) had percent predicted FEV1 of 93.1025% at Visit 3 (did not meet Product Specific Guidance required percent predicted FEV1 on the first day of double-blind treatment period). Subject (b) (6) had percent predicted FEV1 of 97.1258% at Visit 1, 97.8402% at Visit 2, and 91.0534% at Visit 3 (did not meet Product Specific Guidance required percent predicted FEV1 at either visit during placebo run-in period or on the first day of double-blind treatment period). Subject (b) (6) had percent predicted FEV1 of 85.8664% at Visit 3 (did not meet Product Specific Guidance required percent predicted FEV1 on the first day of double-blind treatment period). Subject (b) (6) had percent predicted FEV1 of 87.1836% at Visit 1, 90.0272% at Visit 2, and 89.2967% at Visit 3 (did not meet Product Specific Guidance required percent predicted FEV1 at either visit during placebo run-in period or on the first day of double-blind treatment period). Subject (b) (6) had percent predicted FEV1 of not recorded at Visit 1, 96.6751% at Visit 2, and 94.2712% at Visit 3 (did not meet Product Specific Guidance required percent predicted FEV1 at either visit during placebo run-in period or on the first day of double-blind treatment period). Subject (b) (6) had percent predicted FEV1 of 33.5241% at Visit 3 (did not meet Product Specific Guidance required percent predicted FEV1 on the first day of double-blind treatment period). Since these subjects did not meet Inclusion Criterion 5, they are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.
MGR001-3001	(b) (6)	Included	Exclude	Did not meet requirement in Statistical Analysis Plan that Day 29 (Visit 5) average pre-dose measurements are within ± 2 hours of Day 1 (Visit 3) average pre-dose measurements and/or subjects with post-screening visit pre-dose assessments completed after 12 noon

(b) (6)

According to Applicant's response to IR question 12 that was submitted on 2/26/2018, the Applicant does not believe that spirometry performed outside of a ± 1 hour window for the Day 29 trough FEV₁ endpoint as stated in the Study Protocol is not a valid reason to exclude subjects from the Day 29 Per Protocol Set. Instead, the Applicant stated that a ± 2 hour window for the Day 29 trough FEV₁ endpoint as pre-specified in the Statistical Analysis Plan (Section 8.1.4) was used in the Applicant's relevant sensitivity analyses and would allow for the predictable situation that some patients would attend the clinic earlier or later than stated in the protocol.

According to Applicant's response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018, these subjects had Day 29 out of window spirometry assessments where Day 29 (Visit 5) average pre-dose assessments are not within ± 2 hours of Day (Visit 3) average pre-dose time-points and/or subjects with pre-dose assessments completed after 12 noon and were included in the Applicant's PPS.

These subjects should be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in FDA Day 1 endpoint PP population since the Day 1 endpoint is not affected by this protocol deviation.

(b) (6)

(b) (6)

	(b) (6)			
MGR001-3001		Included	Exclude	Short-acting beta agonist use within 6 hours of lung function testing (Visit 3) and subject did not meet requirement in Statistical Analysis Plan that Day 29 (Visit 5) average pre-dose measurements are within ± 2 hours of Day 1 (Visit 3) average pre-dose measurements and/or subjects with post-screening visit pre-dose assessments completed after 12 noon According to the Applicant's response to IR question 3 that was submitted on 2/1/2018, these subjects used a short-acting beta agonist (albuterol) during or within six hours prior to spirometry measurements and these spirometry measurements were used in calculation of Day 1 FEV1 AUEC0-12 endpoint during Visit 3 (Day 1 Visit). As described in Section 4.1.4.2.4 in the Clinical Study Report, if a subject took albuterol during the 0 to 12-hour post dose spirometry assessments on Day 1, then for the Per Protocol Analysis of the Day 1 FEV₁ AUEC₀₋₁₂ endpoint, all serial spirometry assessments collected after the albuterol use were set to missing. Based on the missing spirometry assessments during 0 to 12-hour post dose spirometry assessments, these subjects are recommended to be excluded from the FDA PP and FDA Day 1 PP based on Section 4.1.4.2.4 of the Clinical Study Report. According to Applicant's response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018, this subject had Day 29 out of window spirometry assessments where Day 29 (Visit 5) average pre-dose assessments are not within ± 2 hours of Day (Visit 3) average pre-dose time-points and/or subjects with pre-dose assessments completed after 12 noon and was included in the Applicant's PPS. These subjects should be excluded from FDA PP and FDA Day 1 endpoint PP populations because of short-acting beta agonist use within 6 hours of lung function testing (Visit 3) and excluded from FDA PP and Day 29 endpoint PP populations because Day 29 (Visit 5) average pre-dose measurements are within ± 2 hours of Day 1 (Visit 3) average pre-dose measurements and/or subjects with post-

				screening visit pre-dose assessments completed after 12 noon.
MGR001-3001	(b) (6)	Included	Exclude	Short-acting beta agonist use within 6 hours of lung function testing (Visit 3) and did not meet required 75-125% compliance with study treatment for double-blind study treatment period According to the Applicant’s response to IR question 3 that was submitted on 2/1/2018, these subjects used a short-acting beta agonist (albuterol) during or within six hours prior to spirometry measurements and these spirometry measurements were used in calculation of Day 1 FEV1 AUEC0-12 endpoint during Visit 3 (Day 1 Visit). As described in Section 4.1.4.2.4 in the Clinical Study Report, if a subject took albuterol during the 0 to 12-hour post dose spirometry assessments on Day 1, then for the Per Protocol Analysis of the Day 1 FEV₁ AUEC₀₋₁₂ endpoint, all serial spirometry assessments collected after the albuterol use were set to missing. Based on the missing spirometry assessments during 0 to 12-hour post dose spirometry assessments, these subjects are recommended to be excluded from the FDA PP and FDA Day 1 PP based on Section 4.1.4.2.4 of the Clinical Study Report. According to the FDA Statistician’s calculation and verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the required 75-125% compliance with the study treatment during the double-blind study treatment period. The Applicant was noted to have incorrectly calculated the expected number of doses (denominator) used in calculation of double-blind study treatment period compliance based on the study design. These subjects should be excluded from FDA PP and FDA Day 29 endpoint PP population. These subjects should be excluded from FDA PP and FDA Day 1 endpoint PP populations because of short-acting beta agonist use within 6 hours of lung function testing (Visit 3) and excluded from FDA PP and Day 29 endpoint PP populations because subjects did not meet required 75-125% compliance with study treatment for double-blind study treatment period.
MGR001-3001		Included	Exclude	Subject dosed with study treatment prior to completion of pre-dose spirometry assessments at Visit 5 and visit was not rescheduled

				According to Applicant's response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018 and Listing 16.2.2-1.3, these subjects were dosed with study treatment prior to completion of pre-dose spirometry assessments at Visit 5 and this visit was not rescheduled. These subjects should be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in FDA Day 1 endpoint PP population since the Day 1 endpoint is not affected by this protocol deviation.
MGR001-3001	(b) (6)	Included	Exclude	Subject dosed with study treatment prior to completion of pre-dose spirometry assessments at Visit 5 and visit was not rescheduled and subject did not meet requirement in Statistical Analysis Plan that Day 29 (Visit 5) average pre-dose measurements are within ± 2 hours of Day 1 (Visit 3) average pre-dose measurements and/or subjects with post-screening visit pre-dose assessments completed after 12 noon According to Applicant's response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018 and Listing 16.2.2-1.3, these subjects were dosed with study treatment prior to completion of pre-dose spirometry assessments at Visit 5 and this visit was not rescheduled. According to Applicant's response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018, this subject had Day 29 out of window spirometry assessments where Day 29 (Visit 5) average pre-dose assessments are not within ± 2 hours of Day (Visit 3) average pre-dose time-points and/or subjects with pre-dose assessments completed after 12 noon. These subjects should be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in FDA Day 1 endpoint PP population since the Day 1 endpoint is not affected by these protocol deviations.
MGR001-3001		Included	Exclude	Subject dosed with study treatment prior to completion of pre-dose spirometry assessments at Visit 5 and visit was not rescheduled and Visit 5 completed out of pre-specified study visit window (Day 29 ± 2 days) According to Applicant's response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018 and Listing 16.2.2-1.3, these subjects were dosed with study treatment prior to completion of pre-dose spirometry assessments at Visit 5 and this visit was not rescheduled. Based on the Applicant's response to IR question 7 that submitted on 2/1/2018 and IR question 6 submitted on 2/26/2018, it was

				determined by the FDA Statistician that these subjects were included in the Applicant's Per Protocol Set and completed their Visit 5 outside the Applicant's pre-specified visit window of Day 29 ±2 days. These subjects should be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in FDA Day 1 endpoint PP population since the Day 1 endpoint is not affected by these protocol deviations.
MGR001-3001	(b) (6)	Included	Exclude	Adverse event (not treatment failure) lead to study discontinuation According to Applicant's response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018 and ae.xpt data set, Subject (b) (6) experienced an adverse event of allergic rhinitis from Day 18 (b) (6) to Day 23 (b) (6) that lead to subject discontinuation from the study and thus Day 29 (Visit 5) data is not available. An adverse event of allergic rhinitis is not considered to be a treatment failure by FDA and therefore, this subject is recommended to be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in the FDA Day 1 endpoint PP population.
MGR001-3001	(b) (6)	Included	Exclude	Adverse event (not treatment failure) lead to study discontinuation According to Applicant's response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018 and ae.xpt data set, Subject (b) (6) experienced an adverse event of acute bronchitis from Day 4 (b) (6) to Day 24 (b) (6) that lead to subject discontinuation from the study and thus Day 29 (Visit 5) data is not available. An adverse event of acute bronchitis is not considered to be a treatment failure by FDA and therefore, this subject is recommended to be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in the FDA Day 1 endpoint PP population.
MGR001-3001	(b) (6)	Included	Exclude	Adverse event (not treatment failure) lead to study discontinuation According to Applicant's response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018 and ae.xpt data set, Subject (b) (6) experienced an adverse event of pneumonia from Day 10 (b) (6) to Day 13 (1/10/2015) that lead to subject discontinuation from the

				study and thus Day 29 (Visit 5) data is not available. An adverse event of pneumonia is not considered to be a treatment failure by FDA and therefore, this subject is recommended to be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in the FDA Day 1 endpoint PP population.
MGR001-3001	(b) (6)	Included	Exclude	Adverse event (not treatment failure) lead to study discontinuation According to Applicant's response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018 and ae.xpt data set, Subject (b) (6) experienced an adverse event of inguinal hernia from Day 9 (b) (6) to Ongoing that lead to subject discontinuation from the study and thus Day 29 (Visit 5) data is not available. An adverse event of inguinal hernia is not considered to be a treatment failure by FDA and therefore, this subject is recommended to be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in the FDA Day 1 endpoint PP population.
MGR001-3001		Included	Exclude	Adverse event (not treatment failure) lead to study discontinuation According to Applicant's response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018 and ae.xpt data set, Subject (b) (6) experienced an adverse event of bronchitis from Day 7 (b) (6) to Day 19 (b) (6) that lead to subject discontinuation from the study and thus Day 29 (Visit 5) data is not available. An adverse event of bronchitis is not considered to be a treatment failure by FDA and therefore, this subject is recommended to be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in the FDA Day 1 endpoint PP population.
MGR001-3001		Included	Exclude	Adverse events (not treatment failure) led to study discontinuation According to Applicant's response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018 and ae.xpt data set, Subject (b) (6) experienced adverse events of insomnia and anxiety from Day 2 (b) (6) to Day 7 (b) (6) that lead to subject discontinuation from the study and thus Day 29 (Visit 5) data is not available.

				Adverse events of insomnia and anxiety are not considered to be a treatment failure by FDA and therefore, this subject is recommended to be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in the FDA Day 1 endpoint PP population.
MGR001-3001	(b) (6)	Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved after excluding spirometry measurements with “Unacceptable” Grade - Did not meet Inclusion Criterion 6 According to the FDA Statistician’s verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the Study Protocol’s requirement of demonstration of 12% reversibility after bronchodilator after excluding those spirometry measurements with “Unacceptable” PFT grading. According to the Applicant’s response to IR question 1 including adre.xpt data set that was submitted on 3/22/2018, spirometry measurements with “Unacceptable” PFT grading did not meet the American Thoracic Society Guidelines (2005) for technical quality or repeatability. Since these spirometry measurements did not meet the ATS Guidelines for technical quality, they cannot be used to determine whether a subject met an inclusion criterion. Since these subjects did not meet Inclusion Criterion 6, they are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.
MGR001-3001		Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved after excluding spirometry measurements with “Unacceptable” Grade - Did not meet Inclusion Criterion 6 and did not meet required 75-125% compliance with study treatment for double-blind study treatment period According to the FDA Statistician’s verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the Study Protocol’s requirement of demonstration of 12% reversibility after bronchodilator after excluding those spirometry measurements with “Unacceptable” PFT grading. According to the Applicant’s response to IR question 1 including adre.xpt data set that was submitted on 3/22/2018, spirometry measurements with “Unacceptable” PFT grading did not meet the American Thoracic Society Guidelines (2005) for technical quality or repeatability. Since these spirometry measurements did not meet the ATS Guidelines for technical quality, they cannot be used to determine whether

				a subject met an inclusion criterion. According to the FDA Statistician’s calculation and verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the required 75-125% compliance with the study treatment during the double-blind study treatment period. Since these subjects did not meet Inclusion Criterion 6, they are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.
MGR001-3001	(b) (6)	Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved after excluding spirometry measurements with “Unacceptable” Grade - Did not meet Inclusion Criterion 6 and did not meet requirement in Statistical Analysis Plan that Day 29 (Visit 5) average pre-dose measurements are within ± 2 hours of Day 1 (Visit 3) average pre-dose measurements and/or subjects with post-screening visit pre-dose assessments completed after 12 noon According to the FDA Statistician’s verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the Study Protocol’s requirement of demonstration of 12% reversibility after bronchodilator after excluding those spirometry measurements with “Unacceptable” PFT grading. According to the Applicant’s response to IR question 1 including adre.xpt data set that was submitted on 3/22/2018, spirometry measurements with “Unacceptable” PFT grading did not meet the American Thoracic Society Guidelines (2005) for technical quality or repeatability. Since these spirometry measurements did not meet the ATS Guidelines for technical quality, they cannot be used to determine whether a subject met an inclusion criterion. According to Applicant’s response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018, these subjects had Day 29 out of window spirometry assessments where Day 29 (Visit 5) average pre-dose assessments are not within ±2 hours of Day (Visit 3) average pre-dose time-points and/or subjects with pre-dose assessments completed after 12 noon and were included in the Applicant’s PPS. Since these subjects did not meet Inclusion Criterion 6, they are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.

MGR001-3001	(b) (6)	Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved after excluding spirometry measurements with “Unacceptable” Grade - Did not meet Inclusion Criterion 6 and short-acting beta agonist use within 6 hours of lung function testing (Visit 3) According to the FDA Statistician’s verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the Study Protocol’s requirement of demonstration of 12% reversibility after bronchodilator after excluding those spirometry measurements with “Unacceptable” PFT grading. According to the Applicant’s response to IR question 1 including adre.xpt data set that was submitted on 3/22/2018, spirometry measurements with “Unacceptable” PFT grading did not meet the American Thoracic Society Guidelines (2005) for technical quality or repeatability. Since these spirometry measurements did not meet the ATS Guidelines for technical quality, they cannot be used to determine whether a subject met an inclusion criterion. According to the Applicant’s response to IR question 3 that was submitted on 2/1/2018, these subjects used a short-acting beta agonist (albuterol) during or within six hours prior to spirometry measurements and these spirometry measurements were used in calculation of Day 1 FEV1 AUEC0-12 endpoint during Visit 3 (Day 1 Visit). As described in Section 4.1.4.2.4 in the Clinical Study Report, if a subject took albuterol during the 0 to 12-hour post dose spirometry assessments on Day 1, then for the Per Protocol Analysis of the Day 1 FEV₁ AUEC₀₋₁₂ endpoint, all serial spirometry assessments collected after the albuterol use were set to missing. Based on the missing spirometry assessments during 0 to 12-hour post dose spirometry assessments, these subjects are recommended to be excluded from the FDA PP and FDA Day 1 PP based on Section 4.1.4.2.4 of the Clinical Study Report. Since this subject did not meet Inclusion Criterion 6, this subject is recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.

MGR001-3001	(b) (6)	Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved after excluding spirometry measurements with “Unacceptable” Grade - Did not meet Inclusion Criterion 6 and Visit 5 completed out of pre-specified study visit window (Day 29 ±2 days) According to the FDA Statistician’s verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the Study Protocol’s requirement of demonstration of 12% reversibility after bronchodilator after excluding those spirometry measurements with “Unacceptable” PFT grading. According to the Applicant’s response to IR question 1 including adre.xpt data set that was submitted on 3/22/2018, spirometry measurements with “Unacceptable” PFT grading did not meet the American Thoracic Society Guidelines (2005) for technical quality or repeatability. Since these spirometry measurements did not meet the ATS Guidelines for technical quality, they cannot be used to determine whether a subject met an inclusion criterion. Based on the Applicant’s response to IR question 7 that submitted on 2/1/2018 and IR question 6 submitted on 2/26/2018, it was determined by the FDA Statistician that these subjects were included in the Applicant’s Per Protocol Set and completed their Visit 5 outside the Applicant’s pre-specified visit window of Day 29 ±2 days. These subjects’ inclusion into the Day 1 PP population is not affected by this protocol deviation since the Day 1 endpoint is not affected by Visit 5 being out of the visit window. Since this subject did not meet Inclusion Criterion 6, this subject is recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.

MGR001-3001	(b) (6)	Included	Exclude	Has insufficient data from Day 1 (Visit 3) to calculate Day 1 endpoint after FEV1 data that was determined to be poor quality following “Best Test Review” is set to missing and subject did not meet requirement in Statistical Analysis Plan that Day 29 (Visit 5) average pre-dose measurements are within ± 2 hours of Day 1 (Visit 3) average pre-dose measurements and/or subjects with post-screening visit pre-dose assessments completed after 12 noon Subject has insufficient data from Day 1 (Visit 3) to calculate Day 1 endpoint after FEV1 data that was determined to be poor quality following “Best Test Review” is set to missing. Data from spirometry loops that were determined to be poor quality during “Best Test Review” cannot be used in statistical analysis or determination of inclusion/exclusion status. According to Applicant’s response to IR question 12 that was submitted on 2/26/2018, the Applicant does not believe that spirometry performed outside of a ±1 hour window for the Day 29 trough FEV1 endpoint as stated in the Study Protocol is not a valid reason to exclude subjects from the Day 29 Per Protocol Set. Instead, the Applicant stated that a ±2 hour window for the Day 29 trough FEV1 endpoint as pre-specified in the Statistical Analysis Plan (Section 8.1.4) was used in the Applicant’s relevant sensitivity analyses and would allow for the predictable situation that some patients would attend the clinic earlier or later than stated in the protocol. According to Applicant’s response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018, these subjects had Day 29 out of window spirometry assessments where Day 29 (Visit 5) average pre-dose assessments are not within ±2 hours of Day (Visit 3) average pre-dose time-points and/or subjects with pre-dose assessments completed after 12 noon and were included in the Applicant’s PPS. This subject should be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.

Additional Comments

1. Use the Applicant’s Per Protocol Set, specifically adsl.xpt data set submitted on 12/29/2018) for starting point for Per Protocol Population subject adjustments. The adsl.xpt data set can be found at:
<\\cdsesub1\evsprod\anda208891\0000\m5\datasets\mgr001-3001\analysis\adam\datasets\adsl.xpt>

2. Since the Applicant's Full Analysis Set (FAS) was considered definitive while testing superiority according to their study protocol, this population is analogous to the FDA's mITT population. Both of the Applicant's definitions for the Full Analysis Set (Original Study Protocol and Amendment 1) are not consistent with the current FDA Modified Intent-to-Treat population definition and are not acceptable. Use the current FDA mITT population for superiority analysis which is defined as all randomized subjects who applied or used at least one dose of assigned drug product.
3. The Applicant's definition for the Per Protocol Set (PPS) is not acceptable as it is not consistent with the currently accepted definition of the FDA Per Protocol Population the Applicant's definition of the PPS does not require subjects to meet all inclusion/exclusion criteria and complete the evaluation within the designated visit window and this is not acceptable. Additionally, since the Applicant used a single Per Protocol population in this study for both co-primary endpoints, any protocol violation that affected either co-primary endpoints (not both co-primary endpoints as defined in the study by the Applicant) should result in a subject being excluded from the Applicant's PPS. Therefore, conduct FDA statistical analysis for bioequivalence two ways: 1) single Per Protocol Population (FDA PP Population) and 2) two separate Per Protocol Populations (FDA Day 1 and FDA Day 29 PP Populations).
4. Verify that the Applicant followed the Study Protocol, Study Report, and Statistical Analysis Plan for their statistical methods and analysis, handling of missing and data, study design, and their calculation of the statistical results. Verify that any changes made to the statistical methods and analyses after the study commenced after acceptable.
5. Verify that the Applicant followed Section 4.2.1.6 (Exposure and Treatment Compliance) of the Study Report and Section 7.2.1 (Treatment Compliance) of the Statistical Analysis Plan for all subjects with the following recommended adjustments to the method for calculating study drug compliance. The Applicant incorrectly calculated the number of expected doses for the double-blind treatment period by using the incorrect formula of " $2 \times (\text{date of expected last dose} - \text{date of first dose} + 1)$ ". The correct number of expected doses is not based on the start or end date of a study treatment but is based on the study design and is the same for all subjects enrolled in the study. Use 56 as the expected number of doses for the double-blind treatment period ($28 \text{ days} \times 2 = 56$) in calculation and verification of subject's double-blind treatment compliance. Adjustments made to the number of doses used by the subject based on (b) (4) data is acceptable and should be used in verification of double-blind treatment compliance. Exclude any subjects from the FDA Per Protocol Population and FDA Day 29 Per Protocol Population (except those subjects recommended to be included in the Per Protocol Populations since they were treatment failures) that did not meet the required double-blind treatment compliance of 75-125%.
6. Verify and exclude any subjects from the FDA PP Population and FDA Day 29 Per Protocol Population (except those subjects recommended to be included in the Per

- Protocol Populations since they were treatment failures) whose Visit 5 was outside of the Study Protocol's specified study visit window of Day 29 ±2 days (Day 27 to Day 31).
7. Verify and exclude any subjects (except those subjects recommended to be included in the Per Protocol Populations since they were treatment failures) from FDA PP, FDA Day 1 PP, and FDA Day 29 PP Populations that did not meet Inclusion Criterion 5 (Percent Predicted FEV1) based on the version of the Study Protocol that each subject was enrolled under. Include any subjects who met Inclusion Criterion 5 and were excluded from the Applicant's Per Protocol Set solely based on this reason.
 8. Verify and exclude any subjects (except those subjects recommended to be included in the Per Protocol Populations since they were treatment failures) from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations that did not meet Inclusion Criterion 6 (Percent Reversibility of FEV1). Include any subjects who met Inclusion Criterion 6 and were excluded from the Applicant's Per Protocol Set solely based on this reason.
 9. Verify that subjects who were enrolled in the study twice were appropriately handled with respect to study design and statistical analyses and consistent with their pre-specified study design. Make any necessary subject adjustments to FDA PP populations if needed.
 10. Verify that the Applicant's method of Blind Sample Size Re-estimation (BSSR) was conducted appropriately and consistent with their pre-specified study design. Make any necessary subject adjustments to FDA PP populations if needed.
 11. Verify that the Applicant's method of pooling sites was conducted appropriately and consistent with their pre-specified study design. Make any necessary subject adjustments to FDA PP populations if needed.
 12. Verify that no spirometry measurements that were graded as "Unacceptable" according to ATS Guidelines (2005) were used in the statistical analysis (bioequivalence or superiority analysis) or in determining if a subject met all Inclusion/Exclusion Criteria and make any necessary subjects adjustments to FDA PP populations if needed. See Applicant's IR response to Question 1 (adre31.xpt data set) submitted on March 22, 2018 for list of subjects with spirometry measurements that were graded as "Unacceptable."

Per Protocol Population Recommendations for FDA Day 1 Population

Study #	Subject number	Applicant included/ excluded	FDA Day 1 PP Include/ Exclude	Reason
MGR001-3001	(b) (6)	Included	Exclude	Short-acting beta agonist use within 6 hours of lung function testing (Visit 3) According to the Applicant's response to IR question 3 that was submitted on 2/1/2018, these subjects used a short-acting beta agonist (albuterol) during or within six hours prior to spirometry measurements and these spirometry measurements were used in calculation of Day 1 FEV₁ AUEC₀₋₁₂ endpoint during Visit 3 (Day 1 Visit). As described in Section 4.1.4.2.4 in the Clinical Study Report, if a subject took albuterol during the 0 to 12-hour post dose spirometry assessments on Day 1, then for the Per Protocol Analysis of the Day 1 FEV₁ AUEC₀₋₁₂ endpoint, all serial spirometry assessments collected after the albuterol use were set to missing. Based on the missing spirometry assessments during 0 to 12-hour post dose spirometry assessments, these subjects are recommended to be excluded from the FDA PP and FDA Day 1 PP based on Section 4.1.4.2.4 of the Clinical Study Report. These subjects are recommended to be included in the FDA Day 29 PP since the short-acting beta agonist (albuterol) use occurred after the two Visit 3 pre-dose FEV₁ spirometry measurements were collected that form part of the baseline for the Day 29 trough FEV₁ endpoint.
MGR001-3001		Included	Exclude	Short-acting beta agonist use within 6 hours of lung function testing (Visit 3) and Visit 5 completed out of pre-specified study visit window (Day 29 ±2 days) According to the Applicant's response to IR question 3 that was submitted on 2/1/2018, these subjects used a short-acting beta agonist (albuterol) during or within six hours prior to spirometry measurements and these spirometry measurements were used in calculation of Day 1 FEV₁ AUEC₀₋₁₂ endpoint during Visit 3 (Day 1 Visit). As described in Section 4.1.4.2.4 in the Clinical Study Report, if a subject took albuterol during the 0 to 12-hour post dose spirometry assessments on Day 1, then for the Per Protocol Analysis of the Day 1 FEV₁ AUEC₀₋₁₂ endpoint, all serial spirometry assessments collected after the albuterol use were set to missing. Based on the

				missing spirometry assessments during 0 to 12-hour post dose spirometry assessments, these subjects are recommended to be excluded from the FDA PP and FDA Day 1 PP based on Section 4.1.4.2.4 of the Clinical Study Report. Based on the Applicant's response to IR question 7 that submitted on 2/1/2018 and IR question 6 submitted on 2/26/2018, it was determined by the FDA Statistician that these subjects were included in the Applicant's Per Protocol Set and completed their Visit 5 outside the Applicant's pre-specified visit window of Day 29 ±2 days. As a result, these subjects should be excluded from FDA PP and FDA Day 29 endpoint PP population. Therefore, these subjects are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP population.
MGR001-3001	(b) (6)	Included	Exclude	Short-acting beta agonist use within 6 hours of lung function testing (Visit 3), Visit 5 completed out of pre-specified study visit window (Day 29 ±2 days), and Did not meet required 75-125% compliance for double-blind study treatment period According to the Applicant's response to IR question 3 that was submitted on 2/1/2018, these subjects used a short-acting beta agonist (albuterol) during or within six hours prior to spirometry measurements and these spirometry measurements were used in calculation of Day 1 FEV1 AUEC0-12 endpoint during Visit 3 (Day 1 Visit). As described in Section 4.1.4.2.4 in the Clinical Study Report, if a subject took albuterol during the 0 to 12-hour post dose spirometry assessments on Day 1, then for the Per Protocol Analysis of the Day 1 FEV₁ AUEC₀₋₁₂ endpoint, all serial spirometry assessments collected after the albuterol use were set to missing. Based on the missing spirometry assessments during 0 to 12-hour post dose spirometry assessments, this subject is recommended to be excluded from the FDA PP and FDA Day 1 PP based on Section 4.1.4.2.4 of the Clinical Study Report. Based on the Applicant's response to IR question 7 that submitted on 2/1/2018 and IR question 6 submitted on 2/26/2018, it was determined by the FDA Statistician that this subject was included in the Applicant's Per Protocol Set and completed their Visit 5 outside the Applicant's pre-specified visit window of Day 29 ±2 days. According to the FDA Statistician's calculation and verification, this subject was included in

				the Applicant’s Per Protocol Set and did not meet the required 75-125% compliance with the study treatment during the double-blind study treatment period. The Applicant was noted to have incorrectly calculated the expected number of doses (denominator) based on the study design. As a result, this subject is recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP population.
MGR001-3001	(b) (6)	Included	Exclude	Missing data for 2 hours to 6 hours post-dose time for Day 1 endpoint According to Table 2 of Appendix 16.1.9.3.4.6, Subject (b) (6) is missing data for the 2 hours to 6 hours post-dose time points on Day 1. According to Section 4.5.4 of the Statistical Analysis Plan (“Handling Missing Co-primary Endpoint Data”), Subject (b) (6) Day 1 endpoint should be set to missing since data for 2 hour to 6 hours post-dose time point on Day 1 is missing. As a result, this subject is recommended to be excluded from the FDA PP and FDA Day 1 PP population but to be included in the FDA Day 29 PP population as the missing data for 2 hours to 6 hours post-dose time point does not affect the Day 29 endpoint.
MGR001-3001	(b) (6)	Included	Exclude	Used prohibited concomitant medication (corticosteroid) – Did not meet Inclusion Criterion 9, Did not meet required Double-blind Study drug compliance of 75-125%, and Early Termination Visit data improperly carried forward for Day 29 endpoint (Visit 5 completed out of pre-specified study visit window - Day 29 ±2 days) Subject (b) (6) experienced an adverse event of “asthma exacerbation” from (b) (6) (Day 1) to (b) (6) (Day 6). According to Applicant’s response to IR question 2 that was submitted on 2/26/2018, the adverse event started between hour 4 and hour 6 serial spirometry measurements on Day 1 and all serial spirometry measurements on Day 1 after hour 6 were set to missing. Subject took Prednisone 40mg oral QD from (b) (6) to Ongoing (Day 2 to Ongoing). Subject included in Applicant’s PPS with Day 1 endpoint set to missing. Applicant improperly carried forward data from Early Termination Visit on Day 15 (b) (6) for Day 29 endpoint.

				Subject (b) (6) should be excluded from FDA PP and FDA Day 1 endpoint PP population since there is insufficient FEV1 data to calculate a Day 1 AUEC0-12 value and excluded from FDA PP and FDA Day 29 endpoint PP population since data from ET visit was improperly carried forward (prohibited concomitant medication and double-blind study drug compliance).
MGR001-3001	(b) (6)	Included	Exclude	Used prohibited concomitant medication (inhaled corticosteroid) – Did not meet Inclusion Criterion 9, Short-acting beta agonist use within 6 hours of lung function testing (Visit 3), Did not meet required Double-blind Study drug compliance of 75-125%, and Early Termination Visit data improperly carried forward for Day 29 endpoint Subject (b) (6) experienced an adverse event of “asthma exacerbation” from (b) (6) (Day 1) to (b) (6) (Day 1). According to Applicant’s response to IR question 2 that was submitted on 2/26/2018, the adverse event started between hour 3 and hour 4 serial spirometry measurements on Day 1 and all serial spirometry measurements on Day 1 after hour 4 were set to missing. Subject took Flovent inhaler 1 puff BID from (b) (6) to Ongoing (Day 1 to Ongoing). Subject included in Applicant’s PPS with Day 1 endpoint set to missing. Applicant improperly carried forward data from Early Termination Visit on Day 8 (b) (6) for Day 29 endpoint. Subject (b) (6) should be excluded from FDA PP and FDA Day 1 endpoint PP population since there is insufficient FEV1 data to calculate a Day 1 AUEC0-12 value and excluded from FDA PP and FDA Day 29 endpoint PP population since data from ET visit was improperly carried forward (prohibited concomitant medication and double-blind study drug compliance).
MGR001-3001		Included	Exclude	Product Specific Guidance and Study Protocol required FEV₁ Percent Predicted not met on First Day of Study Treatment - Did not meet Inclusion Criterion 5 According to Applicant’s response to IR question 12A that was submitted on 2/1/2018, Subject (b) (6) had a mean FEV₁ Percent Predicted of 93.1% at Visit 3. Since this subject was enrolled under the Original version of the Study Protocol and was taking an ICS and/or LABA prior to screening, the pre-specified study

				protocol for Inclusion Criterion 5 required the mean FEV₁ Percent Predicted at Visit 3 to be between 50% to 85% of FEV₁ Percent Predicted. The Applicant's justification in IR Comment 12A stated that although the mean FEV₁ Percent Predicted at Visit 3 did not meet Inclusion Criterion 5, the mean of FEV₁ Percent Predicted at Visit 2 (71.1%) and mean FEV₁ Percent Predicted at Visit 3 (93.1%) were within the range of 50-85% that this subject was not excluded from the Per Protocol Set. This rationale is not acceptable since this is different than what is pre-specified in the Applicant's Study Protocol and the requirement in the Product Specific Guidance. This subject is recommended to be excluded from the FDA PP, FDA Day 1, and FDA Day 29 PP populations.
MGR001-3001	(b) (6)	Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved - Did not meet Inclusion Criterion 6 According to Applicant's response to IR question 13a that was submitted on 2/1/2018, Subjects (b) (6) did not meet Study Protocol's requirement of demonstration of 12% reversibility after bronchodilator and subjects were entered into the double-blind treatment phase in error. Since these subjects did not meet Inclusion Criterion they are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.
MGR001-3001	(b) (6)	Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved - Did not meet Inclusion Criterion 6 According to the Applicant's response to IR question 10b that was submitted on 2/26/2018, these subjects did not meet Study Protocol's requirement of demonstration of 12% reversibility after bronchodilator and subjects were entered into the double-blind treatment phase in error. Since these subjects did not meet Inclusion Criterion 6, they are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations. Several subjects had additional protocol deviations. Subject (b) (6) did not meet required 75-125% compliance with study treatment for double-blind study treatment period. Subject (b) (6) had Visit 5 completed out of pre-

	(b) (6)			specified study visit window (Day 29 ±2 days) and did not meet required 75-125% compliance with study treatment for double-blind study treatment period. Subject (b) (6) had Visit 5 completed out of pre-specified study visit window (Day 29 ±2 days). Subject (b) (6) did not meet required 75-125% compliance with study treatment for double-blind study treatment period. Subject (b) (6) did not meet required 75-125% compliance with study treatment for double-blind study treatment period.
MGR001-3001		Included	Exclude	Did not meet required percent predicted FEV1 during the screening period and on first day of double-blind treatment period - Did not meet Inclusion Criterion 5 According to the FDA Statistician's calculation and verification, these subjects were included in the Applicant's Per Protocol Set and did not meet the required percent predicted FEV1 during the screening period and on first day of double-blind treatment period (Violation of Inclusion Criterion 5). The Study Protocol required subjects to meet percent predicted FEV1 at Visit 1 (Screening Visit), Visit 2 (Run-in Visit), and Visit 3 (First day of double-blind treatment period) while the Product Specific Guidance recommends pre-bronchodilator percent predicted FEV1 be met during the screening visit and on the first day of treatment. As a result, subjects were recommended to be excluded from the FDA PP populations if they did not meet percent predicted FEV1 at Visit 1 or Visit 2 (once during placebo run-in period) and at Visit 3 (first day of double-blind treatment period). Subject (b) (6) had percent predicted FEV1 of 93.1025% at Visit 3 (did not meet Product Specific Guidance required percent predicted FEV1 on the first day of double-blind treatment period). Subject (b) (6) had percent predicted FEV1 of 97.1258% at Visit 1, 97.8402% at Visit 2, and 91.0534% at Visit 3 (did not meet Product Specific Guidance required percent predicted FEV1 at either visit during placebo run-in period or on the first day of double-blind treatment period). Subject (b) (6) had percent predicted FEV1 of 85.8664% at Visit 3 (did not meet Product Specific

				Guidance required percent predicted FEV1 on the first day of double-blind treatment period). Subject (b) (6) had percent predicted FEV1 of 87.1836% at Visit 1, 90.0272% at Visit 2, and 89.2967% at Visit 3 (did not meet Product Specific Guidance required percent predicted FEV1 at either visit during placebo run-in period or on the first day of double-blind treatment period). Subject (b) (6) had percent predicted FEV1 of not recorded at Visit 1, 96.6751% at Visit 2, and 94.2712% at Visit 3 (did not meet Product Specific Guidance required percent predicted FEV1 at either visit during placebo run-in period or on the first day of double-blind treatment period). Subject (b) (6) had percent predicted FEV1 of 33.5241% at Visit 3 (did not meet Product Specific Guidance required percent predicted FEV1 on the first day of double-blind treatment period). Since these subjects did not meet Inclusion Criterion 5, they are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.
MGR001-3001	(b) (6)	Included	Exclude	Short-acting beta agonist use within 6 hours of lung function testing (Visit 3) and subject did not meet requirement in Statistical Analysis Plan that Day 29 (Visit 5) average pre-dose measurements are within ± 2 hours of Day 1 (Visit 3) average pre-dose measurements and/or subjects with post-screening visit pre-dose assessments completed after 12 noon According to the Applicant's response to IR question 3 that was submitted on 2/1/2018, these subjects used a short-acting beta agonist (albuterol) during or within six hours prior to spirometry measurements and these spirometry measurements were used in calculation of Day 1 FEV1 AUEC0-12 endpoint during Visit 3 (Day 1 Visit). As described in Section 4.1.4.2.4 in the Clinical Study Report, if a subject took albuterol during the 0 to 12-hour post dose spirometry assessments on Day 1, then for the Per Protocol Analysis of the Day 1 FEV1 AUEC0-12 endpoint, all serial spirometry assessments collected after the albuterol use were set to missing. Based on the missing spirometry assessments during 0 to 12-hour post dose spirometry assessments, these subjects are recommended to be excluded from the FDA PP and FDA Day 1 PP based on Section 4.1.4.2.4 of the Clinical Study Report. According to Applicant's response to IR

				question 12 (ir12fl.xpt) that was submitted on 2/26/2018, this subject had Day 29 out of window spirometry assessments where Day 29 (Visit 5) average pre-dose assessments are not within ±2 hours of Day (Visit 3) average pre-dose time-points and/or subjects with pre-dose assessments completed after 12 noon and was included in the Applicant's PPS. These subjects should be excluded from FDA PP and FDA Day 1 endpoint PP populations because of short-acting beta agonist use within 6 hours of lung function testing (Visit 3) and excluded from FDA PP and Day 29 endpoint PP populations because Day 29 (Visit 5) average pre-dose measurements are within ± 2 hours of Day 1 (Visit 3) average pre-dose measurements and/or subjects with post-screening visit pre-dose assessments completed after 12 noon.
MGR001-3001	(b) (6)	Included	Exclude	Short-acting beta agonist use within 6 hours of lung function testing (Visit 3) and did not meet required 75-125% compliance with study treatment for double-blind study treatment period According to the Applicant's response to IR question 3 that was submitted on 2/1/2018, these subjects used a short-acting beta agonist (albuterol) during or within six hours prior to spirometry measurements and these spirometry measurements were used in calculation of Day 1 FEV1 AUEC0-12 endpoint during Visit 3 (Day 1 Visit). As described in Section 4.1.4.2.4 in the Clinical Study Report, if a subject took albuterol during the 0 to 12-hour post dose spirometry assessments on Day 1, then for the Per Protocol Analysis of the Day 1 FEV₁ AUEC₀₋₁₂ endpoint, all serial spirometry assessments collected after the albuterol use were set to missing. Based on the missing spirometry assessments during 0 to 12-hour post dose spirometry assessments, these subjects are recommended to be excluded from the FDA PP and FDA Day 1 PP based on Section 4.1.4.2.4 of the Clinical Study Report. According to the FDA Statistician's calculation and verification, these subjects were included in the Applicant's Per Protocol Set and did not meet the required 75-125% compliance with the study treatment during the double-blind study treatment period. The Applicant was noted to have incorrectly calculated the expected number of doses (denominator) used in calculation of double-blind study treatment period compliance based on the study design. These subjects

				should be excluded from FDA PP and FDA Day 29 endpoint PP population. These subjects should be excluded from FDA PP and FDA Day 1 endpoint PP populations because of short-acting beta agonist use within 6 hours of lung function testing (Visit 3) and excluded from FDA PP and Day 29 endpoint PP populations because subjects did not meet required 75-125% compliance with study treatment for double-blind study treatment period.
MGR001-3001	(b) (6)	Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved after excluding spirometry measurements with “Unacceptable” Grade - Did not meet Inclusion Criterion 6 According to the FDA Statistician’s verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the Study Protocol’s requirement of demonstration of 12% reversibility after bronchodilator after excluding those spirometry measurements with “Unacceptable” PFT grading. According to the Applicant’s response to IR question 1 including adre.xpt data set that was submitted on 3/22/2018, spirometry measurements with “Unacceptable” PFT grading did not meet the American Thoracic Society Guidelines (2005) for technical quality or repeatability. Since these spirometry measurements did not meet the ATS Guidelines for technical quality, they cannot be used to determine whether a subject met an inclusion criterion. Since these subjects did not meet Inclusion Criterion 6, they are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.
MGR001-3001		Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved after excluding spirometry measurements with “Unacceptable” Grade - Did not meet Inclusion Criterion 6 and did not meet required 75-125% compliance with study treatment for double-blind study treatment period According to the FDA Statistician’s verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the Study Protocol’s requirement of demonstration of 12% reversibility after bronchodilator after excluding those spirometry measurements with “Unacceptable” PFT grading. According to the

				Applicant’s response to IR question 1 including adre.xpt data set that was submitted on 3/22/2018, spirometry measurements with “Unacceptable” PFT grading did not meet the American Thoracic Society Guidelines (2005) for technical quality or repeatability. Since these spirometry measurements did not meet the ATS Guidelines for technical quality, they cannot be used to determine whether a subject met an inclusion criterion. According to the FDA Statistician’s calculation and verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the required 75-125% compliance with the study treatment during the double-blind study treatment period. Since these subjects did not meet Inclusion Criterion 6, they are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.
MGR001-3001	(b) (6)	Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved after excluding spirometry measurements with “Unacceptable” Grade - Did not meet Inclusion Criterion 6 and did not meet requirement in Statistical Analysis Plan that Day 29 (Visit 5) average pre-dose measurements are within ± 2 hours of Day 1 (Visit 3) average pre-dose measurements and/or subjects with post-screening visit pre-dose assessments completed after 12 noon According to the FDA Statistician’s verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the Study Protocol’s requirement of demonstration of 12% reversibility after bronchodilator after excluding those spirometry measurements with “Unacceptable” PFT grading. According to the Applicant’s response to IR question 1 including adre.xpt data set that was submitted on 3/22/2018, spirometry measurements with “Unacceptable” PFT grading did not meet the American Thoracic Society Guidelines (2005) for technical quality or repeatability. Since these spirometry measurements did not meet the ATS Guidelines for technical quality, they cannot be used to determine whether a subject met an inclusion criterion. According to Applicant’s response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018, these

				subjects had Day 29 out of window spirometry assessments where Day 29 (Visit 5) average pre-dose assessments are not within ± 2 hours of Day (Visit 3) average pre-dose time-points and/or subjects with pre-dose assessments completed after 12 noon and were included in the Applicant's PPS. Since these subjects did not meet Inclusion Criterion 6, they are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.
MGR001-3001	(b) (6)	Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved after excluding spirometry measurements with "Unacceptable" Grade - Did not meet Inclusion Criterion 6 and short-acting beta agonist use within 6 hours of lung function testing (Visit 3) According to the FDA Statistician's verification, these subjects were included in the Applicant's Per Protocol Set and did not meet the Study Protocol's requirement of demonstration of 12% reversibility after bronchodilator after excluding those spirometry measurements with "Unacceptable" PFT grading. According to the Applicant's response to IR question 1 including adre.xpt data set that was submitted on 3/22/2018, spirometry measurements with "Unacceptable" PFT grading did not meet the American Thoracic Society Guidelines (2005) for technical quality or repeatability. Since these spirometry measurements did not meet the ATS Guidelines for technical quality, they cannot be used to determine whether a subject met an inclusion criterion. According to the Applicant's response to IR question 3 that was submitted on 2/1/2018, these subjects used a short-acting beta agonist (albuterol) during or within six hours prior to spirometry measurements and these spirometry measurements were used in calculation of Day 1 FEV1 AUEC0-12 endpoint during Visit 3 (Day 1 Visit). As described in Section 4.1.4.2.4 in the Clinical Study Report, if a subject took albuterol during the 0 to 12-hour post dose spirometry assessments on Day 1, then for the Per Protocol Analysis of the Day 1 FEV1 AUEC0-12 endpoint, all serial spirometry assessments collected after the albuterol use were set to missing. Based on the missing spirometry assessments during 0 to 12-hour post dose spirometry assessments, these subjects are recommended to be excluded from the FDA PP and FDA Day 1 PP based on Section 4.1.4.2.4 of the Clinical

				Study Report. Since this subject did not meet Inclusion Criterion 6, this subject is recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.
MGR001-3001	(b) (6)	Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved after excluding spirometry measurements with “Unacceptable” Grade - Did not meet Inclusion Criterion 6 and Visit 5 completed out of pre-specified study visit window (Day 29 ±2 days) According to the FDA Statistician’s verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the Study Protocol’s requirement of demonstration of 12% reversibility after bronchodilator after excluding those spirometry measurements with “Unacceptable” PFT grading. According to the Applicant’s response to IR question 1 including adre.xpt data set that was submitted on 3/22/2018, spirometry measurements with “Unacceptable” PFT grading did not meet the American Thoracic Society Guidelines (2005) for technical quality or repeatability. Since these spirometry measurements did not meet the ATS Guidelines for technical quality, they cannot be used to determine whether a subject met an inclusion criterion. Based on the Applicant’s response to IR question 7 that submitted on 2/1/2018 and IR question 6 submitted on 2/26/2018, it was determined by the FDA Statistician that these subjects were included in the Applicant’s Per Protocol Set and completed their Visit 5 outside the Applicant’s pre-specified visit window of Day 29 ±2 days. These subjects’ inclusion into the Day 1 PP population is not affected by this protocol deviation since the Day 1 endpoint is not affected by Visit 5 being out of the visit window. Since this subject did not meet Inclusion Criterion 6, this subject is recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.
MGR001-3001		Included	Exclude	Has insufficient data from Day 1 (Visit 3) to calculate Day 1 endpoint after FEV1 data that was determined to be poor quality following “Best Test Review” is set to missing and subject did not meet requirement in Statistical Analysis Plan that Day 29 (Visit 5) average pre-dose measurements are within ± 2 hours of Day 1 (Visit 3) average pre-dose measurements and/or subjects

			with post-screening visit pre-dose assessments completed after 12 noon Subject has insufficient data from Day 1 (Visit 3) to calculate Day 1 endpoint after FEV1 data that was determined to be poor quality following “Best Test Review” is set to missing. Data from spirometry loops that were determined to be poor quality during “Best Test Review” cannot be used in statistical analysis or determination of inclusion/exclusion status. According to Applicant’s response to IR question 12 that was submitted on 2/26/2018, the Applicant does not believe that spirometry performed outside of a ± 1 hour window for the Day 29 trough FEV1 endpoint as stated in the Study Protocol is not a valid reason to exclude subjects from the Day 29 Per Protocol Set. Instead, the Applicant stated that a ± 2 hour window for the Day 29 trough FEV1 endpoint as pre-specified in the Statistical Analysis Plan (Section 8.1.4) was used in the Applicant’s relevant sensitivity analyses and would allow for the predictable situation that some patients would attend the clinic earlier or later than stated in the protocol. According to Applicant’s response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018, these subjects had Day 29 out of window spirometry assessments where Day 29 (Visit 5) average pre-dose assessments are not within ± 2 hours of Day (Visit 3) average pre-dose time-points and/or subjects with pre-dose assessments completed after 12 noon and were included in the Applicant’s PPS. This subject should be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.

Additional Comments

1. Use the Applicant’s Per Protocol Set, specifically adsl.xpt data set submitted on 12/29/2018) for starting point for Per Protocol Population subject adjustments. The adsl.xpt data set can be found at:
<\\cdsesub1\evsprod\anda208891\0000\m5\datasets\mgr001-3001\analysis\adam\datasets\adsl.xpt>
2. Since the Applicant’s Full Analysis Set (FAS) was considered definitive while testing superiority according to their study protocol, this population is analogous to the FDA’s mITT population. Both of the Applicant’s definitions for the Full Analysis Set (Original Study Protocol and Amendment 1) are not consistent with the current FDA Modified

Intent-to-Treat population definition and are not acceptable. Use the current FDA mITT population for superiority analysis which is defined as all randomized subjects who applied or used at least one dose of assigned drug product.

3. The Applicant's definition for the Per Protocol Set (PPS) is not acceptable as it is not consistent with the currently accepted definition of the FDA Per Protocol Population the Applicant's definition of the PPS does not require subjects to meet all inclusion/exclusion criteria and complete the evaluation within the designated visit window and this is not acceptable. Additionally, since the Applicant used a single Per Protocol population in this study for both co-primary endpoints, any protocol violation that affected either co-primary endpoints (not both co-primary endpoints as defined in the study by the Applicant) should result in a subject being excluded from the Applicant's PPS. Therefore, conduct FDA statistical analysis for bioequivalence two ways: 1) single Per Protocol Population (FDA PP Population) and 2) two separate Per Protocol Populations (FDA Day 1 and FDA Day 29 PP Populations).
4. Verify that the Applicant followed the Study Protocol, Study Report, and Statistical Analysis Plan for their statistical methods and analysis, handling of missing and data, study design, and their calculation of the statistical results. Verify that any changes made to the statistical methods and analyses after the study commenced after acceptable.
5. Verify that the Applicant followed Section 4.2.1.6 (Exposure and Treatment Compliance) of the Study Report and Section 7.2.1 (Treatment Compliance) of the Statistical Analysis Plan for all subjects with the following recommended adjustments to the method for calculating study drug compliance. The Applicant incorrectly calculated the number of expected doses for the double-blind treatment period by using the incorrect formula of "2 X (date of expected last dose – date of first dose +1)". The correct number of expected doses is not based on the start or end date of a study treatment but is based on the study design and is the same for all subjects enrolled in the study. Use 56 as the expected number of doses for the double-blind treatment period (28 days X 2 = 56) in calculation and verification of subject's double-blind treatment compliance. Adjustments made to the number of doses used by the subject based on (b) (4) data is acceptable and should be used in verification of double-blind treatment compliance. Exclude any subjects from the FDA Per Protocol Population and FDA Day 29 Per Protocol Population (except those subjects recommended to be included in the Per Protocol Populations since they were treatment failures) that did not meet the required double-blind treatment compliance of 75-125%.
6. Verify and exclude any subjects from the FDA PP Population and FDA Day 29 Per Protocol Population (except those subjects recommended to be included in the Per Protocol Populations since they were treatment failures) whose Visit 5 was outside of the Study Protocol's specified study visit window of Day 29 ±2 days (Day 27 to Day 31).
7. Verify and exclude any subjects (except those subjects recommended to be included in the Per Protocol Populations since they were treatment failures) from FDA PP, FDA Day 1 PP, and FDA Day 29 PP Populations that did not meet Inclusion Criterion 5 (Percent

Predicted FEV1) based on the version of the Study Protocol that each subject was enrolled under. Include any subjects who met Inclusion Criterion 5 and were excluded from the Applicant's Per Protocol Set solely based on this reason.

8. Verify and exclude any subjects (except those subjects recommended to be included in the Per Protocol Populations since they were treatment failures) from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations that did not meet Inclusion Criterion 6 (Percent Reversibility of FEV1). Include any subjects who met Inclusion Criterion 6 and were excluded from the Applicant's Per Protocol Set solely based on this reason.
9. Verify that subjects who were enrolled in the study twice were appropriately handled with respect to study design and statistical analyses and consistent with their pre-specified study design. Make any necessary subject adjustments to FDA PP populations if needed.
10. Verify that the Applicant's method of Blind Sample Size Re-estimation (BSSR) was conducted appropriately and consistent with their pre-specified study design. Make any necessary subject adjustments to FDA PP populations if needed.
11. Verify that the Applicant's method of pooling sites was conducted appropriately and consistent with their pre-specified study design. Make any necessary subject adjustments to FDA PP populations if needed.
12. Verify that no spirometry measurements that were graded as "Unacceptable" according to ATS Guidelines (2005) were used in the statistical analysis (bioequivalence or superiority analysis) or in determining if a subject met all Inclusion/Exclusion Criteria and make any necessary subjects adjustments to FDA PP populations if needed. See Applicant's IR response to Question 1 (adre31.xpt data set) submitted on March 22, 2018 for list of subjects with spirometry measurements that were graded as "Unacceptable."

Per Protocol Population Recommendations for FDA Day 29 Population

Study #	Subject number	Applicant included/ excluded	FDA Week 4 PP Include/ Exclude	Reason
MGR001-3001	(b) (6)	Included	Exclude	Short-acting beta agonist use within 6 hours of lung function testing (Visit 3) and Visit 5 completed out of pre-specified study visit window (Day 29 ±2 days) According to the Applicant’s response to IR question 3 that was submitted on 2/1/2018, these subjects used a short-acting beta agonist (albuterol) during or within six hours prior to spirometry measurements and these spirometry measurements were used in calculation of Day 1 FEV1 AUEC0-12 endpoint during Visit 3 (Day 1 Visit). As described in Section 4.1.4.2.4 in the Clinical Study Report, if a subject took albuterol during the 0 to 12-hour post dose spirometry assessments on Day 1, then for the Per Protocol Analysis of the Day 1 FEV1 AUEC0-12 endpoint, all serial spirometry assessments collected after the albuterol use were set to missing. Based on the missing spirometry assessments during 0 to 12-hour post dose spirometry assessments, these subjects are recommended to be excluded from the FDA PP and FDA Day 1 PP based on Section 4.1.4.2.4 of the Clinical Study Report. Based on the Applicant’s response to IR question 7 that submitted on 2/1/2018 and IR question 6 submitted on 2/26/2018, it was determined by the FDA Statistician that these subjects were included in the Applicant’s Per Protocol Set and completed their Visit 5 outside the Applicant’s pre-specified visit window of Day 29 ±2 days. As a result, these subjects should be excluded from FDA PP and FDA Day 29 endpoint PP population. Therefore, these subjects are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP population.
MGR001-3001		Included	Exclude	Short-acting beta agonist use within 6 hours of lung function testing (Visit 3), Visit 5 completed out of pre-specified study visit window (Day 29 ±2 days), and Did not meet required 75-125% compliance for double-blind study treatment period According to the Applicant’s response to IR question 3 that was submitted on 2/1/2018, these subjects used a short-acting beta agonist (albuterol) during or within six

				hours prior to spirometry measurements and these spirometry measurements were used in calculation of Day 1 FEV1 AUEC0-12 endpoint during Visit 3 (Day 1 Visit). As described in Section 4.1.4.2.4 in the Clinical Study Report, if a subject took albuterol during the 0 to 12-hour post dose spirometry assessments on Day 1, then for the Per Protocol Analysis of the Day 1 FEV1 AUEC0-12 endpoint, all serial spirometry assessments collected after the albuterol use were set to missing. Based on the missing spirometry assessments during 0 to 12-hour post dose spirometry assessments, this subject is recommended to be excluded from the FDA PP and FDA Day 1 PP based on Section 4.1.4.2.4 of the Clinical Study Report. Based on the Applicant’s response to IR question 7 that submitted on 2/1/2018 and IR question 6 submitted on 2/26/2018, it was determined by the FDA Statistician that this subject was included in the Applicant’s Per Protocol Set and completed their Visit 5 outside the Applicant’s pre-specified visit window of Day 29 ±2 days. According to the FDA Statistician’s calculation and verification, this subject was included in the Applicant’s Per Protocol Set and did not meet the required 75-125% compliance with the study treatment during the double-blind study treatment period. The Applicant was noted to have incorrectly calculated the expected number of doses (denominator) based on the study design. As a result, this subject is recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP population.
MGR001-3001	(b) (6)	Included	Exclude	Used prohibited concomitant medication (corticosteroid) – Did not meet Inclusion Criterion 9, Did not meet required Double-blind Study drug compliance of 75-125%, and Early Termination Visit data improperly carried forward for Day 29 endpoint (Visit 5 completed out of pre-specified study visit window - Day 29 ±2 days) Subject (b) (6) experienced an adverse event of “asthma exacerbation” from (b) (6) (Day 1) to (b) (6) (Day 6). According to Applicant’s response to IR question 2 that was submitted on 2/26/2018, the adverse event started between hour 4 and hour 6 serial spirometry measurements on Day 1 and all serial spirometry measurements on Day 1 after hour 6 were set to missing. Subject took Prednisone 40mg oral QD

				from (b) (6) to Ongoing (Day 2 to Ongoing). Subject included in Applicant’s PPS with Day 1 endpoint set to missing. Applicant improperly carried forward data from Early Termination Visit on Day 15 (b) (6) for Day 29 endpoint. Subject (b) (6) should be excluded from FDA PP and FDA Day 1 endpoint PP population since there is insufficient FEV1 data to calculate a Day 1 AUEC0-12 value and excluded from FDA PP and FDA Day 29 endpoint PP population since data from ET visit was improperly carried forward (prohibited concomitant medication and double-blind study drug compliance).
MGR001-3001	(b) (6)	Included	Exclude	Used prohibited concomitant medication (inhaled corticosteroid) – Did not meet Inclusion Criterion 9, Short-acting beta agonist use within 6 hours of lung function testing (Visit 3), Did not meet required Double-blind Study drug compliance of 75-125%, and Early Termination Visit data improperly carried forward for Day 29 endpoint Subject (b) (6) experienced an adverse event of “asthma exacerbation” from (b) (6) (Day 1) to (b) (6) (Day 1). According to Applicant’s response to IR question 2 that was submitted on 2/26/2018, the adverse event started between hour 3 and hour 4 serial spirometry measurements on Day 1 and all serial spirometry measurements on Day 1 after hour 4 were set to missing. Subject took Flovent inhaler 1 puff BID from (b) (6) to Ongoing (Day 1 to Ongoing). Subject included in Applicant’s PPS with Day 1 endpoint set to missing. Applicant improperly carried forward data from Early Termination Visit on Day 8 (b) (6) for Day 29 endpoint. Subject (b) (6) should be excluded from FDA PP and FDA Day 1 endpoint PP population since there is insufficient FEV1 data to calculate a Day 1 AUEC0-12 value and excluded from FDA PP and FDA Day 29 endpoint PP population since data from ET visit was improperly carried forward (prohibited concomitant medication and double-blind study drug compliance).
MGR001-3001	(b) (6)	Included	Exclude	Visit 4 data (FEV1) improperly carried forward for Day 29 endpoint and subject did not meet required 75-125% compliance with study treatment for double-blind study treatment period

				According to the Applicant’s response to IR question 8 that was submitted on 2/26/2018, Subject (b) (6) discontinued from the study on (b) (6) (Day 29) due to “withdrawal by subject.” According to adef22.xpt data set, the subject’s last day of exposure to the study medication (double-blind treatment) was Day 28 and FEV1 spirometry data from Visit 4 collected on Day 15 (b) (6) was carried forward and used in the primary bioequivalence analysis for the Day 29 endpoint. According to the FDA Statistician’s calculation and verification, this subject was included in the Applicant’s Per Protocol Set and did not meet the required 75-125% compliance with the study treatment during the double-blind study treatment period. The Applicant was noted to have incorrectly calculated the expected number of doses (denominator) used in calculation of double-blind study treatment period compliance based on the study design. Subject (b) (6) should be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in FDA Day 1 endpoint PP population since the Day 1 endpoint is not affected by FEV1 spirometry data from Visit 4 improperly carried forward for Day 29 endpoint and since the Day 1 endpoint is not affected by compliance with the study treatment during the double-blind treatment period.
MGR001-3001	(b) (6)	Included	Exclude	Used prohibited concomitant medication (corticosteroid) According to Applicant’s response to IR question 12a (Table 9) that was submitted on 2/1/2018, these subjects used a prohibited concomitant medication of oral or parenteral corticosteroid during the double-blind treatment period. Subject (b) (6) used Prednisone 30mg PO QD from (b) (6) (Day 20) to (b) (6) (Day 24) and Singulair 10mg PO QD from (b) (6) (Day 20) to Ongoing. Subject (b) (6) used Prednisone 40mg PO QD from (b) (6) (Day 7) to (b) (6) (Day 10). Subject (b) (6) used Prednisone 20mg PO BID from (b) (6) (Day 3) to (b) (6) (Day 6). Subject (b) (6) used Methylprednisolone Acetate 80mg IV once on (b) (6) (Day 18). Subject (b) (6) used Dexamethasone 10mg IV

				once on (b) (6) (Day 3). These subjects should be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in FDA Day 1 endpoint PP population since the Day 1 endpoint is not affected since all prohibited concomitant medications were first taken after Day 1.
MGR001-3001	(b) (6)	Included	Exclude	Used prohibited concomitant medication (inhaled corticosteroid) during double-blind treatment period According to the Applicant's response to IR question 4 submitted on 2/26/2018 and Concomitant Medication data set (cm.xpt), Subject (b) (6) used Qvar (Beclomethasone Dipropionate) 80µg inhaled BID on (b) (6) (Day 32). Visit 5 for this subject occurred on (b) (6) (Day 33). This subject was included in the Applicant's PPS and used a prohibited concomitant medication (inhaled corticosteroid) during the double-blind treatment period that would affect the Day 29 endpoint. Subject (b) (6) should be excluded from FDA PP and FDA Day 29 endpoint PP population and included in the FDA Day 1 PP as the Day 1 endpoint is not affected since the prohibited concomitant medication use occurred after Day 1.
MGR001-3001	(b) (6)	Included	Exclude	Used prohibited concomitant medication (inhaled short acting anti-muscarinic) during double-blind treatment period According to the Applicant's response to IR question 4 submitted on 2/26/2018 and Concomitant Medication data set (cm.xpt), Subject (b) (6) used Ipratropium Bromide and Albuterol Sulfate 0.5mg/3mg per 3mL (Combivent) 1 nebulizer inhaled on (b) (6) (Day 17). This subject was included in the Applicant's PPS and used a prohibited concomitant medication (inhaled short acting anti-muscarinic) during the double-blind treatment period that would affect the Day 29 endpoint. Subject (b) (6) should be excluded from FDA PP and FDA Day 29 endpoint PP population and included in the FDA Day 1 PP as the Day 1 endpoint is not affected since the prohibited concomitant medication use occurred after Day 1.
MGR001-3001	(b) (6)	Included	Exclude	Visit 5 completed out of pre-specified study visit window (Day 29 ±2 days)

(b) (6)

Based on the Applicant's response to IR question 7 that submitted on 2/1/2018 and IR question 6 submitted on 2/26/2018, it was determined by the FDA Statistician that these subjects were included in the Applicant's Per Protocol Set and completed their Visit 5 outside the Applicant's pre-specified visit window of Day 29 ±2 days. These subjects' inclusion into the Day 1 PP population is not affected by this protocol deviation since the Day 1 endpoint is not affected by Visit 5 being out of the visit window.

	(b) (6)			
MGR001-3001		Included	Exclude	Product Specific Guidance and Study Protocol required FEV₁ Percent Predicted not met on First Day of Study Treatment - Did not meet Inclusion Criterion 5 According to Applicant's response to IR question 12A that was submitted on 2/1/2018, Subject (b) (6) had a mean FEV₁ Percent Predicted of 93.1% at Visit 3. Since this subject was enrolled under the Original version of the Study Protocol and was taking an ICS and/or LABA prior to screening, the pre-specified study protocol for Inclusion Criterion 5 required the mean FEV₁ Percent Predicted at Visit 3 to be between 50% to 85% of FEV₁ Percent Predicted. The Applicant's justification in IR Comment 12A stated that although the mean FEV₁ Percent Predicted at Visit 3 did not meet Inclusion Criterion 5, the mean of FEV₁ Percent Predicted at Visit 2 (71.1%) and mean FEV₁ Percent Predicted at Visit 3 (93.1%) were within the range of 50-85% that this subject was not excluded from the Per Protocol Set. This rationale is not acceptable since this is different than what is pre-specified in the Applicant's

				Study Protocol and the requirement in the Product Specific Guidance. This subject is recommended to be excluded from the FDA PP, FDA Day 1, and FDA Day 29 PP populations.
MGR001-3001	(b) (6)	Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved - Did not meet Inclusion Criterion 6 According to Applicant's response to IR question 13a that was submitted on 2/1/2018, Subjects (b) (6) (b) (6) did not meet Study Protocol's requirement of demonstration of 12% reversibility after bronchodilator and subjects were entered into the double-blind treatment phase in error. Since these subjects did not meet Inclusion Criterion 6, they are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.
MGR001-3001		Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved - Did not meet Inclusion Criterion 6 According to the Applicant's response to IR question 10b that was submitted on 2/26/2018, these subjects did not meet Study Protocol's requirement of demonstration of 12% reversibility after bronchodilator and subjects were entered into the double-blind treatment phase in error. Since these subjects did not meet Inclusion Criterion 6, they are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations. Several subjects had additional protocol deviations. Subject (b) (6) did not meet required 75-125% compliance with study treatment for double-blind study treatment period. Subject (b) (6) had Visit 5 completed out of pre-specified study visit window (Day 29 ±2 days) and did not meet required 75-125% compliance with study treatment for double-blind study treatment period. Subject (b) (6) had Visit 5 completed out of pre-specified study visit window (Day 29 ±2 days). Subject (b) (6) did not meet required 75-125% compliance with study treatment for double-blind study treatment period. Subject (b) (6) did not meet required 75-125% compliance with study treatment for double-blind study treatment period.

	(b) (6)			
MGR001-3001		Included	Exclude	Did not meet required 75-125% compliance with study treatment for double-blind study treatment period According to the FDA Statistician's calculation and verification, these subjects were included in the Applicant's Per Protocol Set and did not meet the required 75-125% compliance with the study treatment during the double-blind study treatment period. The Applicant was noted to have incorrectly calculated the expected number of doses (denominator) used in calculation of double-blind study treatment period compliance based on the study design. These subjects should be excluded from FDA PP and FDA Day 29 endpoint PP population and included in FDA Day 1 endpoint PP population since the Day 1 endpoint is not affected by compliance with the study treatment during the double-blind treatment period.

	(b) (6)			
MGR001-3001		Included	Exclude	Did not meet required percent predicted FEV1 during the screening period and on first day of double-blind treatment period - Did not meet Inclusion Criterion 5 According to the FDA Statistician’s calculation and verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the required percent predicted FEV1 during the screening period and on first day of double-blind treatment period (Violation of Inclusion Criterion 5). The Study Protocol required subjects to meet percent predicted FEV1 at Visit 1 (Screening Visit), Visit 2 (Run-in Visit), and Visit 3 (First day of double-blind treatment period) while the Product Specific Guidance recommends pre-bronchodilator percent predicted FEV1 be met during the screening visit and on the first day of treatment. As a result, subjects were recommended to be excluded from the FDA PP populations if they did not meet percent predicted FEV1 at Visit 1 or Visit 2 (once during placebo run-in period) and at Visit 3 (first day of double-blind treatment period). Subject (b) (6) had percent predicted FEV1 of 93.1025% at Visit 3 (did not meet Product Specific Guidance required percent predicted FEV1 on the first day of double-blind treatment period). Subject (b) (6) had percent predicted FEV1 of 97.1258% at Visit 1, 97.8402% at Visit 2, and 91.0534% at Visit 3 (did not meet Product Specific Guidance required percent predicted FEV1 at either visit during placebo run-in period or on the first day of double-blind treatment period). Subject (b) (6) had percent predicted FEV1 of 85.8664% at Visit 3 (did not meet Product Specific Guidance required percent predicted FEV1 on the first day of double-blind treatment period). Subject (b) (6) had percent predicted FEV1 of 87.1836% at Visit 1, 90.0272% at Visit 2, and 89.2967% at Visit 3 (did not meet Product Specific Guidance required percent predicted FEV1 at either visit during placebo run-in period or on the first day of double-blind treatment period). Subject (b) (6) had percent predicted FEV1 of not recorded at Visit 1, 96.6751% at Visit 2, and 94.2712%

				at Visit 3 (did not meet Product Specific Guidance required percent predicted FEV1 at either visit during placebo run-in period or on the first day of double-blind treatment period). Subject (b) (6) had percent predicted FEV1 of 33.5241% at Visit 3 (did not meet Product Specific Guidance required percent predicted FEV1 on the first day of double-blind treatment period). Since these subjects did not meet Inclusion Criterion 5, they are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.
MGR001-3001	(b) (6)	Included	Exclude	Did not meet requirement in Statistical Analysis Plan that Day 29 (Visit 5) average pre-dose measurements are within ± 2 hours of Day 1 (Visit 3) average pre-dose measurements and/or subjects with post-screening visit pre-dose assessments completed after 12 noon According to Applicant's response to IR question 12 that was submitted on 2/26/2018, the Applicant does not believe that spirometry performed outside of a ±1 hour window for the Day 29 trough FEV₁ endpoint as stated in the Study Protocol is not a valid reason to exclude subjects from the Day 29 Per Protocol Set. Instead, the Applicant stated that a ±2 hour window for the Day 29 trough FEV₁ endpoint as pre-specified in the Statistical Analysis Plan (Section 8.1.4) was used in the Applicant's relevant sensitivity analyses and would allow for the predictable situation that some patients would attend the clinic earlier or later than stated in the protocol. According to Applicant's response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018, these subjects had Day 29 out of window spirometry assessments where Day 29 (Visit 5) average pre-dose assessments are not within ±2 hours of Day (Visit 3) average pre-dose time-points and/or subjects with pre-dose assessments completed after 12 noon and were included in the Applicant's PPS. These subjects should be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in FDA Day 1 endpoint PP population since the Day 1 endpoint is not affected by this protocol deviation.

(b) (6)

(b) (6)

	(b) (6)			
MGR001-3001		Included	Exclude	Short-acting beta agonist use within 6 hours of lung function testing (Visit 3) and subject did not meet requirement in Statistical Analysis Plan that Day 29 (Visit 5) average pre-dose measurements are within ± 2 hours of Day 1 (Visit 3) average pre-dose measurements and/or subjects with post-screening visit pre-dose assessments completed after 12 noon According to the Applicant's response to IR question 3 that was submitted on 2/1/2018, these subjects used a short-acting beta agonist (albuterol) during or within six hours prior to spirometry measurements and these spirometry measurements were used in calculation of Day 1 FEV1 AUEC0-12 endpoint during Visit 3 (Day 1 Visit). As described in Section 4.1.4.2.4 in the Clinical Study Report, if a subject took albuterol during the 0 to 12-hour post dose spirometry assessments on Day 1, then for the Per Protocol Analysis of the Day 1 FEV1 AUEC0-12 endpoint, all serial spirometry assessments collected after the albuterol use were set to missing. Based on the missing spirometry assessments during 0

				to 12-hour post dose spirometry assessments, these subjects are recommended to be excluded from the FDA PP and FDA Day 1 PP based on Section 4.1.4.2.4 of the Clinical Study Report. According to Applicant's response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018, this subject had Day 29 out of window spirometry assessments where Day 29 (Visit 5) average pre-dose assessments are not within ± 2 hours of Day (Visit 3) average pre-dose time-points and/or subjects with pre-dose assessments completed after 12 noon and was included in the Applicant's PPS. These subjects should be excluded from FDA PP and FDA Day 1 endpoint PP populations because of short-acting beta agonist use within 6 hours of lung function testing (Visit 3) and excluded from FDA PP and Day 29 endpoint PP populations because Day 29 (Visit 5) average pre-dose measurements are within ± 2 hours of Day 1 (Visit 3) average pre-dose measurements and/or subjects with post-screening visit pre-dose assessments completed after 12 noon.
MGR001-3001	(b) (6)	Included	Exclude	Short-acting beta agonist use within 6 hours of lung function testing (Visit 3) and did not meet required 75-125% compliance with study treatment for double-blind study treatment period According to the Applicant's response to IR question 3 that was submitted on 2/1/2018, these subjects used a short-acting beta agonist (albuterol) during or within six hours prior to spirometry measurements and these spirometry measurements were used in calculation of Day 1 FEV₁ AUEC₀₋₁₂ endpoint during Visit 3 (Day 1 Visit). As described in Section 4.1.4.2.4 in the Clinical Study Report, if a subject took albuterol during the 0 to 12-hour post dose spirometry assessments on Day 1, then for the Per Protocol Analysis of the Day 1 FEV₁ AUEC₀₋₁₂ endpoint, all serial spirometry assessments collected after the albuterol use were set to missing. Based on the missing spirometry assessments during 0 to 12-hour post dose spirometry assessments, these subjects are recommended to be excluded from the FDA PP and FDA Day 1 PP based on Section 4.1.4.2.4 of the Clinical Study Report. According to the FDA Statistician's calculation and verification, these subjects were included in the Applicant's Per Protocol Set and did not meet the required 75-125% compliance with the study treatment during the double-blind study treatment

				period. The Applicant was noted to have incorrectly calculated the expected number of doses (denominator) used in calculation of double-blind study treatment period compliance based on the study design. These subjects should be excluded from FDA PP and FDA Day 29 endpoint PP population. These subjects should be excluded from FDA PP and FDA Day 1 endpoint PP populations because of short-acting beta agonist use within 6 hours of lung function testing (Visit 3) and excluded from FDA PP and Day 29 endpoint PP populations because subjects did not meet required 75-125% compliance with study treatment for double-blind study treatment period.
MGR001-3001	(b) (6)	Included	Exclude	Subject dosed with study treatment prior to completion of pre-dose spirometry assessments at Visit 5 and visit was not rescheduled According to Applicant's response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018 and Listing 16.2.2-1.3, these subjects were dosed with study treatment prior to completion of pre-dose spirometry assessments at Visit 5 and this visit was not rescheduled. These subjects should be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in FDA Day 1 endpoint PP population since the Day 1 endpoint is not affected by this protocol deviation.
MGR001-3001		Included	Exclude	Subject dosed with study treatment prior to completion of pre-dose spirometry assessments at Visit 5 and visit was not rescheduled and subject did not meet requirement in Statistical Analysis Plan that Day 29 (Visit 5) average pre-dose measurements are within ± 2 hours of Day 1 (Visit 3) average pre-dose measurements and/or subjects with post-screening visit pre-dose assessments completed after 12 noon According to Applicant's response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018 and Listing 16.2.2-1.3, these subjects were dosed with study treatment prior to completion of pre-dose spirometry assessments at Visit 5 and this visit was not rescheduled. According to Applicant's response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018, this subject had Day 29 out of window spirometry assessments where Day 29 (Visit 5) average pre-dose assessments are not within ± 2 hours of Day (Visit 3)

				average pre-dose time-points and/or subjects with pre-dose assessments completed after 12 noon. These subjects should be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in FDA Day 1 endpoint PP population since the Day 1 endpoint is not affected by these protocol deviations.
MGR001-3001	(b) (6)	Included	Exclude	Subject dosed with study treatment prior to completion of pre-dose spirometry assessments at Visit 5 and visit was not rescheduled and Visit 5 completed out of pre-specified study visit window (Day 29 ±2 days) According to Applicant’s response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018 and Listing 16.2.2-1.3, these subjects were dosed with study treatment prior to completion of pre-dose spirometry assessments at Visit 5 and this visit was not rescheduled. Based on the Applicant’s response to IR question 7 that submitted on 2/1/2018 and IR question 6 submitted on 2/26/2018, it was determined by the FDA Statistician that these subjects were included in the Applicant’s Per Protocol Set and completed their Visit 5 outside the Applicant’s pre-specified visit window of Day 29 ±2 days. These subjects should be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in FDA Day 1 endpoint PP population since the Day 1 endpoint is not affected by these protocol deviations.
MGR001-3001		Included	Exclude	Adverse event (not treatment failure) lead to study discontinuation According to Applicant’s response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018 and ae.xpt data set, Subject (b) (6) experienced an adverse event of allergic rhinitis from Day 18 (b) (6) to Day 23 (b) (6) that lead to subject discontinuation from the study and thus Day 29 (Visit 5) data is not available. An adverse event of allergic rhinitis is not considered to be a treatment failure by FDA and therefore, this subject is recommended to be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in the FDA Day 1 endpoint PP population.
MGR001-3001		Included	Exclude	Adverse event (not treatment failure) lead to study discontinuation

				According to Applicant’s response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018 and ae.xpt data set, Subject (b) (6) experienced an adverse event of acute bronchitis from Day 4 (b) (6) to Day 24 (b) (6) that lead to subject discontinuation from the study and thus Day 29 (Visit 5) data is not available. An adverse event of acute bronchitis is not considered to be a treatment failure by FDA and therefore, this subject is recommended to be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in the FDA Day 1 endpoint PP population.
MGR001-3001	(b) (6)	Included	Exclude	Adverse event (not treatment failure) lead to study discontinuation According to Applicant’s response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018 and ae.xpt data set, Subject (b) (6) experienced an adverse event of pneumonia from Day 10 (b) (6) to Day 13 (b) (6) that lead to subject discontinuation from the study and thus Day 29 (Visit 5) data is not available. An adverse event of pneumonia is not considered to be a treatment failure by FDA and therefore, this subject is recommended to be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in the FDA Day 1 endpoint PP population.
MGR001-3001	(b) (6)	Included	Exclude	Adverse event (not treatment failure) lead to study discontinuation According to Applicant’s response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018 and ae.xpt data set, Subject (b) (6) experienced an adverse event of inguinal hernia from Day 9 (b) (6) to Ongoing that lead to subject discontinuation from the study and thus Day 29 (Visit 5) data is not available. An adverse event of inguinal hernia is not considered to be a treatment failure by FDA and therefore, this subject is recommended to be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in the FDA Day 1 endpoint PP population.
MGR001-3001	(b) (6)	Included	Exclude	Adverse event (not treatment failure) lead to study discontinuation According to Applicant’s response to IR question 12

				(ir12fl.xpt) that was submitted on 2/26/2018 and ae.xpt data set, Subject (b) (6) experienced an adverse event of bronchitis from Day 7 (b) (6) to Day 19 (b) (6) that lead to subject discontinuation from the study and thus Day 29 (Visit 5) data is not available. An adverse event of bronchitis is not considered to be a treatment failure by FDA and therefore, this subject is recommended to be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in the FDA Day 1 endpoint PP population.
MGR001-3001	(b) (6)	Included	Exclude	Adverse events (not treatment failure) led to study discontinuation According to Applicant’s response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018 and ae.xpt data set, Subject (b) (6) experienced adverse events of insomnia and anxiety from Day 2 (b) (6) to Day 7 (b) (6) that lead to subject discontinuation from the study and thus Day 29 (Visit 5) data is not available. Adverse events of insomnia and anxiety are not considered to be a treatment failure by FDA and therefore, this subject is recommended to be excluded from FDA PP and FDA Day 29 endpoint PP populations and included in the FDA Day 1 endpoint PP population.
MGR001-3001		Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved after excluding spirometry measurements with “Unacceptable” Grade - Did not meet Inclusion Criterion 6 According to the FDA Statistician’s verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the Study Protocol’s requirement of demonstration of 12% reversibility after bronchodilator after excluding those spirometry measurements with “Unacceptable” PFT grading. According to the Applicant’s response to IR question 1 including adre.xpt data set that was submitted on 3/22/2018, spirometry measurements with “Unacceptable” PFT grading did not meet the American Thoracic Society Guidelines (2005) for technical quality or repeatability. Since these spirometry measurements did not meet the ATS Guidelines for technical quality, they cannot be used to determine whether a subject met

				an inclusion criterion. Since these subjects did not meet Inclusion Criterion 6, they are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.
MGR001-3001	(b) (6)	Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved after excluding spirometry measurements with “Unacceptable” Grade - Did not meet Inclusion Criterion 6 and did not meet required 75-125% compliance with study treatment for double-blind study treatment period According to the FDA Statistician’s verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the Study Protocol’s requirement of demonstration of 12% reversibility after bronchodilator after excluding those spirometry measurements with “Unacceptable” PFT grading. According to the Applicant’s response to IR question 1 including adre.xpt data set that was submitted on 3/22/2018, spirometry measurements with “Unacceptable” PFT grading did not meet the American Thoracic Society Guidelines (2005) for technical quality or repeatability. Since these spirometry measurements did not meet the ATS Guidelines for technical quality, they cannot be used to determine whether a subject met an inclusion criterion. According to the FDA Statistician’s calculation and verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the required 75-125% compliance with the study treatment during the double-blind study treatment period. Since these subjects did not meet Inclusion Criterion 6, they are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.
MGR001-3001		Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved after excluding spirometry measurements with “Unacceptable” Grade - Did not meet Inclusion Criterion 6 and did not meet requirement in Statistical Analysis Plan that Day 29 (Visit 5) average pre-dose measurements are within ± 2 hours of Day 1 (Visit 3) average pre-dose measurements and/or subjects with post-screening visit pre-dose assessments completed after 12 noon

				According to the FDA Statistician’s verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the Study Protocol’s requirement of demonstration of 12% reversibility after bronchodilator after excluding those spirometry measurements with “Unacceptable” PFT grading. According to the Applicant’s response to IR question 1 including adre.xpt data set that was submitted on 3/22/2018, spirometry measurements with “Unacceptable” PFT grading did not meet the American Thoracic Society Guidelines (2005) for technical quality or repeatability. Since these spirometry measurements did not meet the ATS Guidelines for technical quality, they cannot be used to determine whether a subject met an inclusion criterion. According to Applicant’s response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018, these subjects had Day 29 out of window spirometry assessments where Day 29 (Visit 5) average pre-dose assessments are not within ±2 hours of Day (Visit 3) average pre-dose time-points and/or subjects with pre-dose assessments completed after 12 noon and were included in the Applicant’s PPS. Since these subjects did not meet Inclusion Criterion 6, they are recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.
MGR001-3001	(b) (6)	Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved after excluding spirometry measurements with “Unacceptable” Grade - Did not meet Inclusion Criterion 6 and short-acting beta agonist use within 6 hours of lung function testing (Visit 3) According to the FDA Statistician’s verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the Study Protocol’s requirement of demonstration of 12% reversibility after bronchodilator after excluding those spirometry measurements with “Unacceptable” PFT grading. According to the Applicant’s response to IR question 1 including adre.xpt data set that was submitted on 3/22/2018, spirometry measurements with “Unacceptable” PFT grading did not meet the American Thoracic Society Guidelines (2005) for technical quality or repeatability. Since these spirometry measurements

				did not meet the ATS Guidelines for technical quality, they cannot be used to determine whether a subject met an inclusion criterion. According to the Applicant’s response to IR question 3 that was submitted on 2/1/2018, these subjects used a short-acting beta agonist (albuterol) during or within six hours prior to spirometry measurements and these spirometry measurements were used in calculation of Day 1 FEV1 AUEC0-12 endpoint during Visit 3 (Day 1 Visit). As described in Section 4.1.4.2.4 in the Clinical Study Report, if a subject took albuterol during the 0 to 12-hour post dose spirometry assessments on Day 1, then for the Per Protocol Analysis of the Day 1 FEV1 AUEC0-12 endpoint, all serial spirometry assessments collected after the albuterol use were set to missing. Based on the missing spirometry assessments during 0 to 12-hour post dose spirometry assessments, these subjects are recommended to be excluded from the FDA PP and FDA Day 1 PP based on Section 4.1.4.2.4 of the Clinical Study Report. Since this subject did not meet Inclusion Criterion 6, this subject is recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.
MGR001-3001	(b) (6)	Included	Exclude	Post-bronchodilator reversibility of at least 12% not achieved after excluding spirometry measurements with “Unacceptable” Grade - Did not meet Inclusion Criterion 6 and Visit 5 completed out of pre-specified study visit window (Day 29 ±2 days) According to the FDA Statistician’s verification, these subjects were included in the Applicant’s Per Protocol Set and did not meet the Study Protocol’s requirement of demonstration of 12% reversibility after bronchodilator after excluding those spirometry measurements with “Unacceptable” PFT grading. According to the Applicant’s response to IR question 1 including adre.xpt data set that was submitted on 3/22/2018, spirometry measurements with “Unacceptable” PFT grading did not meet the American Thoracic Society Guidelines (2005) for technical quality or repeatability. Since these spirometry measurements did not meet the ATS Guidelines for technical quality, they cannot be used to determine whether a subject met an inclusion criterion.

				Based on the Applicant’s response to IR question 7 that submitted on 2/1/2018 and IR question 6 submitted on 2/26/2018, it was determined by the FDA Statistician that these subjects were included in the Applicant’s Per Protocol Set and completed their Visit 5 outside the Applicant’s pre-specified visit window of Day 29 ±2 days. These subjects’ inclusion into the Day 1 PP population is not affected by this protocol deviation since the Day 1 endpoint is not affected by Visit 5 being out of the visit window. Since this subject did not meet Inclusion Criterion 6, this subject is recommended to be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.
MGR001-3001	(b) (6)	Included	Exclude	Has insufficient data from Day 1 (Visit 3) to calculate Day 1 endpoint after FEV1 data that was determined to be poor quality following “Best Test Review” is set to missing and subject did not meet requirement in Statistical Analysis Plan that Day 29 (Visit 5) average pre-dose measurements are within ± 2 hours of Day 1 (Visit 3) average pre-dose measurements and/or subjects with post-screening visit pre-dose assessments completed after 12 noon Subject has insufficient data from Day 1 (Visit 3) to calculate Day 1 endpoint after FEV1 data that was determined to be poor quality following “Best Test Review” is set to missing. Data from spirometry loops that were determined to be poor quality during “Best Test Review” cannot be used in statistical analysis or determination of inclusion/exclusion status. According to Applicant’s response to IR question 12 that was submitted on 2/26/2018, the Applicant does not believe that spirometry performed outside of a ±1 hour window for the Day 29 trough FEV1 endpoint as stated in the Study Protocol is not a valid reason to exclude subjects from the Day 29 Per Protocol Set. Instead, the Applicant stated that a ±2 hour window for the Day 29 trough FEV1 endpoint as pre-specified in the Statistical Analysis Plan (Section 8.1.4) was used in the Applicant’s relevant sensitivity analyses and would allow for the predictable situation that some patients would attend the clinic earlier or later than stated in the protocol.

				According to Applicant's response to IR question 12 (ir12fl.xpt) that was submitted on 2/26/2018, these subjects had Day 29 out of window spirometry assessments where Day 29 (Visit 5) average pre-dose assessments are not within ± 2 hours of Day (Visit 3) average pre-dose time-points and/or subjects with pre-dose assessments completed after 12 noon and were included in the Applicant's PPS. This subject should be excluded from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations.

Additional Comments

1. Use the Applicant's Per Protocol Set, specifically adsl.xpt data set submitted on 12/29/2018) for starting point for Per Protocol Population subject adjustments. The adsl.xpt data set can be found at:
<\\cdsub1\evsprod\anda208891\0000\m5\datasets\mgr001-3001\analysis\adam\datasets\adsl.xpt>
2. Since the Applicant's Full Analysis Set (FAS) was considered definitive while testing superiority according to their study protocol, this population is analogous to the FDA's mITT population. Both of the Applicant's definitions for the Full Analysis Set (Original Study Protocol and Amendment 1) are not consistent with the current FDA Modified Intent-to-Treat population definition and are not acceptable. Use the current FDA mITT population for superiority analysis which is defined as all randomized subjects who applied or used at least one dose of assigned drug product.
3. The Applicant's definition for the Per Protocol Set (PPS) is not acceptable as it is not consistent with the currently accepted definition of the FDA Per Protocol Population the Applicant's definition of the PPS does not require subjects to meet all inclusion/exclusion criteria and complete the evaluation within the designated visit window and this is not acceptable. Additionally, since the Applicant used a single Per Protocol population in this study for both co-primary endpoints, any protocol violation that affected either co-primary endpoints (not both co-primary endpoints as defined in the study by the Applicant) should result in a subject being excluded from the Applicant's PPS. Therefore, conduct FDA statistical analysis for bioequivalence two ways: 1) single Per Protocol Population (FDA PP Population) and 2) two separate Per Protocol Populations (FDA Day 1 and FDA Day 29 PP Populations).
4. Verify that the Applicant followed the Study Protocol, Study Report, and Statistical Analysis Plan for their statistical methods and analysis, handling of missing and data, study design, and their calculation of the statistical results. Verify that any changes made to the statistical methods and analyses after the study commenced after acceptable.
5. Verify that the Applicant followed Section 4.2.1.6 (Exposure and Treatment Compliance) of the Study Report and Section 7.2.1 (Treatment Compliance) of the Statistical Analysis

Plan for all subjects with the following recommended adjustments to the method for calculating study drug compliance. The Applicant incorrectly calculated the number of expected doses for the double-blind treatment period by using the incorrect formula of “ $2 \times (\text{date of expected last dose} - \text{date of first dose} + 1)$ ”. The correct number of expected doses is not based on the start or end date of a study treatment but is based on the study design and is the same for all subjects enrolled in the study. Use 56 as the expected number of doses for the double-blind treatment period ($28 \text{ days} \times 2 = 56$) in calculation and verification of subject’s double-blind treatment compliance. Adjustments made to the number of doses used by the subject based on (b) (4) data is acceptable and should be used in verification of double-blind treatment compliance. Exclude any subjects from the FDA Per Protocol Population and FDA Day 29 Per Protocol Population (except those subjects recommended to be included in the Per Protocol Populations since they were treatment failures) that did not meet the required double-blind treatment compliance of 75-125%.

6. Verify and exclude any subjects from the FDA PP Population and FDA Day 29 Per Protocol Population (except those subjects recommended to be included in the Per Protocol Populations since they were treatment failures) whose Visit 5 was outside of the Study Protocol’s specified study visit window of Day 29 $\pm$ 2 days (Day 27 to Day 31).
7. Verify and exclude any subjects (except those subjects recommended to be included in the Per Protocol Populations since they were treatment failures) from FDA PP, FDA Day 1 PP, and FDA Day 29 PP Populations that did not meet Inclusion Criterion 5 (Percent Predicted FEV1) based on the version of the Study Protocol that each subject was enrolled under. Include any subjects who met Inclusion Criterion 5 and were excluded from the Applicant’s Per Protocol Set solely based on this reason.
8. Verify and exclude any subjects (except those subjects recommended to be included in the Per Protocol Populations since they were treatment failures) from the FDA PP, FDA Day 1 PP, and FDA Day 29 PP populations that did not meet Inclusion Criterion 6 (Percent Reversibility of FEV1). Include any subjects who met Inclusion Criterion 6 and were excluded from the Applicant’s Per Protocol Set solely based on this reason.
9. Verify that subjects who were enrolled in the study twice were appropriately handled with respect to study design and statistical analyses and consistent with their pre-specified study design. Make any necessary subject adjustments to FDA PP populations if needed.
10. Verify that the Applicant’s method of Blind Sample Size Re-estimation (BSSR) was conducted appropriately and consistent with their pre-specified study design. Make any necessary subject adjustments to FDA PP populations if needed.
11. Verify that the Applicant’s method of pooling sites was conducted appropriately and consistent with their pre-specified study design. Make any necessary subject adjustments to FDA PP populations if needed.
12. Verify that no spirometry measurements that were graded as “Unacceptable” according to ATS Guidelines (2005) were used in the statistical analysis (bioequivalence or superiority

analysis) or in determining if a subject met all Inclusion/Exclusion Criteria and make any necessary subjects adjustments to FDA PP populations if needed. See Applicant's IR response to Question 1 (adre31.xpt data set) submitted on March 22, 2018 for list of subjects with spirometry measurements that were graded as "Unacceptable."

APPEARS THIS WAY ON
ORIGINAL



Michael
Spagnola

Digitally signed by Michael Spagnola
Date: 6/27/2018 10:53:05AM
GUID: 56f3fc6e00e3bf2df523cd48bdc61031



Carol
Kim

Digitally signed by Carol Kim
Date: 6/27/2018 12:06:59PM
GUID: 508da70a00028df5288765ab0807f9a5



Mark
Ritter

Digitally signed by Mark Ritter
Date: 6/27/2018 11:38:00AM
GUID: 508da6e80002732e6afdd41c9bb5d417

DIVISION OF BIOEQUIVALENCE REVIEW FOR DRY POWDER INHALER PRODUCTS

ANDA No.	208891		
Drug Product Name	Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder		
Strength(s)	0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ 0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation		
Applicant Name	Mylan Pharmaceuticals Inc.		
Applicant Address	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310		
US Agent Name and the Mailing Address	Wayne Talton, Head of Global Regulatory Affairs wayne.talton@mylan.com OR Beth Britton, Senior Director of Regulatory Affairs beth.britton@mylan.com		
US agent's Telephone Number	(304) 554-6551 (WT) (304) 554-6184 (BB)		
US Agent's Fax Number	(304) 285-6407		
Original Submission Date(s)	December 29, 2015 February 15, 2016 (concentration data, graphs and SAS output for pharmacokinetic studies; tabular listing of all clinical studies; information on unblinding, randomization and datasets for the pharmacodynamic study) September 22, 2016 (Response to ECD/Bioequivalence) January 12, 2017 (Response to ECD/Bioequivalence)		
Submission Date(s) of Amendment(s) Under Review	March 2, 2017 (Bridging in vitro BE studies) August 28, 2017 (Resubmission/After Action- Complete; Bioequivalence/Other) March 22, 2018 (Bioequivalence/Response to Discipline Review Letter)		
Primary Reviewer	Tian Ma, Ph.D.		
Secondary Reviewer	Vipra Kundoor, Ph.D.		
Tertiary Reviewer	Bing V. Li, Ph.D.		
Study Number (s)	MGR001-1006	MGR001-1007	MGR001-1016
Study Type (s)	Fasting	Fasting	Fasting (repeat)
Strength (s)	100/50 mcg ¹	500/50 mcg	250/50 mcg
Clinical Site	Worldwide Clinical Trials Early Phase Services, LLC		
Clinical Site Address	2455 NE Loop 410, Suite 150 San Antonio, Texas 78217		
Analytical Site	Mylan Pharmaceuticals Inc.		

¹ From now on in this review, product strength of “x/y mcg” will be used to indicate the strength of fluticasone propionate and salmeterol xinafoate (EQ y mcg base) per inhalation, respectively.

Analytical Site Address	Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505		
Study Number (s)	MGR001-1005	MGR001-1014	
Study Type (s)	Fasting (failed, but was used in pooled analysis by the applicant with MGR001-1014)	Fasting (failed, but was used in pooled analysis by the applicant with MGR001-1005)	
Strength (s)	250/50 mcg	250/50 mcg	
Clinical Site	Worldwide Clinical Trials Early Phase Services, LLC		
Clinical Site Address	2455 NE Loop 410, Suite 150 San Antonio, Texas 78217		
Analytical Site	Mylan Pharmaceuticals Inc.		
Analytical Site Address	Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505		
Study Number (s)	057755-02-04	MGF-PRO-2015-080	057755-02-07
Study Type (s)	In Vitro BE [single actuation content (SAC) and aerodynamic particle size distribution (APSD)]	In Vitro BE (SAC and APSD)	In Vitro BE (SAC and APSD)
Strength (s)	100/50 mcg	250/50 mcg	500/50 mcg
Analytical Site	(b) (4)	Mylan Global Respiratory Group	(b) (4)
Analytical Site Address	(b) (4)	IPC008, Discovery Park House, Floor 3 Sandwich, Kent. CT13 9ND. UK	(b) (4)
Study Number (s)	MGR-REP-2015-092	MGR-PRO-REP-2015-103	MGR-REP-2015-093
Study Type (s)	Pressure Differential (4 kPa) (SAC and APSD)	Pressure Differential (4 kPa) (SAC and APSD)	Pressure Differential (4 kPa) (SAC and APSD)
Strength (s)	100/50 mcg	250/50 mcg	500/50 mcg
Analytical Site	(b) (4)	Mylan Global Respiratory Group	(b) (4)
Analytical Site Address	(b) (4)	IPC008, Discovery Park House, Floor 3 Sandwich, Kent. CT13 9ND. UK	(b) (4)
Study Number (s)	MGR-PRO-2016-106	MGR-PRO-2016-107	MGR-PRO-2016-108
Study Type (s)	In vitro bridging (SAC and APSD)	In vitro bridging (SAC and APSD)	In vitro bridging (SAC and APSD)
Strength (s)	100/50 mcg	250/50 mcg	500/50 mcg

Analytical Site	Mylan Global Respiratory Group	Mylan Global Respiratory Group	(b) (4)
Analytical Site Address	IPC008, Discovery Park House, Floor 3 Sandwich, Kent. CT13 9ND. UK	IPC008, Discovery Park House, Floor 3 Sandwich, Kent. CT13 9ND. UK	
Study Number (s)	MGR000-1003		
Study Type (s)	Flow Profiling		
Strength (s)	N/A (empty inhaler which did not contain drug or placebo)		
Clinical Site	Site	Principal Investigator	Address
	1	Dominik Kappeler	Inamed Clinical Unit, 82131 Gauting, Germany
	2	Isabelle Schenkenberger	Clinical Research Berlin GbR, 10787 Berlin, Germany
	3	Prof. Dr. med. Walter Dorsch	Practice for Child and Adolescent Medicine, Allergy, Pediatric Pulmonology, Naturopathic, 81379 Munich, Germany
	4	Dr. med. Manfred Praun	Practice for Child and Adolescent Medicine Dr. Praun & Dr. Stiebing, 82205 Gilching, Germany
	5 (not activated)	Prof. Dr. med. Stefan Zielen	University Hospital Johann Wolfgang Goethe-Universität Frankfurt/Main, Centre for children and adolescents, Departement of paediatric pneumology, allergology and cystic fibrosis, 60590 Frankfurt/Main, Germany
Clinical Site Address	Please see table above		
OSI Status	<u>Backlog, Year 1 and Year 2 ANDAs</u>		<u>Post October 1, 2014 ANDAs</u>
	☐ Pending ☐ Complete ☐ N/A (Waiver) ²		☐ To Be Determined by OSIS ☐ Pending ☒ Complete

² Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☐ Not granted ☒ N/A		
QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ N/A		
Formulation	☒ Adequate ☐ Inadequate		
Will Response to CR Result in a Reformulation?	☐ Possibly ☒ No ☐ N/A		
BE Guidance Version Used for Evaluation of Current ANDA	Draft Guidance on Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder (Recommended Sep 2013)		
Deficiency Classification	☐ Major (Deficiencies to be communicated by CR) ☐ Minor ☒ N/A (Review is Adequate)		
Overall Review Result	☒ Adequate ☐ Inadequate		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1,2,10,14,22	Fasting	100/50 mcg	ACCEPTABLE
1,2,10,14,22	Fasting	500/50 mcg	ACCEPTABLE
22,34	Fasting	250/50 mcg	ACCEPTABLE
1,2,10,14	Fasting (Failed, but was used in pooled analysis by the applicant with MGR001-1014)	250/50 mcg	N/A (for information)
1,2,10,14	Fasting (Failed, but was used in pooled analysis by the applicant with MGR001-1005)	250/50 mcg	N/A (for information)
1,10,14,22,34	In Vitro BE (SAC and APSD)	100/50 mcg	ACCEPTABLE
1,10,14,22,34	In Vitro BE (SAC and APSD)	250/50 mcg	ACCEPTABLE
1,10,14,22,34	In Vitro BE (SAC and APSD)	500/50 mcg	ACCEPTABLE
1,10,14,22,34	Pressure Differential (4 kPa) (SAC and APSD)	100/50 mcg	ACCEPTABLE
1,10,14,22,34	Pressure Differential (4 kPa) (SAC and APSD)	250/50 mcg	ACCEPTABLE
1,10,14,22,34	Pressure Differential (4 kPa) (SAC and APSD)	500/50 mcg	ACCEPTABLE
16,34	In Vitro BE (SAC and APSD) Bridging	100/50 mcg	ACCEPTABLE
16,34	In Vitro BE (SAC and APSD) Bridging	250/50 mcg	ACCEPTABLE

16,34	In Vitro BE (SAC and APSD) Bridging	500/50 mcg	ACCEPTABLE
1,2,10,22	Flow Profiling	N/A (empty inhaler which did not contain drug or placebo)	N/A (for information)

Note: The clinical endpoint study (MGR001-3001) and device orientation (including study MGR000-1004) are reviewed by Division of Clinical Review (DCR) in the current review cycle and for the future.

1 EXECUTIVE SUMMARY

This is a review of a study amendment.

On 12/29/2015, Mylan Pharmaceuticals Inc. has submitted the current application for Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder, 0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ 0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation. The test product, also refers to as MGR001 by the applicant, contains fluticasone propionate (FP) and salmeterol xinafoate (SX) inhalation powder in CRC749 inhaler device. The reference standard (RS) is Advair Diskus® 100/50 (fluticasone propionate and salmeterol xinafoate), 0.1 mg/EQ 0.05 mg base per inhalation; Advair Diskus® 250/50 (fluticasone propionate and salmeterol xinafoate), 0.25 mg/EQ 0.05 mg base per inhalation; and Advair Diskus® 500/50 (fluticasone propionate and salmeterol xinafoate), 0.5 mg/EQ 0.05 mg base per inhalation manufactured by GLAXO GRP LTD (approved on August 24, 2000 under NDA 021077). The reference-listed drug (RLD) is the same as the RS.

Consistent with the current Draft Bioequivalence (BE) Guidance on Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder (recommended Sep 2013)³ (product-specific guidance), the applicant submitted results of the following studies comparing the test and reference products:

- Four fasting pharmacokinetic (PK) BE studies (#MGR001-1006 for the 100/50 mcg strength, #s MGR001-1005 and MGR001-1014 for the 250/50 mcg strength, and #MGR001-1007 for the 500/50 mcg strength)
- One clinical endpoint study (#MGR001-3001 at the 100/50 mcg strength)
- Two types [single actuation content (SAC) and aerodynamic particle size distribution (APSD)] of in vitro BE studies for each of the three strengths of the drug product (#057755-02-04 for the 100/50 mcg strength, #MGR-PRO-2015-080 for the 250/50 mcg strength, and #057755-02-07 for the 500/50 mcg strength)

In addition, as recommended by the Agency to the applicant during pre-ANDA communications^{4,5} due to difference in device resistance and device orientation as compared to the RLD product, the applicant also submitted the following studies:

³<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM367643.pdf> Last accessed: 12/16/2016.

⁴ \\cdsnas\OGDS6\CONTROLS\2012-docs\12-0731.pdf

- Two types (SAC and APSD) of in vitro studies at 4 kPa fixed pressure drop for each of the three strengths of the drug product (#MGR-REP-2015-092 for the 100/50 mcg strength, # MGR-PRO-REP-2015-103 for the 250/50 mcg strength, and #057755-02-08 for the 500/50 mcg strength) comparing the test and RLD products
- One flow profiling study (#MGR000-1003) comparing the empty test and RLD devices
- One device orientation study (#MGR000-1004) using empty test device

In the original BE review dated 3/22/2017⁶, the applicant's fasting BE studies for the 100/50 and 500/50 mcg strengths were deemed inadequate due to method validation deficiencies. The 2 PK studies for the 250/50 mcg strength were considered unacceptable because they each failed to meet the BE criteria of 80.00-125.00%. All of the in vitro BE studies were considered incomplete due to multiple deficiencies. The clinical endpoint study was incomplete due to missing information on study design and Office of Study Integrity and Surveillance (OSIS) inspectional deficiencies. In addition, Division of Clinical Review (DCR)'s per-protocol set (PPS) recommendation, which is required for the Agency's statistical analysis of the current study, was pending the applicant's response to the complete response (CR).

For additional studies submitted by the applicant to support device resistance difference and device orientation difference as compared to the RLD product, all of the in vitro studies at 4 kPa fixed pressure drop were considered unacceptable due to insufficient number of units used in the study. The flow profiling study was considered unacceptable due to the use of non-US reference product. Based on consult response from Office of Surveillance and Epidemiology (OSE)/ Division of Medication Error Prevention and Analysis (DMEPA), the device orientation study was considered insufficient to provide information to conclude that the test product can be substituted for the RLD.

On 3/28/2017, the Agency issued a Complete Response (CR) letter to the applicant⁷.

On 3/2/2017, prior to the Agency's issuance of the 3/28/2017 CR letter, the applicant submitted an unsolicited amendment to support their (b) (4). BE-related studies in this submission are in vitro bridging studies for each of the three strengths of the drug product (#MGR-PRO-2016-106 for the 100/50 mcg strength, # MGR-PRO-2016-107 for the 250/50 mcg strength, and # MGR-PRO-2016-106 for the 500/50 mcg strength). Since this submission is close to the GDUFA goal date, this submission was not reviewed by the Agency in the original review cycle, and was deferred to be reviewed in the current review cycle.

⁵ <\\cdsnas\OGDS6\CONTROLS\2013-docs\13-0422.pdf>

⁶ GDRP: ANDA-208891-ORIG-1, Bioequivalence Primary Review, A208891N000DB_N12292015, 3/22/2017.

⁷ GDRP: ANDA-208891-ORIG-1, Upload Final Decision, A208891N000CR, 3/28/2017.

On 4/3/2017, the applicant submitted a meeting request for a face-to-face meeting to discuss with the Agency about certain issues raised in the CR letter (including in vitro bridging studies, in vitro studies at 4 kPa fixed pressure drop, PK studies, flow profiling study, and device orientation). The face-to-face meeting was held on 7/3/2017, and agreement was reached for the aforementioned studies.⁸

On 4/4/2017, the applicant submitted a clarification request to seek written response from the Agency for certain additional clarifications (including question regarding OSIS inspectional findings for the clinical endpoint study). Based on communication with OSIS, DBI provided clarification response to the applicant's question⁹.

On 8/28/2017, the applicant submitted the post-CR response, which is reviewed in the current cycle.

Please note that the clinical endpoint study (MGR001-3001) and device orientation (including study MGR000-1004) were reviewed by Division of Bioequivalence I (DBI) in the original review cycle, and they are reviewed by Division of Clinical Review (DCR) starting from the current review cycle.

The findings and outcome of the rest of the studies based on the current submission are summarized as follows:

Fasting studies

100/50 mcg and 500/50 mcg strengths

In the current amendment submitted on 8/28/2017, the applicant addressed the method validation deficiencies for the 100/50 and 500/50 mcg strengths of the PK BE studies. Hence, these 2 PK BE studies are **acceptable**.

250/50 mcg strength

In the current amendments, the applicant submitted a repeat PK BE study for the 250/50 mcg strength. This fasting study was designed as a single-dose, two-way crossover study in healthy male and female subjects. The applicant's repeat fasting BE study for the 250/50 mcg strength is **acceptable**. The reviewer's results are summarized in the table below.

⁸ GDRP: ANDA-208891-GI-1-MEETING-18, Documents, A208891N000DPM-Response01.doc, 8/10/2017.

⁹ GDRP: ANDA-208891-GI-1-MEETING-18, Respond to Bioequivalence questions, A208891N000DB_MR04042017, 7/25/2017.

Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder 3 x 250/50 mcg							
Fasting Bioequivalence Study, Study No. MGR001-1016, N=63 (Male=29 and Female=34) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
FP							
Parameter (units)	Test	N	Reference	N	Ratio	90% C.I.	
Group 1, 2 and 3 (trt*troup = 2)							
LAUCT (hr *pg/ml)	1278.49	59*	1190.68	59*#	1.07	101.85	113.20
LAUCI (hr *pg/ml)	1338.01	59*	1240.91	59*#	1.08	102.37	113.58
LCMAX (pg/ml)	165.06	59*	163.92	59*#	1.01	94.76	107.00
SA							
Parameter (units)	Test	N	Reference	N	Ratio	90% C.I.	
Group 1, 2 and 3 (trt*troup = 2)							
LAUCT (hr *pg/ml)	677.89	49*^	659.47	49*^#	1.03	98.59	107.17
LAUCI (hr *pg/ml)	710.94	49*^	694.03	49*^#	1.02	98.38	106.66
LCMAX (pg/ml)	295.53	49*^	313.07	49*^#	0.94	87.04	102.38

* Subjects (b) (6) were excluded by the reviewer due to dosing deviations.

^ Subjects (b) (6), (b) (6) were excluded by the reviewer due to missing samples that potentially affect Cmax.

The last time point (48 hrs) for Subjects (b) (6) Period 2 (reference treatment) were treated as missing by the reviewer due to protocol deviations related to centrifugation settings.

Note: The subjects were dosed in 3 groups. For both FP and SA, the treatment*group interaction was not statistically significant (p>0.1) for LAUC_{0-t}, LAUC_{0-∞} and LCmax, thus the reviewer combined three groups for statistical analysis as per the current DB practice.

Two types of pivotal in vitro BE studies (SAC and APSD) for each of the 3 strengths

In the current submissions, the applicant addressed the deficiencies related to the 100/50 mcg, 250/50 mcg and 500/50 mcg strengths of the pivotal in vitro BE studies. Hence these studies are **acceptable**.

Two types of in vitro studies (SAC and APSD) at 4 kPa fixed pressure drop for each of the 3 strengths

In the current submissions, the applicant addressed the deficiencies related to the 100/50 mcg, 250/50 mcg and 500/50 mcg strengths of the in vitro studies at 4 kPa fixed pressure drop. Hence these studies are **acceptable**.

Two types of in vitro bridging studies (SAC and APSD) for each of the 3 strengths

In the current submissions, the applicant submitted in vitro bridging studies for each of the 3 strength. The 100/50 mcg, 250/50 mcg and 500/50 mcg strengths of the in vitro bridging studies are **acceptable**.

Flow Profiling Study

In the current submissions, the applicant addressed the deficiencies related to the flow profiling study. Please note that the flow profiling study is a supportive study.

The application is **acceptable**.

APPEARS THIS WAY ON
ORIGINAL

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3 BACKGROUND

3.1 Background about the Applicant's Communication with the Agency

The applicant (Mylan) acquired MGR001 in 12/2011 from Pfizer Inc. (Pfizer).¹⁰ Prior to ANDA submission, the Agency had 2 meetings with Pfizer and 3 meetings with Mylan.

On 12/29/2015, the original ANDA was submitted, followed by multiple submissions in response to ECDs issued by various disciplines including DBI.

On 3/2/2017, the applicant submitted an unsolicited amendment (including in vitro bridging studies) to support their [REDACTED] (b) (4). Since this submission is close to the GDUFA goal date, it was not reviewed in the original review cycle, and is deferred by the Agency to be reviewed in the current review cycle.

On 3/28/2017, the Agency issued a Complete Response (CR) letter to the applicant¹¹.

On 4/3/2017, the applicant submitted a meeting request for a face-to-face meeting to discuss with the Agency about certain issues raised in the CR letter. The issues that are BE-related are regarding in vitro bridging studies, in vitro studies at 4 kPa fixed pressure drop, PK studies, flow profiling study, and device orientation. The BE review of this request was completed on 7/6/2017¹². The face-to-face meeting was held on 7/3/2017, and the meeting minutes was finalized by the Agency on 8/7/2017¹³.

On 4/4/2017, the applicant submitted a clarification request to seek written response from the Agency for certain additional clarifications. The clarification question that is BE related is regarding a deficiency on OSIS inspectional findings for the clinical endpoint study. The BE review of this clarification request was completed on 7/25/2017¹⁴ and the Agency's written response was issued on 8/10/2017¹⁵.

On 8/28/2017, the applicant submitted the post-CR response, which is reviewed in the current cycle.

On 10/19/2017, the applicant submitted a face-to-face meeting request "*to help facilitate and accelerate the review*" of the current ANDA. No specific questions were raised by the applicant in this meeting request. The face-to-face meeting was held on 3/1/2018 and the Agency asked multiple clarification questions to the applicant. The clarification

¹⁰ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 2.5\Clinical Overview, p. 3 of 21).

¹¹ GDRP: ANDA-208891-ORIG-1, Upload Final Decision, A208891N000CR, 3/28/2017.

¹² GDRP: ANDA-208891-GI-1-MEETING-17, Respond to Bioequivalence questions, A208891N000DB_MR04032017, 7/6/2017.

¹³ GDRP: ANDA-208891-GI-1-MEETING-17, Documents, A208891N000DPM-MeetingMinutes01.pdf, 8/7/2017.

¹⁴ GDRP: ANDA-208891-GI-1-MEETING-18, Respond to Bioequivalence questions, A208891N000DB_MR04042017, 7/25/2017.

¹⁵ GDRP: ANDA-208891-GI-1-MEETING-18, Documents, A208891N000DPM-Response01.doc, 8/10/2017.

question asked by DBI to the Agency was related to whether the applicant used blinding approach for their in vitro BE studies, which is also one of the deficiencies issued in the 2/23/2018 Discipline Review Letter (DRL) as mentioned below. The meeting minutes was finalized by the Agency on 8/7/2017¹⁶.

3.2 Background about Review-Related Information in the Current Review Cycle

In the original review cycle, DBI took the lead in reviewing the clinical endpoint study and threshold analysis/human factor study/device orientation, with input from DCR, Office of Research and Standards (ORS), Office of Translational Science (OTS), OSIS, DMEPA, and Office of Generic Drug Policy (OGDP). Starting from the current review cycle, DCR is and will be taking the lead in reviewing the aforementioned studies.

Therefore, the applicant's response to deficiencies issued by DBI in the 3/28/2017 CR letter regarding the aforementioned studies (deficiency #s 46-50, as well as the clinical endpoint study-related information in deficiency #2) are reviewed by DCR in this review cycle.

On 2/23/2018, DBI issued a DRL to the applicant. The applicant's response was received on 3/22/2018.

On 4/19/2018, DBI met with Division of Bioequivalence III (DBIII), Office of Regulatory Science (ORS), and OSIS to discuss device resistance issue (DBIII and ORS only) and the in vitro BE study blinding issue (DBIII, ORS and OSIS).¹⁷

On 5/18/2018, DBI sent consult request to ORS/Division of Therapeutic Performance (DTP) for the evaluation of whether 2 APSD studies with modified chi-square test failing at 25% difference but passing at 30% difference would be considered acceptable. On 5/29/2018, ORS provided their consult response to DBI.¹⁸

Currently there is 1 citizen petition related to the FP/SX DPI. On 12/16/2009, Ropes & Gray LLP, on behalf of GlaxoSmithKline, submitted a citizen petition to FDA (Docket No. FDA-2009-P-0597) regarding applications that reference generic copies of oral inhalation products containing fluticasone propionate and/or salmeterol xinafoate. The issues raised by this petition are currently under review by the Agency, and FDA has not made a final decision on these issues. The reviewer's comments and deficiency comments in this review reflect FDA's current thinking only.

¹⁶ GDRP: ANDA-208891-GI-1-MEETING-17, Documents, A208891N000DPM-MeetingMinutes01.pdf, 8/7/2017.

¹⁷ \\fda.gov\wodc\CDER\OGD\All\OGDS11\DIVISION\BIO\BIO1\DBI meeting minutes\DBI non-Bio Management Meeting\2018\ A208891N000DB-MeetingMinutes01-04192018.doc.

¹⁸ GDRP: ANDA-208891-ORIG-1-AMEND-22, Respond to Consult Request, 23136539_Consult response_ORIS.doc, 5/25/2018.

4 SUBMISSION SUMMARY

GENERAL

General Deficiencies

4.1 Deficiency Comment #1

The following observations were noted in your 12/29/2015 submission:

- a) According to the certificates of analysis (COAs), the 3 exhibit batches for each of the 100/50 mcg and 500/50 mcg strengths had device configuration (clinical device: [REDACTED] (b) (4) different from the proposed commercial device [REDACTED] (b) (4). These exhibit batches were used in pharmacokinetic (PK) studies, in vitro studies for the 100/50 mcg and 500/50 mcg strengths, and the clinical endpoint study.
- b) In your batch formula document (12/29/2015 submission, Module 3.2.P.3.2\Batch Formula, p. 1 of 2), you stated that “[t]here are no difference between the batch formula of the registration and commercial batches [REDACTED] (b) (4)
[REDACTED] (b) (4)
- c) In your pharmaceutical development report (12/29/2015 submission, Module 3.2.P.2\Pharmaceutical Development, p. 541, 544, 667 and 671 of 676), you stated that the exhibit batch [REDACTED] (b) (4)
[REDACTED] (b) (4) would be provided (12/29/2015 submission, Module 3.2.P.2\Pharmaceutical Development, p. 430, 667, 671 and 675 of 676).
- d) In your 12/29/2016 submission, Module 2.3.P\Drug Product Part 1 – FPSX – Mylan Dublin, p. 97 of 107, you stated that exhibit batches were manufactured [REDACTED] (b) (4)

Please provide [REDACTED] (b) (4) as mentioned in c) above for each strength of the drug product.

In Controlled Correspondence 844398, based on your statement of [REDACTED] (b) (4) difference between batches used in the pivotal clinical studies and commercial batches, the Agency recommended you to demonstrate in vitro bioequivalence (BE) according to the *Draft Guidance on Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder at 60 L/min.* [REDACTED] (b) (4)
[REDACTED]
[REDACTED]

(b) (4) please conduct in vitro BE studies [single actuation content (SAC) and aerodynamic particle size distribution (APSD) studies] comparing reference listed drug (RLD) product and the test product with final commercial formulation (b) (4) device (b) (4) and manufacturing process (b) (4) (b) (4) and manufactured (b) (4) as bridging studies. These studies should be conducted for each strength of the product, and should be conducted according to *Draft Guidance on Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder* (recommended September 2013, will be referred to as product-specific guidance in the rest of this deficiency letter) at **30, 60, and 90 L/min**, and use at least 3 batches each of T and unexpired R products with no fewer than 10 units from each batch.

In the above APSD studies, please include a standard curve and quality control (QC) samples with three validated concentrations in the range of expected study concentrations with each analytical batch, as outlined in the *Guidance for Industry - Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal sprays for Local Actions* (posted April 2003).

Applicant's Response to Deficiency Comment #1:



Mylan refers the Agency to their Preliminary written feedback (OGD Response Preliminary Meeting Comments to Mylan's request for Face-to-Face meeting dated 7 July 2017), where the Agency concurred that this information may be sufficient, pending review of the data,

‘Based on the additional information you provided as well as the Agency’s additional evaluation, the Agency considers your in vitro bridging studies at 60 L/min flow rate may suffice at this moment (please note that this bridging data has not yet been reviewed, so the acceptability of this data is to be determined), but the Agency reserves the right to ask for data at 30 L/min and 90 L/min flow rates if in the future it is determined that the device difference impacts product performance.’

Based on the above comments from the Agency, Mylan considers that the data package to demonstrate in vitro bioequivalence (using single point calibration supported by linearity demonstrated during validation, together with checks on consistency of UV response and LOQ during the study analytical runs) between MGR001 manufactured (b) (4) and RLD, which was provided in Mylan’s Fulfilment of Commitments Submission. Sequence 0015 dated 02 March 2017, Section 3.2.P.2, is complete.

Reviewer’s Comment:

The applicant stated that (b) (4). The reviewer verified this statement from the applicant’s Description of Manufacturing Process and Process Controls¹⁹.

As detailed in the written response to the applicant’s 4/3/2017 meeting request, the Agency considers the applicant’s in vitro bridging studies at 60 L/min flow rate (submitted in the 3/2/2017 unsolicited amendment that was not reviewed in the original review cycle due to the submission date too close to GDUFA date) may suffice at this moment (please note that this bridging data had not being reviewed at the time of the aforementioned written response), but the Agency reserves the right to ask for data at 30 L/min and 90 L/min flow rates if in the future it is determined that the device difference impacts product performance. According to the drug product review²⁰, the revision from clinical device to commercial device is not expected to affect the product performance. Therefore, the in vitro bridging studies at 60 L/min flow rate are considered sufficient.

The applicant’s response is **acceptable**.

The reviewer’s evaluation of the in vitro bridging studies is in Section 5.2.4.

4.2 Deficiency Comment #2

Please provide COAs for the following RLD batches used in the clinical endpoint study or in vitro BE studies: 4ZP4083 (clinical endpoint study), 5ZP8178, 5ZP8397, 5ZP0114, 4ZP7022, and 5ZP8689 (in vitro studies).

Applicant’s Response to Deficiency Comment #2:

¹⁹ GS Review: ANDA 208891, Resubmission/After Action- Complete; Bioequivalence/Other, 8/28/2017 (Module 3.2.P.3.3)Description of Manufacturing Process and Process Controls, p. 13-18 of 19).

²⁰ GDRP: ANDA-208891-ORIG-1-AMEND-22, Drug Product Primary Review, A208891_DS DP LBL_02b.docx, 5/23/2018.

Testing by Mylan was completed on the RLD lots used in the in vitro studies referred to in ANDA 208891, sequence 0000, Section 3.2.P.2. As requested, Certificates of Analysis for RLD batches are provided, as described in Table 2-1.

RLD lot 4ZP4083, which was used in the clinical endpoint study, (b) (4)

The [packing list](#) documenting this shipment is included with this response. This lot is now expired and testing cannot be completed, hence a Certificate of Analysis (CoA) for lot 4ZP4083 is not available. The RLD sourced and supplied for use in this study was procured from the GlaxoSmithKline commercial supply chain via a

(b) (4)

(b) (4). The RLD is a commercial product tested and released to the specification registered in the NDA and is therefore deemed suitable for use in these studies without additional testing. Samples of the RLD are held by all participating clinical sites in compliance with FDA Bioequivalence Regulations (21CFR320.38/21CFR320.63).

In addition, Mylan have provided CoAs for RLD batches used in the in vitro equivalence studies between MGR001 (b) (4) and the RLD referred to Mylan's Fulfilment of Commitments Submission. Sequence 0015 dated 02 March 2017, Section 3.2.P.2. RLD batch numbers are described in [Table 2-2](#).

The RLD used in the repeat PK BE study, MGR001-1016 (refer to Bioequivalence Question 37) is batch 6ZP6787 which is also listed in [Table 2-2](#).

The CoA for MGR001 [lot 60000354](#), which was used in the MGR001-1016 PK BE study, is also provided.

Table 2-1: Certificates of Analysis Provided for RLD Batches Used in Initial In Vitro Studies (ANDA 208891, Sequence 0000)

Study	Study Number	Strength (mcg)	Batch Number
In Vitro Studies	057755-02-04, 057755-02-06	100/50	5ZP8178 5ZP8397
	MGR-PRO-2015-080, MGR-PRO-2015-103	250/50	5ZP0114
	057755-02-07, 057755-02-08	500/50	4ZP7022 5ZP8689

Table 2-2: Certificates of Analysis Provided for RLD Batches Used in the In Vitro Equivalence Studies Utilizing MGR001 (b) (4) (ANDA 208891, Sequence 0015)

Study	Study Number	Strength (mcg)	Batch Number
In Vitro Studies	MGR-PRO-2016-106	100/50	6ZP4764 6ZP7030 6ZP7784

	MGR-PRO-2016-107	250/50	6ZP5994 6ZP6450 6ZP6787 ¹
	MGR-PRO-2016-108	500/50	6ZP7124 6ZP7898 6ZP7951

¹ RLD batch 6ZP6787 also used in PK BE study MGR001-1016.

Reviewer’s Comment:

The applicant provided the requested COAs, except the reference product lot (lot #4ZP4083) from the clinical endpoint study. Since the review responsibility of the clinical endpoint study is transferred to DCR, the acceptability of the applicant’s response regarding reference product COA for the clinical endpoint study is deferred to DCR.

Based on the reference product COAs, the reviewer updated the batch information in Section 5.2.1.

The applicant’s response is **acceptable**.

IN VITRO STUDIES

Deficiencies Related to Pre-Study Method Validation for In Vitro Studies

Method Validation – Common to Single Actuation Content (SAC) and Aerodynamic Particle Size Distribution (APSD) Studies

4.3 Deficiency Comment #3

It is noted that method validation results for SAC Method # MGR-METH-546070 (Section C of this method) is almost the same as method validation results for Method # MDR-RGMETH-0032 (12/29/2015 submission, Module 3.2.P.5.3\Uniformity of delivered dose Validation Report – MDR-RGMETH-0032). Please clarify if these are the same method validation studies.

Similarly, it is noted that method validation results for APSD Method # MGR-METH-546069 (Section C of this method) is almost the same as method validation results for Method # MDR-RGMETH-0031 (12/29/2015 submission, Module 3.2.P.5.3\Aerodynamic Particle Size Distribution Validation Report – MDR-RGMETH-0031). For the former method validation results, you also included “achievable LOQ of method” that was not reported in the latter method validation report. Please clarify if these are the same method validation studies.

Please provide street address as well as study dates for your method validation studies for each of aforementioned 4 methods. During Office of Study Integrity and Surveillance (OSIS) inspection at (b) (4) it was found out that the analytical methods performed by (b) (4) were developed and validated by Mylan Global Respiratory Group

prior to the transfer to (b) (4), according to (b) (4) method transfer protocol. Since the method validation and in vitro BE studies for the 100/50 and 500/50 mcg strengths were conducted at different sites, please provide method transfer report for method transfer from Mylan Global Respiratory Group to (b) (4) (b) (4). Please be advised that if method validation studies were conducted at different sites from any of the in vitro BE studies, then method transfer studies (e.g. precision and accuracy studies for the HPLC method; and precision study for the SAC and APSD method) are needed to support method transfer between different study sites. Please also be advised that method transfer studies for the SAC and APSD methods should be conducted using unexpired RLD product.

Applicant’s Response to Deficiency Comment #3:

Mylan Global Respiratory analytical procedures used during development of MGR001 (MGR-METH-546069 and MGR-METH-546070) were transferred to the commercial manufacturing site and assigned analytical procedure numbers within the site’s quality systems of MDR-RGMETH-0031 and MDR-RGMETH-0032 respectively. These procedures were also transferred to (b) (4) (b) (4) used for bio-equivalence testing (in-vitro) of the drug product, who assigned the numbers (b) (4) to the analytical procedures. The linkage across the analytical procedures is provided in Table 3-1.

Table 3-1: Analytical Procedure Numbers at the development site (MGR), the proposed commercial QC site (MDR), and facility (b) (4) involved with Bioequivalence Testing (in vitro) of the Drug Product

Analytical Procedure	Facility		(b) (4)
	MGR (Mylan Pharma UK Ltd)	MDR (Mylan Dublin Respiratory / McDermott Laboratories)	
APSD	MGR-METH-546069	MDR-RGMETH-0031	
SAC	MGR-METH-546070	MDR-RGMETH-0032	

Validation results for SAC Method # MGR-METH-546070

The validation results for SAC procedure MGR-METH-546070 (Section C) are from the same validation study conducted for the validation of analytical procedure MDR-RGMETH-0032.

Validation results for APSD Method # MGR-METH-546069

The validation results for APSD procedure MGR-METH-546069 (Section C) are from the same validation study conducted for the validation of analytical procedure MDR-RGMETH-0031. Mylan provided details of “achievable LOQ of method” in MGR-METH-546069 (Section C) version 6.0 which was submitted to the Agency in ANDA 208891, Sequence 0009, Easily Correctable Deficiency Response Bioequivalence: Reference # 10126483, and subsequently provided MGR-METH-546069 version 8.0 in ANDA 208891, Sequence 0015, Section 3.2.P.2.

(b) (4)

(b) (4) The acceptance criteria in the original protocol were met confirming linearity over the range of the method. The validation for MDR-RGMETH-0031 has been supplemented and is provided in Section 3.2.P.5.3 [Aerodynamic Particle Size Distribution Validation Report – MDR-RGMETH-0031](#).

Validation Studies

Analytical procedures MGR-METH-546069 and MGR-METH-546070, used during the development of MGR001, were validated by MGR. The facility address and the dates of when the validation studies were performed are provided in [Table 3-2](#).

Table 3-2: Analytical Procedure Validation Information Associated with Bioequivalence Testing (in vitro) of the Drug Product

Analytical Procedure	MGR-METH-546070	MGR-METH-546069
Validation study dates	17 June 2013 – 11 September 2013	Original validation: 14 June 2013 - 06 November 2013. Revalidation of achievable lower LOQ: 23 January 2014 to 11 February 2014. Effect of drying time of cups coated with silicon oil on recovery of Fluticasone propionate and salmeterol: 09 January to 24 January 2014.
Validation study site address	Mylan Pharma UK Ltd, IPC 008, Discovery Park House, Floor 3, Ramsgate Road, Sandwich, Kent, CT13 9ND. United Kingdom.	

Analytical Procedure Transfers Studies

In vitro SAC and APSD studies (Bioequivalence Testing (in vitro) of Drug Product) were performed by both (b) (4) and MGR. Mylan Global Respiratory analytical procedures used during development of MGR001 (MGR-METH-546069 and MGR-METH-546070) were transferred to (b) (4). These procedures were assigned the numbers (b) (4) (b) (4). Facility details (as submitted in ANDA 208891 Sequence 0000, Section 3.2.P.3.1) are provided in [Table 3-3](#) together with the method transfer reports from MGR to (b) (4). The analytical procedure transfer exercise was conducted by joint testing using MGR001 batches.

In addition, in order to confirm that (b) (4) was qualified to test RLD additional training was given by MGR, Sandwich in the use of the device holders for both products as described in [MGR-MEMO-2014-377](#). The acceptable use of the device holders at (b) (4) was completed using batches of Advair which were within expiry date. This was documented in [MGR-MEMO-2014-396](#).

Table 3-3: Analytical Procedure Transfer Information for Bioequivalence Testing (in vitro) of the Drug Product (MGR to (b) (4))

Transfer Site	Analytical Procedure at Transfer Site	Receiving Site	Analytical Procedure at Receiving Site	Method Transfer Report
MGR (Sandwich), Mylan Pharma UK Ltd, IPC 008,	MGR-METH-546069	(b) (4)	(b) (4)	MGR-REP-2013-025 MGR-REP-2013-038

Discovery Park House, Floor 3, Ramsgate Road, Sandwich, Kent, CT13 9ND, (b) (4)	MGR-METH-546070	(b) (4)	(b) (4)	MGR-REP-2013-027 MGR-REP-2014-038 MGR-REP-2014-039 MGR-REP-2014-042

(b) (4) then transferred analytical procedures (b) (4) to (b) (4). Facility details (as submitted in ANDA 208891 Sequence 0000, Section 3.2.P.3.1) are provided in Table 3-4. The analytical procedure transfer exercise was conducted using MGR001 batches, and used an equivalence testing approach which using confidence intervals, compared mean FPM or emitted dose data generated across the two sites.

In addition, in order to confirm that (b) (4) was qualified to test RLD, additional training was given by MGR in the use of the device holders for both products. The acceptable use of the device holders at (b) (4) was confirmed by testing of batches of Advair which were within expiry date. This was documented in MGR-MEMO-2015-260.

Table 3-4: Analytical Procedure Transfer Information for Bioequivalence Testing (in vitro) of the Drug Product (b) (4)

Transfer Site	Analytical Procedure at	Receiving Site	Analytical Procedure at	Method Transfer Report
(b) (4)				

In protocol MGR-PRO-2016-108 test methods for use of device holders were included in the method table. The protocol and test methods were provided in ANDA 208891, Sequence 0015, Section 3.2.P.2. These methods were issued by Mylan in August 2016 to replace instructions for external contract laboratories that had previously been documented in Mylan SOPs. As training and verification of acceptable use of the device holders had already been confirmed at (b) (4) in 2015 no further method transfer was required.

Reviewer's Comment:

The applicant stated that the validation result for SAC procedure MGR-METH-546070 (Section C) and for APSD procedure MGR-METH-546069 (Section C) are from the same validation study conducted for the validation of analytical procedures MDR-RGMETH-0032 and MDR-RGMETH-0031. The applicant also provided supplement method validation to extend the linearity range from 0.1-10.0 mcg/mL for FP and 0.05-0.8 mcg/mL for SA to 0.01-20 mcg/mL for FP and 0.01-1.6 mcg/mL for SA (please see Section 4.6).

For the UPLC method, the applicant evaluated precision and accuracy of the UPLC method using UPLC systems in (b) (4). Although the applicant did not provide acceptance criteria, the %CV is $\leq 0.4\%$, and the %accuracy is between 99.7-100.2% for FP and SA, which is reasonable.

For APSD and SAC methods, the applicant provided method transfer reports for method transfer from MGR to (b) (4), Athlone, and then method transfer reports for method transfer from (b) (4). These method transfer studies are evaluated below.

Method transfer from MGR to (b) (4)

The method transfer used test batches (b) (4) with unknown identity. Based on their naming convention, these 2 batches are likely development batches. According to internal communication with Drug Product reviewer, the use of development batches for method transfer is considered acceptable.

For the APSD method transfer, 6 devices for each strength were tested at each site by 3 analysts across 4 days on 2 workstations. The applicant considered that successful method transfer was demonstrated as 90% CI for the ratio of mean FPM generated across the 2 sites for both strengths are within the 0.80-1.11 acceptance criteria.

For the SAC method transfer, 6 devices for each strength were tested at each site by 3 analysts across 2 days. Results of the method transfer study for the 500/50 mcg strength met the acceptance criteria, as 90% CI for the ratio of mean SAC generated across the 2 sites are within the 0.95-1.05 acceptance criteria. However, for the 100/50 mcg strength, the method transfer failed for FP in the original testing (90% CI: 1.01-1.06). The applicant initially suspected that standard solution preparation was a potential cause for the failure. However, following re-training of (b) (4) analyst, the repeat method transfer study failed again for both FP (90% CI: 1.05-1.10) and SA (90% CI: 1.03-1.07) for the 100/50 mcg strength.

²¹ According to the method transfer report, the applicant considers that the 100/50 mcg and 500/50 mcg strengths is representative of all 3 product strengths and therefore this bracketing approach is suitable for the method transfer.

Based on investigation, the applicant concluded that the difference between the data generated at the 2 sites was due to the difference in force used to present the device to the apparatus (it was observed that (b) (4) analysts were presenting the device to the mouthpiece adaptor with greater force than Mylan analysts). Since the force to hold the device to the mouthpiece is difficult to define and quantify, the applicant considers that there was no value in repeating the method transfer study. The applicant stated that the %CV for all testing at (b) (4) demonstrated that the analysts were well trained and produce %CV consistent with those generated by Mylan analysts. Therefore, the applicant concluded that the difference between the sites reflects the variability in the test method, and considered (b) (4) qualified to perform SAC studies.

Since 1) the method transfer for the 500/50 mcg meets the acceptance criteria, 2) the %CV of SAC of the 100/50 mcg strength are consistent with those generated by Mylan analysts, and 3) the test and reference product in the pivotal in vitro studies were tested at the same site, the reviewer will not pursue this issue further.

The applicant also provided memos confirming that multiple analysts in (b) (4) were trained and were able to demonstrate acceptable use the device holders for both test and reference product.

Method transfer from (b) (4)

The method transfer used test batches (b) (4) with unknown identity. Based on their naming convention, these 2 batches are likely development batches. According to internal communication with Drug Product assessor, the use of development batches for method transfer is considered acceptable.

For the APSD method transfer, 6 devices for each strength were tested at each site by 3 analysts across 4 days on 2 workstations. The applicant stated in the method transfer report [8/28/2017 submission, Module 3.2.P.2\Method Transfer Report – (b) (4) (b) (4), p. 17 of 52] that “[a]n equivalence testing approach will be used to compare the mean Fine Particle Mass (FPM) generated across the two sites. This involves calculating a 90% confidence interval (CI) for the ratio of geometric means between the two sites. Successful method transfer is demonstrated if 90% CI for the ratio of means falls within 0.90-1.11... Mylan Global Respiratory Group will determine the success of the method transfer”. Based on the 3/22/2018 DRL response, results of the method transfer study for both strengths met the acceptance criteria, as 90% CI for the ratio of mean FPM generated across the 2 sites meets the 0.90-1.11 acceptance criteria.

For the SAC method transfer, 6 devices for each strength were tested at each site by 3 analysts across 2 days. Similar to the APSD method transfer, the applicant stated in the method transfer report [8/28/2017 submission, Module 3.2.P.2\Method Transfer Report – (b) (4), p. 11 of 26] that “[a]n equivalence testing approach will be used to compare the mean emitted dose generated across the two sites. This involves calculating a 90% confidence interval (CI) for the ratio of geometric means between the two sites. Successful method transfer is demonstrated if 90% CI for the ratio

of means falls within 0.95-1.05... Mylan Global Respiratory Group will determine the success of the method transfer". Based on the 3/22/2018 DRL response, results of the method transfer study for both strengths met the acceptance criteria, as 90% CI for the ratio of mean SAC generated across the 2 sites meets the 0.95-1.05 acceptance criteria.

The applicant also stated that training and verification of acceptable use of the device holders had been confirmed at (b) (4).

Address of method validation studies, method transfer studies, and in vitro studies

The reviewer verified that the address of in vitro studies in Section 5.3 is either the same as the address of the method validation study conducted at MGR (in vitro pivotal BE study # MGR-PRO-2015-080; in vitro study at 4 kPa pressure drop # MGR-PRO-REP-2015-103; and in vitro bridging study #s MGR-PRO-2016-106 and MGR-PRO-2016-107), or the same as the address of the method transfer studies conducted at (b) (4) (b) (4) (in vitro pivotal BE study #s 057755-02-04 and 057755-02-07; in vitro study at 4 kPa fixed pressure drop #s MGR-REP-2015-092 and 057755-02-08; and in vitro bridging study # MGR-PRO-2016-108).

The applicant's response is **acceptable**.

4.4 Deficiency Comment #4

Please validate accuracy (% recovery at the high and low concentrations) and precision/intermediate precision of the UPLC method that was used in each of the SAC and APSD method. Accuracy and precision should be evaluated with known amounts of fluticasone propionate (FP) and salmeterol (SA) relevant to expected sample concentrations spiked into placebo solution.

Applicant's Response to Deficiency Comment #4:

(b) (4)



Reviewer's Comment:

The applicant provided the data for accuracy, precision and intermediate precision of the UPLC method used in each of the SAC and APSD method for both FP and SA. The applicant did not provide acceptance criteria, but it is noted that the accuracy are between 85-115%, and % precision is within 15%.

The applicant's response is **acceptable**.

Method Validation – SAC Studies only**4.5 Deficiency Comment #5**

Please provide the flow rate, actuation time and volume of air drawn through the delivery system for the intermediate precision study of SAC.

Applicant's Response to Deficiency Comment #5:

The actuation time and flow rate are provided below in Table 5-1 together with the volume of air drawn through the delivery system for the intermediate precision study of SAC.

Table 5-1: Actuation time and volume of air drawn through the delivery system for the intermediate precision study of APSD.

Analytical Procedure	Actuation Time	Flow Rate	Volume of Air
		(drawn through the delivery system)	
MGR-METH-546070	2.0 seconds	60 ± 3 L/min	2 L

Reviewer's Comment:

The applicant provided the actuation time, flow rate, and volume of air drawn through the delivery system for the intermediate precision study of SAC, and these values are consistent with the ones used in the pivotal study.

The applicant's response is **acceptable**.

4.6 Deficiency Comment #6



The applicant's response is **acceptable**.

4.7 Deficiency Comment #7

Please provide actuation time and volume of air drawn through the delivery system for the intermediate precision study of APSD.

Applicant's Response to Deficiency Comment #7:

The actuation time and flow rate are provided below in Table 7-1 together with the volume of air drawn through the delivery system for the intermediate precision study of APSD.

Table 7-1: Actuation time and volume of air drawn through the delivery system for the intermediate precision study of APSD.

Analytical Procedure	Actuation Time	Flow Rate	Volume of Air
		(drawn through the delivery system)	
MGR-METH-546069	4.0 seconds	60 ± 3 L/min	4 L

Reviewer’s Comment:

The applicant provided the actuation time, flow rate, and volume of air drawn through the delivery system for the intermediate precision study of APSD, and these values are consistent with the ones used in the pivotal study.

The applicant’s response is **acceptable**.

4.8 Deficiency Comment #8

Please provide dose counter number for each of the test and RLD device used in the intermediate precision study of APSD.

Applicant’s Response to Deficiency Comment #8:

The dose counter number for each of the MGR001 test and RLD device used in the intermediate precision study of APSD (MGR-RGMETH-0031) is provided in Table 8-1 to [Table 8-4](#).

Table 8-1: Dose Counter Number Information for the intermediate precision study of APSD (MGR-RGMETH-0031) for the MGR001 100/50 strength

Experiment	Day	Analyst	(b) (4) Workstation	Device Number	Dose Counter Number
1	Day 1	1	2	1	53
2	Day 1	2	2	2	55
3	Day 1	2	1	1	56
4	Day 1	1	1	2	52
5	Day 2	2	2	1	55
6	Day 2	1	2	2	56
7	Day 2	1	1	1	57
8	Day 2	2	1	2	54

Table 8-2: Dose Counter Number Information for the intermediate precision study of APSD (MGR-RGMETH-0031) for the RLD 100/50 strength

Experiment	Day	Analyst	(b) (4) Workstation	Device Number	Dose Counter Number
1	Day 1	1	2	1	55
2	Day 1	2	1	2	51
3	Day 1	2	2	1	52
4	Day 1	1	1	2	54
5	Day 2	2	1	1	53
6	Day 2	1	2	2	56

7	Day 2	1	1	1	57
8	Day 2	2	2	2	52

Table 8-3: Dose Counter Number Information for the intermediate precision study of APSD (MGR-RGMETH-0031) for the MGR001 500/50 strength

Experiment	Day	Analyst	(b) (4) Workstation	Device Number	Dose Counter Number
1	Day 1	1	2	1	57
2	Day 1	2	2	2	60
3	Day 1	2	1	1	60
4	Day 1	1	1	2	58
5	Day 2	2	2	1	59
6	Day 2	1	2	2	57
7	Day 2	1	1	1	56
8	Day 2	2	1	2	59

Table 8-4: Dose Counter Number Information for the intermediate precision study of APSD (MGR-RGMETH-0031) for the RLD 500/50 strength

Experiment	Day	Analyst	(b) (4) Workstation	Device Number	Dose Counter Number
1	Day 1	1	2	1	58
2	Day 1	2	2	2	60
3	Day 1	2	1	1	60
4	Day 1	1	1	2	58
5	Day 2	2	2	1	59
6	Day 2	1	2	2	57
7	Day 2	1	1	1	57
8	Day 2	2	1	2	59

Reviewer’s Comment:

The applicant provided the dose counter number for each of the test and reference device used in the intermediate precision study for APSD. The dose counter number used ranged from 51-60, which corresponds to the beginning lifestage.

The applicant’s response is **acceptable**.

4.9 Deficiency Comment #9

According to the method validation report of method MDR-RGMETH-0031 (12/29/2015 submission, Module 3.2.P.5.3\Aerodynamic Particle Size Distribution Validation Report – MDR-RGMETH-0031, p. 9 of 26), 3 columns were used in the intermediate precision study of APSD. However, in your test plan table on the same page, only 2 columns were listed. Therefore, please clarify this discrepancy.

Applicant’s Response to Deficiency Comment #9:

Mylan presented a test plan for the intermediate precision study of APSD (Aerodynamic Particle Size Distribution Validation Report – MDR-RGMETH-0031) as submitted in ANDA 208891 Sequence 0000, Section 3.2.P.5.3. The protocol required the use of two UPLC system and column combinations. The note in the validation report reflects that three columns were used for the study, which was accepted since it increased the variables assessed in intermediate precision.

The discrepancy noted by the FDA is clarified below with respect to each product (MGR001 or RLD) and the specific product strength (100/50 or 500/50) providing information on the individual UPLC system and column combination used. Mylan confirms a column is denoted by column packing material. This information has been clarified in the updated validation report for MDR-RGMETH-0031 ([Aerodynamic Particle Size Distribution Validation Report – MDR-RGMETH-0031](#)).

MGR001 and RLD 500/50 Strength Test Plan

Mylan confirm that for the 500/50 strength MGR001 and RLD drug products the intermediate precision used a combination of two UPLC systems and column as per the test plan detailed in Table 9-1. Details on the specific UPLC system and column for each product are provided as a footnote to Table 9-1.

Table 9-1: Intermediate Precision Test Plan for MGR001 and RLD 500/50 strength detailing actual UPLC System and Column Information

Experiment	Day	Analyst	(b) (4) Workstation	Device Number	UPLC system and column*
1	Day 1	1	2	1	1
2	Day 1	2	2	2	2
3	Day 1	2	1	1	2
4	Day 1	1	1	2	1
5	Day 2	2	2	1	1
6	Day 2	1	2	2	2
7	Day 2	1	1	1	2
8	Day 2	2	1	2	1

* UPLC System and Column for MGR001 500/50 strength product:

(b) (4)

MGR001 and RLD 100/50 Strength Test Plan

The intermediate precision study for MGR001 and RLD (100/50 strength) each used three UPLC system and column combinations. An updated test plan and details of the specific UPLC System and column is provided for MGR001 and the RLD at the 100/50 strength in Table 9-2 and Table 9-3 respectively.

Table 9-2: Intermediate Precision Test Plan for MGR001 100/50 strength detailing actual UPLC System and Column Information

Experiment	Day	Analyst	(b) (4) Workstation	Device Number	UPLC system and column*
1	Day 1	1	2	1	1
2	Day 1	2	2	2	3
3	Day 1	2	1	1	3
4	Day 1	1	1	2	1
5	Day 2	2	2	1	2
6	Day 2	1	2	2	3
7	Day 2	1	1	1	3
8	Day 2	2	1	2	2

* UPLC System and Column for the MGR001 100/50 strength product:

(b) (4)

Table 9-3: Intermediate Precision Test Plan for RLD 100/50 strength detailing actual UPLC System and Column

Experiment	Day	Analyst	(b) (4) Workstation	Device Number	UPLC system and column *
1	Day 1	1	2	1	1
2	Day 1	2	1	2	2
3	Day 1	2	2	1	2
4	Day 1	1	1	2	1
5	Day 2	2	1	1	1
6	Day 2	1	2	2	3
7	Day 2	1	1	1	3
8	Day 2	2	2	2	1

* UPLC System and Column for the RLD 100/50 strength product:

(b) (4)

Reviewer's Comment:

The applicant's response is **acceptable**.

Deficiencies Related to Information Common to All In Vitro Studies (057755-02-04, MGR-PRO-2015-080, 057755-02-07, MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093)

Both SAC and APSD Studies

4.10 Deficiency Comment #10

According to the study protocols, you used randomization scheme to minimize potential laboratory bias during testing. Please clarify if you used any blinding/unblinding approach during each of the SAC and APSD study. If yes, please provide details on what procedures were taken for blinding/unblinding.

Applicant's Response to Deficiency Comment #10:

Mylan can confirm that we did not use a blinding approach in any of the SAC and APSD studies. In accordance with the test methods for APSD and SAC, it is necessary to use a device holder and mouthpiece adaptor during SAC and APSD testing and therefore blinding during laboratory testing is not possible. However, a randomization scheme was incorporated into the study protocol to minimize potential analyst or laboratory bias during the testing. Details of the randomization scheme can be found within the relevant Section of the IVBE protocols (refer to ANDA sequence 0000, Section 3.2.P.2)

Reviewer's note: Based on the above response, the DBI issued the following clarification question to the applicant in the 2/23/2018 DRL:

The Agency acknowledges your statement that you did not use blinding approach in any of the SAC and APSD studies [8/28/2017 submission, Module 1.2\Cover Letter – 0021 – Addendum 5a – Bioequivalence (General and In-Vivo), p. 22 of 65]. You stated that it is necessary to use a device holder and mouthpiece adaptor during SAC and APSD testing and thus blinding during laboratory testing is not possible. According to the *Guidance for Industry - Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal sprays for Local Actions* (posted April 2003), “it is important that the analyst performing the postactuation evaluations of the collected data be blinded to the identity of the samples.” Please clarify if analysts performing the post actuation evaluations were blinded to the identity of the samples in any of the aforementioned in vitro studies.

The applicant provided the following response in the 3/22/2018 DRL response:

All of the in vitro studies were carried out following the requirements outlined in the FDA Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate (2013). These studies have been the subject of discussions held between Mylan and Agency throughout the development of MGR001 (May 12, 2010 meeting between OGD and Pfizer and with Mylan and OGD on December 12, 2012), and at the Scientific Advice Meeting held on October 22, 2015 where FDA directed Mylan to follow the requirements outlined in the FDA Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate (2013). In designing the protocols, Mylan did not refer to Guidance for Industry - Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal sprays for Local Actions (posted April 2003) as this guidance is not applicable to orally inhaled products.

As acknowledged in your comment, blinding of actuation is not possible because of the visible difference in devices and apparatus used between the Test and Reference products. Mylan did not consider that blinding of the subsequent sample analysis would enhance the validity of the dataset, because the studies were conducted under full GMP laboratory controls.

The analysts performing the post actuation evaluations were not systematically blinded to the identity of the samples during the studies. However, different analysts typically performed the actuation and chromatographic analysis steps. Statistical evaluation of the data to generate the population bioequivalence outcome was in all studies carried out using SAS by a Mylan statistician independent of the analytical teams carrying out the data generation. Because of the complexity of these PBE calculations, the analytical teams could not anticipate the outcome of the studies prior to completion of the analytical work and reporting of sample results.

Further details of the GMP laboratory controls and operational details applicable to each study are discussed below.

Additional analysis of the datasets generated in the studies is also provided below. This demonstrates that the characteristics of test and RLD products are reflected consistently in the data and is therefore supportive of the validity of the studies.

Study execution details and GMP laboratory controls applicable to all IVBE studies

Further details of the GMP laboratory controls and operational details applicable to each study are summarized in Figure 1 and discussed in more detail below.



Sample Preparation

Pre-study controls

Devices of each batch were assigned to a specific flow rate. A randomized test order was created using the random number generator in Excel. This information was included in each of the protocols prior to approval.

Sample receipt and labelling at test site

Following receipt of batches of test and reference products and prior to start of studies the removal and labelling from the original shipping containers was performed in a random manner. Each device was assigned a unique sample number in accordance with the randomized test order in the protocol.

Sample preparation

All test devices were fired in the randomised test order described in the relevant protocol and test samples generated in accordance with the test methods and protocol.

All experimental details were documented in laboratory records in accordance with local procedures effective at the time of testing. Any lost sample collections were recorded in the laboratory record and supervisory approval was sought to cease collection and recovery. The preparation of a replacement sample from the next dose or use of a replacement device was predefined in the protocol and documented in the laboratory record.

Sample analysis and data processing

UPLC analysis

Sample solutions were analysed by UPLC in the same randomised order as they had been prepared. All aberrant chromatography was documented and investigated in accordance with local procedures effective at the time of analysis.

For studies 057755-02-07, MGR-REP-2015-093, MGR-PRO-2015-080, MGR-PRO-REP-2015-103, MGR-PRO-2016-106 and MGR-PRO-2016-107 the chromatography analysts responsible for running the UPLC analysis were an independent team not involved in the firing or sample preparation.

For studies 057755-02-04, MGR-REP-2015-092 and MGR-PRO-2016-108, also carried out at [REDACTED] (b) (4) the majority of result sets were processed by chromatography analysts who were not involved in the sample preparation.

Storage of Data and Audit Trails

All raw data is stored by (b) (4) in a raw data server which is not accessible to users or local system administrator.

All processed data and associated audit records are retained in (b) (4) within the specific projects in which the data was acquired. These projects are stored on a different server which is also not directly accessible to users or local system administrator. It is only accessible via the (b) (4) application.

Data Processing

Chromatography was acquired and processed using a validated chromatography data system (b) (4). All changes occurring within (b) (4) are captured within the (b) (4) audit record.

All samples within each chromatographic run were processed within (b) (4) using the same processing method.

In the APSD studies, a small number (<0.5%) of test sample chromatograms for the cascade impactor stages used in the PBE calculation were manually integrated. This was carried out in order to achieve acceptable integration, either to overcome small fluctuations in the baseline or remove small peaks from the front or tail of the main band peak that could not be adequately integrated using the automated processing method. In addition, a larger number of chromatograms from the MT stage (not used in the PBE calculation) were manually integrated to overcome baseline fluctuations. All manual integrations were reviewed and approved of as part of the verification and approval of data process discussed below in accordance with the procedures MGR-SOP-ACD-GEN-0010 version 4.0 and MGRSW-SOP-ACD-GEN-0015 version 1.0 effective at the time of each study.

All chromatograms have previously been supplied to the Agency for review in Section 3.2.P.2 Pharmaceutical Development, providing evidence of the acceptability of the data processing carried out.

Verification and Approval of Data

For studies MGR-PRO-2015-080, MGR-PRO-REP-2015-103, MGR-PRO-2016-106 and MGR-PRO-2016-107 once the chromatography analyst had completed the processing of the data and electronically signed at level 1 in (b) (4) to confirm completion of the testing, the laboratory record containing all testing and chromatographic details (including all manual integrations) was independently verified by a trained colleague who had not been involved in generating any of the data. In accordance with the procedures effective at the time of testing, the verifier reviewed the audit trails and signed the results sets in (b) (4) at level 2.

On completion of this verification process the chromatography analyst transferred the verified results to LIMS using the validated (b) (4)/LIMS interface.

The independent verifier then reviewed and verified that the results had been transferred correctly and authorised the data in LIMS at the test level. LIMS audit records were also reviewed in accordance with procedures MGR-SOP-ACD-GEN-0003 version 5.0 and MGRSW-SOP-ACD-GEN-0027 version 1.0 effective at the time of verification.

Once the results were verified at test level by the verifier, the samples were authorised in LIMS at sample level by an independent analytical team leader who also performed a scientific review and approval of the laboratory records.

For studies 057755-02-04, 057755-02-07, MGR-REP-2015-092, MGR-REP-2015-093 and MGR-PRO-2016-108 once the chromatography analyst had completed the processing of the data and electronically signed at level 1 in (b) (4) to confirm completion of the testing in accordance with (b) (4) procedure (b) (4) revision 14 and UD 008 revision 15, the laboratory record containing all testing and chromatographic details was independently verified by a trained Quality Control colleague who had not been involved in generating any of the data. In accordance with (b) (4) procedure UD 046 revision 04 and UD 046 revision 05 effective at the time of testing the Quality Control colleague verified the audit trails in (b) (4), signed the results sets at level 2 and also locked the (b) (4) result sets. In addition, prior to reporting of data to Mylan, the documentation and (b) (4) results were subjected to a 10% review by Quality Assurance personnel.

Data transfer from (b) (4) to Mylan (Studies 057755-02-04, 057755-02-07, MGRREP-2015-092, MGR-REP-2015-093 and MGR-PRO-2016-108)

Once data had been received by Mylan, the APSD data was transcribed into LIMS in order to calculate parameters (MMAD, GSD and interpolated FPM) to be reported using a validated system. The validity of the data transcribed into LIMS was verified and authorised against documentation provided by (b) (4). The SAC data and APSD were summarised by Mylan in report format. The tables within the summary reports were verified independently against the documentation obtained from (b) (4).

Result Reporting

Appropriate LIMS reports were used to provide the fully authorised data sets to an independent Mylan statistician. The only exception was for SAC data from studies 057755-02-04, 057755-02-07, MGR-REP-2015-092 and MGR-REP-2015-093. The SAC data for these studies was transferred from (b) (4) using a fully verified Excel spreadsheet. The validity of this data was independently verified by comparison with the documentation provided by (b) (4).

Statistical Evaluation

Data was transposed into SAS format and the independent Mylan statistician performed the population bioequivalence assessment in accordance with the guidance.

Analysis of Data for Consistent Representation of MGR001 and RLD product characteristics

For each study and flow rates, it is possible to distinguish MGR001 and RLD products in the APSD stage data, due to small but consistent differences in the ratio of the two actives deposited on some cascade impactor stages. These differences were consistently observed within each study, demonstrating that the identity of each data point as test or reference is correctly assigned in the reported dataset, with any sample misidentification being clearly visible.

For SAC, the populations of test and reference data are not separated in this way. However, comparison between the SAC dataset and the dataset for total emitted dose captured by impactor and accessories in the corresponding APSD studies shows that the SAC study outcome is consistent with the APSD study in which the test and reference sample identities can be confirmed.

Consistent test-reference ratios throughout each study is also demonstrated below by analysis of the running averages through each study period.

APSD Stage Data

Scatterplots showing the relative deposition of the two actives on each impactor stage are provided in Appendix 1. The cascade impactor stages showing clearest discrimination between the products in each study are shown in Table 3. These plots demonstrate that, with very few exceptions, the individual data points are clearly consistent with correct identification as test or reference.

Reviewer’s Comment:

The applicant stated that the analysts performing the post actuation evaluations were not systemically blinded to the identity of the samples during the studies, and different analysts typically performed the actuation and chromatographic analysis steps. In addition, the applicant stated that statistical evaluation was carried out by a statistician independent of the analytical teams. The applicant also pointed out that due to the complexity of the PBE calculations, the analytical team could not anticipate the outcome of the studies prior to completion of the analytical work and reporting of sample results. The applicant also stated that the studies were conducted under full GMP laboratory controls.

Moreover, the applicant pointed out that for each study and flow rates, it is possible to distinguish test and reference products in the APSD stage data, due to small but consistent differences in the ratio of the 2 actives deposited on some CI stages. The applicant stated that these differences were consistently observed within each study, demonstrating that the identity of each data point as test or reference is correctly assigned in the reported dataset, with any sample misidentification being clearly visible.

For SAC, the applicant stated that the population of test and reference data are not separated in this way, but comparison between the SAC dataset and the dataset for total emitted dose captured by impactor and accessories in the corresponding APSD studies shows that the SAC study outcome is consistent with the APSD. The applicant also showed test-reference ratios throughout each study to demonstrate the running averages through each study period.

The applicant’s justification was discussed with DBIII, ORS, and OSIS on 4/19/2018. In the meeting, OSIS reviewer also mentioned that they did not recall seeing any manual integration based on audit trail, and did not see things that raise their concern that there was any mishandling of data or sample switching. The meeting outcome was that accumulatively, there appeared no evidence indicating any significant concerns about the applicant’s in vitro studies caused by a not-fully-blinded procedure. No additional information is needed from the applicant regarding this matter.¹⁷

The applicant’s response is **acceptable**.

4.11 Deficiency Comment #11

In Method #s MGR-METH-546070 (Version 7.0, p. 7 of 38) for SAC study and MGR-METH-546069 (Version 6.0, p. 6 of 37) for APSD study, you stated that during sample preparation, (b) (4)

(b) (4)

(b) (4) Please also clarify if you did sealing for the RLD device as well.

Applicant's Response to Deficiency Comment #11:

(b) (4)

Mylan confirm that the RLD product used for the SAC and APSD studies were procured from the GlaxoSmithKline commercial supply chain via a registered wholesaler, with no modifications made by Mylan prior to testing.

Reviewer's Comment:

(b) (4)

(b) (4). For reference product, the applicant confirmed that no modifications were made by them prior to testing.

The applicant's response is **acceptable**.

4.12 Deficiency Comment #12

According to Method # MGR-METH-546070 (Version 7.0, p. 8 of 38), for emitted dose test set-up, you stated that when attaching the mouthpiece adaptor to the (b) (4) "ensuring that the raised notch is pointing downwards at the 6 o'clock position. (Diskus/Accuhaler attach the mouthpiece adaptor to the (b) (4) ensuring that the raised notch is pointing horizontally at the 9 o'clock position.)" You also had a similar statement about mouthpiece adapter attachment to the throat in Method # MGR-METH-546069 (Version 6.0, p. 8 of 37) for APSD study. It is unclear what "raised notch" is. Therefore, please provide picture(s) to illustrate how test and RLD devices were set up with the testing apparatus in SAC and APSD studies.

APPEARS THIS WAY ON ORIGINAL



Applicant's Response to Deficiency Comment #12:

Mylan have used the description "raised notch" to refer to the projection on the mouthpiece adaptor. This projection fits within the hinge of the mouthpiece adaptor holder to assist with the correct orientation of the device when attached using a device holder clip.

In order to provide further clarity, Mylan have provided pictures to illustrate the position of the raised notch on the mouthpiece adaptor when the mouthpiece adaptor is attached to a throat, and also to a (b) (4) tube. Refer to [Table 12-1](#).

For the Diskus® device, Mylan have provided pictures to illustrate the position of the raised notch on the mouthpiece adaptor when the mouthpiece adaptor is attached to a throat, and also to a (b) (4) tube. Refer to [Table 12-2](#).

Reviewer’s Comment:

Although the pictures provided above did not include test and reference devices, based on the pictures of the mouthpiece adaptor provided, as well as the pictures in MGR-METH-753121 (v. 1.0, effective 8/12/2016) “Method for the Use of the Diskus® and Accuhaler™ Device Holder”, and MGR-METH-753122 (v. 1.0, effective 8/15/2016) “Method for the Use of the CRC749 Device Holder”, the test device were set up vertically when raised notch of mouthpiece adaptor is at 6 o’clock position. In addition, the reference device were set up horizontally when raised notch of mouthpiece adaptor is at 9 o’clock position (please see pictures below). Therefore, the test and reference devices were set up in the correct orientation.



²² GS Review: ANDA 208891, Quality/Quality Information; 3/2/2017 (Module 3.2.P.2\MGR-METH-753121 Version 1.0... Device Holder, and \MGR-METH-753122 Version 1.0... Device Holder – (b) (4) Version R1729.00, p. 3 of 6).

²³ GS Review: ANDA 208891, Quality/Quality Information; 3/2/2017 (Module 3.2.P.2\MGR-METH-753121 Version 1.0... Device Holder, and \MGR-METH-753122 Version 1.0... Device Holder – (b) (4) Version R1729.00, p. 4 of 6).

The applicant's response is **acceptable**.

4.13 Deficiency Comment #13

According to the study methods, the approximate retention time for SA in your HPLC analysis is 2.00 min [Method # MGR-METH-546070 (Version 7.0, p. 13 of 38)] for SAC study and 1.8 to 2.2 min [Method # MGR-METH-546069 (Version 6.0, p. 16 of 37)] for APSD study. In addition, you also stated in the aforementioned methods that % organic is the main factor affecting SA peak retention time and therefore particular care should be given when diluting the buffer solution component with methanol during preparation of the mobile phase.

²⁴ GS Review: ANDA 208891, Quality/Quality Information; 3/2/2017 (Module 3.2.P.2\MGR-METH-753121 Version 1.0... Device Holder, and \MGR-METH-753121 Version 1.0... Device Holder – (b) (4) Version R1728.00, p. 3 of 8).

²⁵ GS Review: ANDA 208891, Quality/Quality Information; 3/2/2017 (Module 3.2.P.2\MGR-METH-753121 Version 1.0... Device Holder, and \MGR-METH-753121 Version 1.0... Device Holder – (b) (4) Version R1728.00, p. 6 of 8).

In contrast, some other studies had SA retention time around the expected retention time (e.g. study MGR-PRO-REP-2015-103). Therefore, please also explain for this inconsistency of SA retention time among different studies. In addition, please specify your approaches taken during sample processing regarding % organic affecting SA peak retention time. Moreover, please explain for wide range of SA retention time as well as deviation from expected SA retention time observed in aforementioned 3 studies, and justify its impact on reliability of sample analysis.

Applicant's Response to Deficiency Comment #13:

Mylan acknowledge the variation in salmeterol retention time amongst the different studies but it does not impact the validity of the data. The retention time differences are not associated with variations in % organic, but are attributed to the use of two different types of UPLC equipment (b) (4) during the studies. The (b) (4)

Reviewer's Comment:

The applicant attributed the retention time difference to the use of 2 different types of UPLC equipment (b) (4) during the studies. The applicant also stated that the (b) (4) equipment gave a shorter SA retention time than the (b) (4), due to different system dead volume.

Based on the Analysis Report for the Determination of UPLC Instrument Equivalency for the Analysis of MGR001²⁶ (provided in applicant's response to Deficiency # 14 below), which was conducted during the method transfer to (b) (4), the SA retention time is shorter in (b) (4) equipment than the (b) (4) (please see screenshot below). This is consistent with the applicant's aforementioned statement.



The applicant's response is **acceptable**.

4.14 Deficiency Comment #14

According to your cover letter (p. 1-2 of 17) in 9/22/2016 submission, (b) (4) methods ((b) (4) for APSD determination and (b) (4) for SAC) differ from analytical procedures MDR-RGMETH-0032 and MDR-RGMETH-0031 only in the system

²⁶ GS Review: ANDA 208891, Resubmission/After Action- Complete; Bioequivalence/Other, 8/28/2017 (Module 3.2.P.2\Analysis Report for the Determination of UPLC...).

suitability requirement for the SA retention time. However, methods MDR-RGMETH-0032 (p. 5 of 8), MDR-RGMETH-0031 (p. 4 of 8), Mylan's (p. 13 of 41) and (b) (4) (p. 11 of 40) method MGR-METH-546070, Mylan's (p. 14 of 40) and (b) (4) (p. 14 of 40) method MGR-METH-546070 all had system suitability requirement for SA retention time (b) (4). Therefore, please specify the difference you stated in the aforementioned cover letter.

Applicant's Response to Deficiency Comment #14:

The difference between system suitability requirements reflects the use of differing UPLC systems giving different salmeterol retention times, as described in the response to Bioequivalence Question 13. The differing system suitability requirements at (b) (4) (b) (4) were managed through Title Pages associated with the (b) (4) methods. These are provided with this response.

Test methods MGR-METH-546069 and MGR-METH-546070 were developed and validated at (b) (4) using a (b) (4) UPLC and system suitability criteria (including salmeterol retention time (b) (4)) were set based upon the data generated during validation.

During transfer of the methods to (b) (4), an assessment was made of equivalency of different types of UPLC systems (see [Analysis Report for the Determination of UPLC Instrument Equivalency for the Analysis of MGR001](#)). It was concluded that the (b) (4) could be regarded as equivalent to (b) (4) UPLC, providing that adjustment was made to the method in respect of UV wavelength switch time and system suitability criteria for salmeterol retention time, to allow for the shorter salmeterol retention time observed on the (b) (4).

These deviations from the Mylan test methods were managed through a (b) (4) non-conformance report (see [Non-conformance Report 12424](#)) which was approved by Mylan, and was implemented through Title Page (b) (4) and Title Page (b) (4) associated with the corresponding (b) (4) methods.

Reviewer's Comment:

The applicant stated that the difference between system suitability requirements reflects the use of differing UPLC systems giving different salmeterol retention times, which was verified by the reviewer in Section 4.13. The applicant also provided (b) (4) non-conformance summary report approved by Mylan to have different system suitability criteria for SA retention time, as well as title pages associated with the (b) (4) methods that mention the different system suitability requirement at (b) (4).

The applicant's response is **acceptable**.

4.15 Deficiency Comment #15

According to the study protocols, SAC studies should be conducted on dose counter #s 60, 30 and 1; while APSD studies should be conducted on dose counter #s 59 and 2. Please list out all SAC and APSD samples that were collected on dose counter numbers other than #s 60, 30 and 1 for SAC studies and #s 59 and 2 for APSD studies. For each of these samples, please provide the detailed reason(s) for using different dose counter numbers, its supporting documents (e.g. investigational report), original actuation data, as well as corrective action taken.

Applicant's Response to Deficiency Comment #15:

As requested, please refer to [Table 15-1](#) for a list of SAC study samples that were collected on dose counter numbers (DCNs) other than 60, 30 and 1, and the reason for alternate DCN use.

Refer to [Table 15-2](#) for a list of APSD study samples that were collected on dose counter DCNs other than 59 and 2, and the reason for alternate DCN use.

All alternate DCN use was in accordance with the study protocol, therefore no investigation reports are available and no corrective actions were required. In all cases, the samples were rejected prior to analysis, and therefore, original analytical test data do not exist.

Reviewer’s Comment:

The applicant provided reasons for using different dose counter numbers for multiple samples. However, it is noted that the applicant did not provide reason for using different dose counter numbers for the following sample. In the 3/22/2018 DRL response, the applicant stated that there was a typo in the original data reported to the applicant by (b) (4) (b) (4) for this sample. The alternate dose counter number was not used and the original actuation data provided is correct. The applicant also provided an updated SAS datafile with the typo corrected.

Flow Rate	Product	Batch	Unit	Stage	Dose Counter Number
Study 057755-02-04 APSD					
60	REF	4ZP3863	40	BOL	57

In the current amendment, the applicant also stated that since all alternative dose counter numbers use was in accordance with the study protocol, no investigation reports are available and no corrective actions were required. Additionally, since all these samples were rejected prior to analysis, original analytical test data do not exist. Based on the reasons provided by the applicant, the reviewer considers the applicant’s rejection of the original samples listed in the applicant response acceptable. The data generated from these acceptable alternative dose counter numbers will be used for reviewer’s statistical analysis in Section 5.2.2.

The applicant’s response is **acceptable**.

4.16 Deficiency Comment #16

Please provide (b) (4) SOP (b) (4) that was effective at the time of the in vitro studies in current application.

Applicant’s Response to Deficiency Comment #16:

Please refer to the new document provided in Section 3.2.P.2 (b) (4) [SOP \(b\) \(4\) Laboratory Investigations, version 17](#) ((b) (4)) which was effective at the time of the in vitro studies referenced in the current application.

Reviewer’s Comment:

As mentioned in the original BE review, the applicant rejected multiple samples due to “atypical” results or “aberrant” results. According to the study protocols, atypical results will be handled according to the current version of (b) (4) SOP (b) (4). Therefore, the reviewer asked the applicant to provide this SOP that was effective at the time of the in vitro studies.

The applicant provided the requested SOP (b) (4) Laboratory Investigations, and the reviewer verified that this SOP was effective at the time of the in vitro studies that was submitted in the original submission.

The applicant's response is **acceptable**.



APSD Studies

4.17 Deficiency Comment #17

According to the study method MGR-METH-546068 (version 6.0, p. 15 of 37), fine particle mass (FPM) is calculated (b) (4) (b) (4) when operated at 60 L/min. However, in study report MGR-REP-2015-096 (version 1.0, p. 14 of 178), you stated that FPM is (b) (4). Therefore, please explain why you changed the calculation method for FPM.

Applicant's Response to Deficiency Comment #17:

Please note, the APSD method number is MGR-METH-546069 not MGR-METH-546068 as quoted in the question above.

When the (b) (4) Impactor (b) (4) is operated at different flow-rates (e.g. 30 L/min, 60 L/min and 90 L/min) the effective cut-off diameters of the individual impactor stages change according to the flow-rate (Marple et al 2003). The standard flow-rate used for assessment of aerodynamic particle size distribution (APSD) of the CRC749 inhaler as per method MGR-METH-546069 is 60 L/min.



The Mylan protocol associated with study report MGR-REP-2015-096 specified that stage data and impactor-sized mass (ISM) were to be reported for APSD measurements.

The study reports included mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle mass (FPM) to comply with the FDA draft guidance on Fluticasone Propionate; Salmeterol Xinafoate (2013) – which states that MMAD, GSD and FPM should be submitted as supportive evidence for equivalent APSD. The guidance does not specify the exact meaning of FPM. (b) (4)
(b) (4) for FPM was considered a more robust value in the context of an experiment where the test flow-rates were varied away from 60 L/min.

Reviewer’s Comment:

The applicant’s response is **acceptable**.

4.18 Deficiency Comment #18

Please provide detailed calculations for calculating MMAD and GSD.

Applicant’s Response to Deficiency Comment #18:

MMAD and GSD are derived assuming a log-normal distribution for the aerosol and the use of a log-probit plot.

Depending on the computing environment used, the calculation of probits may be achieved via built in functions. For example, in Excel, NORM.INV for conversion to probits and NORM.DIST for conversion from probits. The LabWare laboratory information management system (LIMS) software used at Mylan does not have equivalent statistical functions built in to its programming language – so a numerical approximation as shown by Krejcie ([Krejcie et al, 1991](#)) is used. The probit values obtained via the numerical approximation are typically < 0.02 % different from those generated by, for example, the statistical functions in Excel.

Due to concerns regarding potential errors at the extremes of the distribution caused by the transformation to a straight line form, the regression of the log-probit data is reduced to the 10-90 % range, to avoid over-emphasizing the tails of the distribution in the least-squares fitting procedure (see Section 4.7 Statistical Accuracy, Chapter 4 – Particle Size Statistics, Aerosol Technology 2nd Edition by W.C. Hinds).

The detailed calculations for MMAD and GSD are shown in the following worked example to describe the methodology and calculation steps. Note that for readability, full numerical precision is not shown in the examples – within LIMS full precision is held for all calculation steps.

Worked Example

Consider a typical set of analytical data derived from the chemical analysis of an (b) (4) operating at 60 L/min. This could take the following tabular form; refer to [Table 18-1](#). The effective cut-off diameter (ECD) values are derived from equations given in Journal of Aerosol Medicine, [Marple et al](#) Vol. 16 Number 3, pp.301-324. For ease of reference, the appropriate calculations for determining the ECD values for each stage of the (b) (4) and the values at 30 L/min, 60 L/min and 90 L/min are given in [Table 18-2](#)

Reviewer's Comment:

The applicant provided detailed calculation for MMAD and GSD.

The applicant's response is **acceptable**.

Deficiencies Related to Information Common to In Vitro Studies 057755-02-04, MGR-PRO-2015-080, and 057755-02-07Both SAC and APSD Studies**4.19 Deficiency Comment #19**

It is noted that there are multiple incidences of "alternative blister use" and "replacement device use" in in vitro BE studies. Please explain why there were multiple incidences of them, and the impact of it on in vitro BE studies.

Applicant's Response to Deficiency Comment #19:

The reasons for use of alternate blisters have been provided in the response to Bioequivalence question 15 and are all due to errors occurring during sample preparation. In compliance with the protocol the replicates were replaced with the next available dose count number. No analysis of any of these original test solutions was undertaken.

The reasons for the use of replacement inhalers were documented in ANDA 208891, sequence 0009, ECD Response (FDA comment 2, 5 and 6) and in the responses to Bioequivalence questions 24, 25, 28 and 30.

In protocols 057755-02-04 and 057755-02-07 there were a total of 720 replicates tested for APSD and 960 replicates in MGR-PRO-2015-080 (due to the repeat APSD testing at 90L/min). Each APSD replicate is made up of 10 different test solutions. For SAC there were a total of 1080 replicates tested for each of the three protocols.

The table below summarises the number of alternative blisters and replacement inhalers used in the three studies.

Table 19- 1: Number of Alternative Blisters and Replacement Inhalers Used in Studies 057755-02-04 and 057755-02-07 and MGR-PRO-2015-080

Study number	Number of replicates reported	Number of alternative blister use ¹	% of alternate blisters used	Number of replaced inhalers	% of replacement inhalers used	Type of test
057755-02-04	720	8	1.1	15	2.1	APSD
057755-02-04	1080	18	1.7	14	1.3	SAC
MGR-PRO-2015-080	960	5	0.5	9	0.9	APSD
MGR-PRO-2015-080	1080	5	0.5	1	0.1	SAC
057755-02-07	720	3	0.4	2	0.3	APSD
057755-02-07	1080	4	0.4	2	0.2	SAC

¹ If an alternate blister was used for APSD due to an error during SAC replicate this has not been included in the number

Across all the studies less than 1% of replacement/alternate blisters were used when assessed against the total number of replicates. If the population bioequivalence assessment is carried out on a dataset where the data from replacement inhalers is eliminated the outcome is the same as when the dataset includes the replacement inhalers.

Hence the data presented is representative and robust and there is no impact on population bioequivalence.

Reviewer’s Comment:

The applicant stated that alternate dose counter numbers used were all due to errors occurred during sample preparation, and no analysis of any of these original test solutions was undertaken. Since the applicant used the next available dose counter numbers, and the dose counter numbers are still in the respective life stages, the reviewer will not pursue this issue further.

For replacement devices, since excluding samples with replacement devices does not affect study outcome (please see Section 5.3.2), the reviewer will not pursue this issue further.

The applicant’s response is **acceptable**.

SAC Studies

4.20 Deficiency Comment #20

You did not provide actual dose counter numbers and % of label claim in the SAS .xpt dataset for your SAC studies. Therefore, please add a column for actual dose counter number and another column for % of labeled claim in the SAS .xpt file for your SAC studies.

Applicant's Response to Deficiency Comment #20:

As requested, columns for actual dose counter number and % of label claim have been added to the SAS.xpt files for the SAC studies which were previously submitted in ANDA 208891, Sequence 0009, Section 3.2.P.2; refer to updates in Section 3.2.P.2 [sac-transport](#) and [define-sac](#).

SAS.xpt files submitted in Mylan's Fulfilment of Commitments Submission. Sequence 0015 dated 02 March 2017, Section 3.2.P.2 for the in vitro studies conducted with MGR001 manufactured (b) (4), have also been updated in order to include columns for actual dose counter number and % of label claim.

Refer to Section 3.2.P.2:

- [sac-100-transport](#)
- [define-sac-100](#)
- [sac-250-transport](#)
- [define-sac-250](#)
- [sac-500-transport](#)
- [define-sac-500](#)

Reviewer's Comment:

The applicant provided the updated SAC SAS .xpt datasets with actual dose counter numbers and % of label claim included.

The applicant's response is **acceptable**.

APSD Studies

4.21 Deficiency Comment #21

You provided mass balance in the study reports, but did not include it in the SAS .xpt file. Therefore, please add a column for mass balance in your SAS xpt file for APSD studies.

Applicant’s Response to Deficiency Comment #21:

As requested, a column for mass balance has been added to the SAS.xpt files for the APSD studies which were previously submitted in ANDA 208891, Sequence 0009; refer to *Section 3.2.P.2: (b) (4)-transport and define-(b) (4)*

As discussed in ANDA 208891, Sequence 0009, ECD Response, FDA comment 2, where replacement devices were tested, the original data is also provided in updated format; refer to *Section 3.2.P.2: (b) (4)-1-transport and define-(b) (4)*

SAS.xpt files submitted in Mylan’s Fulfilment of Commitments Submission. Sequence 0015 dated 02 March 2017, Section 3.2.P.2 for the in vitro studies conducted with MGR001 manufactured (b) (4), have also been updated in order to include a column for mass balance:

- (b) (4)-100-transport
- define (b) (4)-100
- (b) (4)-250-transport
- define (b) (4)-250
- (b) (4)-500-transport
- define (b) (4)-500

Reviewer’s Comment:

The applicant provided the updated APSD SAS .xpt datasets with mass balance included.

The applicant’s response is **acceptable**.

Deficiency Related to Information Common to In Vitro Studies 057755-02-04, 057755-02-07, MGR-REP-2015-092, and MGR-REP-2015-093

4.22 Deficiency Comment #22

You provided 100% raw analytical data for SAC and APSD testing in your 9/22/2016 submission (Module 3.2.P.2). However, the raw data format you provided for the 4 studies above is rather granular, as each page only contains information for one sample. Please compile the raw data of each run. An example for this compiled raw data format would be your raw data for study MGR-PRO-2015-080 (9/22/2016 submission, Module 3.2.P.2\Attachment 4-4 – MGR-PRO-2015-080 – 250/50 mcg – APSD Raw Data – Comment 4 – Sequence 0009). The raw data should include all samples (including blank/diluent, standards, etc.) in a run in run sequence order.

Applicant’s Response to Deficiency Comment #22:

As requested, for in vitro studies 057755-02-04 (100/50 mcg), 057755-02-07 (500/50 mcg), MGR-REP-2015-092 (4 kPa fixed pressure drop, 100/50 mcg), and MGR-REP-2015-093 (4 kPa fixed pressure drop, 500/50 mcg) conducted at (b) (4), 100% raw data

(including blank/diluent and standards) and corresponding chromatograms, in run sequence order are provided. The 100% raw data files and chromatograms submitted in ANDA 208891, Sequence 0009, Section 3.2.P.2 (in response to FDA comment 4 and comment 3, respectively) have been deleted and new documents presented: refer to [Table 22-1](#).

For in vitro study MGR-PRO-REP-2016-108, conducted with MGR001 manufactured (b) (4), raw data and chromatograms submitted in ANDA 208891, Sequence 0015, Section 3.2.P.2, have been updated as per the format requested. Refer to [Table 22-2](#).

New 100% raw data files and chromatograms for in vitro studies conducted at Mylan, are presented in response to [Bioequivalence Question 23](#).

Table 22-1: Study 057755-02-04, 057755-02-07, MGR-REP-2015-092 and MGR-REP-2015-093 - 100% Raw Data and Chromatogram Documents

Study	APSD testing	SAC testing
057755-02-04 (IVE 100/50 mcg)	Section 3.2.P.2 Pharmaceutical Development 100/50 – Study 057755-02-04 at 30 L/min for APSD – raw data	Section 3.2.P.2 Pharmaceutical Development 100/50 – Study 057755-02-04 at 30 L/min for SAC – raw data
	Section 3.2.P.2 Pharmaceutical Development 100/50 – Study 057755-02-04 at 30 L/min for APSD – chromatograms	Section 3.2.P.2 Pharmaceutical Development 100/50 – Study 057755-02-04 at 30 L/min for SAC – chromatograms
	Section 3.2.P.2 Pharmaceutical Development 100/50 – Study 057755-02-04 at 60 L/min for APSD – raw data	Section 3.2.P.2 Pharmaceutical Development 100/50 – Study 057755-02-04 at 60 L/min for SAC – raw data
	Section 3.2.P.2 Pharmaceutical Development 100/50 – Study 057755-02-04 at 60 L/min for APSD – chromatograms	Section 3.2.P.2 Pharmaceutical Development 100/50 – Study 057755-02-04 at 60 L/min for SAC – chromatograms
	Section 3.2.P.2 Pharmaceutical Development 100/50 – Study 057755-02-04 at 90 L/min for APSD – raw data	Section 3.2.P.2 Pharmaceutical Development 100/50 – Study 057755-02-04 at 90 L/min for SAC – raw data
	Section 3.2.P.2 Pharmaceutical Development 100/50 – Study 057755-02-04 at 90 L/min for APSD – chromatograms	Section 3.2.P.2 Pharmaceutical Development 100/50 – Study 057755-02-04 at 90 L/min for SAC – chromatograms
057755-02-07 (IVE 500/50 mcg)	Section 3.2.P.2 Pharmaceutical Development 500/50 – Study 057755-02-07 at 30 L/min for APSD – raw data	Section 3.2.P.2 Pharmaceutical Development 500/50 – Study 057755-02-07 at 30 L/min for SAC – raw data
	Section 3.2.P.2 Pharmaceutical Development 500/50 – Study 057755-02-07 at 30 L/min for APSD – chromatograms	Section 3.2.P.2 Pharmaceutical Development 500/50 – Study 057755-02-07 at 30 L/min for SAC – chromatograms
	Section 3.2.P.2 Pharmaceutical Development 500/50 – Study 057755-02-07 at 60 L/min for APSD – raw data	Section 3.2.P.2 Pharmaceutical Development 500/50 – Study 057755-02-07 at 60 L/min for SAC – raw data
	Section 3.2.P.2 Pharmaceutical Development 500/50 – Study 057755-02-07 at 60 L/min for APSD – chromatograms	Section 3.2.P.2 Pharmaceutical Development 500/50 – Study 057755-02-07 at 60 L/min for SAC – chromatograms
	Section 3.2.P.2 Pharmaceutical Development 500/50 – Study 057755-02-07 at 90 L/min for APSD – raw data	Section 3.2.P.2 Pharmaceutical Development 500/50 – Study 057755-02-07 at 90 L/min for SAC – raw data

	Section 3.2.P.2 Pharmaceutical Development 500/50 – Study 057755-02-07 at 90 L/min for APSD – chromatograms	Section 3.2.P.2 Pharmaceutical Development 500/50 – Study 057755-02-07 at 90 L/min for SAC – chromatograms
MGR- REP- 2015-092 (4 kPA fixed pressure drop – 100/50 mcg)	Section 3.2.P.2 Pharmaceutical Development 100/50 –Study MGR-REP-2015-092 - 4kPa - APSD – raw data	Section 3.2.P.2 Pharmaceutical Development 100/50 –Study MGR-REP-2015-092 - 4kPa - SAC – raw data
	Section 3.2.P.2 Pharmaceutical Development 100/50 –Study MGR-REP-2015-092 - 4kPa - APSD – chromatograms	Section 3.2.P.2 Pharmaceutical Development 100/50 –Study MGR-REP-2015-092 - 4kPa - SAC – chromatograms
MGR-REP- 2015-093 (4 kPA fixed pressure drop – 500/50 mcg)	Section 3.2.P.2 Pharmaceutical Development 500/50 –Study MGR-REP-2015-093 - 4kPa - APSD – raw data	Section 3.2.P.2 Pharmaceutical Development 500/50 –Study MGR-REP-2015-093 - 4kPa - SAC – raw data
	Section 3.2.P.2 Pharmaceutical Development 500/50 –Study MGR-REP-2015-093 - 4kPa - APSD – chromatograms	Section 3.2.P.2 Pharmaceutical Development 500/50 –Study MGR-REP-2015-093 - 4kPa - SAC – chromatograms

Table 22-2: Study MGR-PRO-REP-2016-108 – 100% Raw Data and Chromatogram Documents (b) (4)

Study	APSD testing	SAC testing
MGR-PRO- REP-2016-108 (IVE 500/50 mcg – (b) (4))	Section 3.2.P.2 Pharmaceutical Development MGR-PRO-2016-108 - IVBE – APSD – 500/50 mcg – Chromatograms and Raw Data	Section 3.2.P.2 Pharmaceutical Development MGR-PRO-2016-108 - IVBE – SAC – 500/50 mcg – Chromatograms and Raw Data

Reviewer’s Comment:

The applicant’s response is **acceptable**.

The reviewer’s evaluation of the chromatograms is in Section 5.2.

Deficiency Related to Information Common to In Vitro Studies MGR-PRO-2015-080, and MGR-PRO-REP-2015-103

4.23 Deficiency Comment #23

You provided raw data for the above studies in 9/22/2016 submission, Module 3.2.P.2. However, it is noted that these raw data are incomplete, as there are many instances that the result IDs in the run are not consecutive (e.g. 9/22/2016 submission, Module 3.2.P.2\Attachment 4-4 – MGR-PRO-2015-080 – 250/50 mcg – SAC Raw Data – Comment 4 – Sequence 0009, p. 4 of 740, result IDs 30078, 30088-30077 were missing). In addition, it is noted that raw data for blank/diluent, system suitability S1 or S2, standard check S1 and S2 are not included in raw data for SAC studies. Similarly, blank/diluent, system suitability standard SHL, LOQ, standard check SHL and SLL were not included in raw data for APSD studies. Moreover, raw data for stage 7, stage 8 for many samples (e.g. p. 6 of aforementioned document) were not included in the raw data for APSD studies. Therefore, please submit 100% raw data (including blank/diluent, standards, etc.) in run sequence order.

Applicant’s Response to Deficiency Comment #23:

As requested, for *in vitro* studies MGR-PRO-2015-080 (250/50 mcg) and MGR-PRO-REP-2015-103 (4 kPa fixed pressure drop, 250/50 mcg) conducted at Mylan, 100% raw data (including blank/diluent and standards) and corresponding chromatograms, in run sequence order are provided. The 100% raw data files and chromatograms submitted in ANDA 208891, Sequence 0009, Section 3.2.P.2 (in response to FDA comment 4 and comment 3, respectively) have been deleted and new documents presented: refer to [Table 23-1](#).

For *in vitro* studies MGR-PRO-REP-2016-106 and MGR-PRO-REP-2016-107, conducted with MGR001 manufactured (b) (4), raw data and chromatograms submitted in ANDA 208891, Sequence 0015, Section 3.2.P.2, have been updated as per the format requested. Refer to [Table 23-2](#).

New 100% raw data files and chromatograms for *in vitro* studies conducted at (b) (4), are presented in response to [Bioequivalence Question 22](#).

Table 23-1: Study MGR-PRO-2015-080 and Study MGR-PRO-REP-2015-103 - 100% Raw Data and Chromatogram Documents

Study	APSD testing	SAC testing
MGR-PRO-2015-080 (IVE 250/50 mcg)	250/50 – Study MGR-PRO-2015-080 at 30 L/min for APSD – raw data	250/50 – Study MGR-PRO-2015-080 at 30 L/min for SAC – raw data
	250/50 – Study MGR-PRO-2015-080 at 30 L/min for APSD – chromatograms	250/50 – Study MGR-PRO-2015-080 at 30 L/min for SAC – chromatograms
	250/50 – Study MGR-PRO-2015-080 at 60 L/min for APSD – raw data	250/50 – Study MGR-PRO-2015-080 at 60 L/min for SAC – raw data
	250/50 – Study MGR-PRO-2015-080 at 60 L/min for APSD – chromatograms	250/50 – Study MGR-PRO-2015-080 at 60 L/min for SAC – chromatograms
	250/50 – Study MGR-PRO-2015-080 at 90 L/min for APSD – raw data	250/50 – Study MGR-PRO-2015-080 at 90 L/min for SAC – raw data
	250/50 – Study MGR-PRO-2015-080 at 90 L/min for APSD – chromatograms	250/50 – Study MGR-PRO-2015-080 at 90 L/min for SAC – chromatograms
MGR-PRO-REP-2015-103 (4 kPa fixed pressure drop – 250/50 mcg)	250/50 – Study MGR-PRO-REP-2015-103 - 4kPa - APSD – raw data	250/50 – Study MGR-PRO-REP-2015-103 - 4kPa - SAC – raw data
	250/50 – Study MGR-PRO-REP-2015-103 - 4kPa - APSD – chromatograms	250/50 – Study MGR-PRO-REP-2015-103 - 4kPa - SAC – chromatograms

Table 23-2: Study MGR-PRO-REP-2016-106 and MGR-PRO-REP-2016-107 - 100% Raw Data and Chromatogram Documents (b) (4)

Study	APSD testing	SAC testing
MGR-PRO-REP-2016-106 (IVE 100/50 mcg – (b) (4))	MGR-PRO-2016-106 - IVBE – APSD – 100/50 mcg – Chromatograms	MGR-PRO-2016-106 - IVBE – SAC – 100/50 mcg – Chromatograms
	MGR-PRO-2016-106 - IVBE – APSD – 100/50 mcg – Raw Data	MGR-PRO-2016-106 - IVBE – SAC – 100/50 mcg – Raw Data

MGR-PRO-REP-2016-107 (IVE 250/50 mcg – (b) (4))	MGR-PRO-2016-107 - IVBE – APSD – 250/50 mcg – Chromatograms	MGR-PRO-2016-107 - IVBE – SAC – 250/50 mcg – Chromatograms
	MGR-PRO-2016-107 - IVBE – APSD – 250/50 mcg – Raw Data	MGR-PRO-2016-107 - IVBE – SAC – 250/50 mcg – Raw Data

Reviewer’s Comment:

The applicant’s response is **acceptable**.

The reviewer’s evaluation of the chromatograms is in Section 5.2.

Deficiencies Related to In Vitro Equivalence Study 057755-02-04 Only

SAC Study

4.24 Deficiency Comment #24

You did not provide reason and supporting document for the rejection of the following sample (p. 8 of 178 of your MGR-REP-2015-096 version 1.0). Therefore, please provide this information.

Product	Batch Number	(b) (4) Device ID	Mylan Unit	Flow Rate (L/min)
REF	5ZP8397	40	180	60

Applicant’s Response to Deficiency Comment #24:

The original sample rejection was due to a leak of liquid from the (b) (4) tube during sample recovery. As no analysis was therefore possible no further investigation was required. A replacement device was used to generate valid data, as per protocol. Refer to Table 24-1 for a summary of the sample rejection information.

Table 24-1: Study 057755-02-04, Batch 5ZP8397, (b) (4) Device ID 40, 60 L/min – Rejection Information

Product	Batch Number	Original Inhaler Number (b) (4) Device ID / Mylan Unit Number)	Replacement Inhaler Number (b) (4) Device ID / Mylan Unit Number)	Flow Rate (L/min)	Reason for Replacement
Advair (REF)	5ZP8397	40 / 180	111 / 180R	60	Leak in sample collection tube, analysis halted.

Reviewer’s Comment:

The applicant provided the reason for sample repeat. The reviewer considers the applicant’s reason for original sample rejection (please see details in the table above) acceptable. However, it should be noted that the applicant only repeated the sample at the

end lifestage in the replacement device. Therefore, this sample will be excluded from the reviewer's statistical analysis.

The applicant's response is **acceptable**.

Based on the information provided, the reviewer analyzed the data in Section 5.3.2.1.

APSD Study

4.25 Deficiency Comment #25

According to study report MGR-REP-2015-096, version 1.0, p. 40 of 178, you stated that "No acceptable data generated for both FP and Sal" for the following sample. Please provide the data obtained as well as supporting document for why this data was not acceptable. Please also provide SOP that pre-defines data acceptability.

Product	Batch Number	Unit	Flow Rate (L/min)	Lifestage
REF	5ZP8178	159	60	BOL

Applicant's Response to Deficiency Comment #25:

During statistical analysis (population bioequivalence), by Mylan, of data generated by (b) (4), the data and APSD profile for this sample were identified as aberrant and therefore (b) (4) were instructed to open an investigation. The (b) (4) (b) (4) is provided.



(b) (4)

The statistical assessment of population bioequivalence was carried out both including and excluding this sample and the aberrant results had no impact on the outcome of the assessment.

Refer to [Section 3.2.P.2 \(b\) \(4\) SOP \(b\) \(4\) Laboratory Investigations, version 17](#) which was the [\(b\) \(4\) Standard Operating Procedure for Laboratory Investigations](#) effective at the time of the study.

Reviewer's Comment:

The applicant stated that the data and APSD profile of this sample was identified as aberrant. However, as evaluated in Section 4.16, SOP [\(b\) \(4\) Laboratory Investigations](#) does not have objective criteria for aberrant and atypical. Therefore, the reviewer considers the original sample rejection not acceptable, hence the original value of this sample was used in the reviewer's statistical analysis.

The applicant's response is **acceptable**.

Deficiencies Related to In Vitro Equivalence Study MGR-PRO-2015-080 Only

Both SAC and APSD Studies

4.26 Deficiency Comment #26

It is noted that the study protocol MGR-PRO-2015-080 you provided is version 3.0. Please provide the effective date of the 2 previous versions of the protocol.

Applicant's Response to Deficiency Comment #26:

The effective dates of the study protocol MGR-PRO-2015-080, versions 1.0 to 3.0 and reasons for change, are listed in **Table 26-1**.

Table 26-1: Study Protocol MGR-PRO-2015-080 Version Effective Dates and Reasons for Change

Study Protocol Version Number	Reason for Change	Effective Date
MGR-PRO-2015-080 version 3.0	Title updated and changes to the trade mark labelling of the Advair® Diskus® devices. Inclusion of Appendix 1 detailing the repeat testing at the 90 L/min flow rate (after it was discovered the flow meter had failed post-study calibration).	13 Nov 2015

MGR-PRO-2015-080 version 2.0	Typographical error in section 4.1- Analytical Test methods: The reporting of data instructions in the table were reversed in error.	26 Oct 2015
MGR-PRO-2015-080 version 1.0	Initial Version.	18 Sep 2015

Reviewer’s Comment:

The applicant provided the effective date of the 2 previous versions of the study protocol. The version 1 of the study protocol (9/18/2015) was effective before the study dates of the SAC (9/21/2015 to 10/30/2015) and APSD (9/21/2015 to 11/25/2015) studies. Minor changes were made from version 1.0 to version 2.0 of the study protocol, and version 3.0 of the protocol included the repeat testing at the 90 L/min flow rate. As will be mentioned in Section 4.27, version 3.0 of the protocol was effective before the repeat testing at the 90 L/min was conducted.

The applicant’s response is **acceptable**.

APSD Study

4.27 Deficiency Comment #27

Please provide study dates of the repeated APSD study for the 90 L/min flow rate.

Applicant’s Response to Deficiency Comment #27:

The study dates of the repeated APSD study for the 90 L/min flow rate are confirmed as 16 Nov 2015 to 25 Nov 2015. For clarity, Table 27-1 shows the original, repeated and overall study dates for study MGR-PRO-2015-080.

Table 27-1: Study Dates for MGR-PRO-2015-080 (Original and Repeat Studies)

ANDA Sequence 0013, Module 1.2 Cover Letter	Breakdown of Overall Study Dates	
	Original Study Dates	Repeated APSD 90 L/min Flow Rate Study Dates
Overall Study Dates (Includes Original and Repeated Study)		
21 Sep 2015 to 25 Nov 2015	21 Sep 2015 to 28 Oct 2015	16 Nov 2015 to 25 Nov 2015

Reviewer’s Comment:

The applicant provided the study dates (11/16/2015 to 11/25/2015) of the repeat APSD study at 90 L/min flow rate, which is after the effective date of version 3.0 of the study protocol (version 3.0 of the study protocol included details of the repeat testing at the 90 L/min flow rate).

The applicant’s response is **acceptable**.

4.28 Deficiency Comment #28

For the following 3 samples that were repeated using new devices, you provided the reason for replacement below in study report MGR-PRO-REP-2015-080 version 1.0 (p. 9, 33, 63 of 192).

Number	Product	Batch Number	Unit	Flow Rate (L/min)	Lifestage	Reason for replacement
1	REF	5ZP0114	91R	30	BOL	Error during sampling. Mouth and throat samples were washed into the same volumetric flask.
2	TEST	631-008	37R	30	BOL	
3	REF	5ZP9882	240R	60	BOL	Stage 5 being sampled instead of stage 4.

- a) For sample #s 1 and 2 above, , mouth and throat samples were to be washed into the same flask for each device according to the study method (MDR-RGMETH-0031, Section 6.2.2, step 1). Therefore, please explain why this was considered as an error.
- b) For sample #3 above, please explain how this “stage 5 being sampled instead of stage 4” was found out.

Applicant’s Response to Deficiency Comment #28:

Part A: Sample #s 1 (REF, 5ZP0114) and 2 (TEST, 631-008)

During sample recovery, the mouth piece adaptor and throat are recovered as a single test solution. The error, which resulted in the stated replacements, was that the mouth and throat test solution for sample #1 (REF, 5ZP0114) and sample #2 (TEST, 631-008) were washed into the same volumetric flask. Therefore, the resulting solution contained both the reference and the test solutions together. This invalidated both original samples and these were replaced with Mylan Unit Numbers 91R and 37R.

Part B: Sample #3 (REF, 5ZP9882)

During processing of the chromatography run for Mylan Unit number 240, it was observed that the peak areas obtained for Stage 4 for both fluticasone propionate and salmeterol were equivalent to those obtained for Stage 5, which is uncharacteristic. In addition, the peak areas for Stage 4 from Mylan Unit number 240 are atypical as compared to the range of Stage 4 peak areas from study MGR-PRO-2015-080 and for example, Mylan Unit number 226 (a different inhaler from the same batch of Reference product). Refer to [Table 28-1](#) for a comparison of peak areas for Stage 4 and Stage 5 solutions.

Reviewer's Comment:

For sample #s 1 and 2 above, the applicant stated that the mouth and throat test solution for sample #s 1 and 2 were washed into the same volumetric flask, which invalidated both original samples. The reviewer agrees that these 2 original samples were rejected correctly.

For sample #3 above, the applicant stated that the peak areas for stage 4 for both FP and SA were equivalent to those obtained for Stage 5, which is uncharacteristic. In addition, the applicant stated that the peak areas for Stage 4 from this sample are atypical as compared to the range of Stage 4 peak areas from the current study. As mentioned in Section 4.23, SOP (b) (4) Laboratory Investigations does not have objective criteria for "aberrant" or "atypical". Therefore, the applicant's ejection of the original value is considered not acceptable, and the original value of this sample will be used in the reviewer's statistical analysis.

The applicant's response is **acceptable**.

4.29 Deficiency Comment #29

For the following sample, the study report showed that it was repeated with a new device [study report MGR-PRO-REP-2015-080 version 1.0 (p. 83 and 95 of 192)], and you stated in your 9/22/2016 submission (Module 1.2\Cover Letter..., p. 2 of 17) that original data was generated. However, you did not provide reason for device replacement in your study report or in your 9/22/2016 submission. Therefore, please explain why its original assay was rejected, and provide supporting documents (e.g. investigational report) for this sample rejection.

Product	Batch Number	Unit	Flow Rate (L/min)	Lifestage
REF	5ZP9304	433R	90	EOL

Applicant's Response to Deficiency Comment #29:

In result set ID 51972, result ID 52040, aberrant chromatography (no fluticasone propionate or salmeterol peaks) was obtained for the mouthpiece and throat test sample for device unit 433, batch 5ZP9304. No issues were noted with any other stage sample or with the preseparator test solution. The original mouth piece and throat solution had not been retained and therefore was not available for reinjection. It was not possible to ascertain if this was an issue with sample preparation or a failure of the UPLC system to inject properly. The investigation was documented in the analytical package. Hence a replacement inhaler (device unit 433R) was obtained. The inhaler was waste shot fired in accordance with the protocol and then tested.

(b) (4)



Reviewer's Comment:

The applicant provided the reason for original sample rejection, and provided chromatograms to show that aberrant chromatography (no FP or SA peaks) was obtained for the mouthpiece and throat test sample for this device. The applicant also stated that no issues were noted with any other stage samples or with the preseparator test solution.

The applicant did not retain original mouth piece and throat solution, thus it was not available for reinjection. The applicant stated that it was not possible to ascertain if this was an issue with sample preparation or a failure of the UPLC system to inject properly.

Although SOP did not provide objective criteria for aberrant values, since 1) this sample is from the reference product (batch # 5ZP9304), 2) no issues were noted with any other stage samples or with the preseparator test solution, and 3) no other samples from this reference batch had similar issues, the reviewer considers this sample rejection reasonable.

The applicant's response is **acceptable**.

Deficiency Related to In Vitro Equivalence Study 057755-02-07 Only**4.30 Deficiency Comment #30**

According to the study report MGR-REP-2015-097 (version 1.0, p. 13 of 178), you stated that *"for units 180 and 221 EOL 60 L/min, no acceptable data will be reported for FP and SA"*. Please provide the data obtained as well as supporting document for why this data was not acceptable. As mentioned above, please also provide SOP that pre-defined data acceptance criteria.

Applicant's Response to Deficiency Comment #30:

An atypical Aerodynamic Particle Size Distribution (APSD) profile led to an investigation by (b) (4) (see (b) (4)) which was opened for end of life

(EoL) (b) (4) testing of, Mylan unit number 180, (b) (4) unit number 35, Test Order 99 for lot 5ZP8689. The APSD profile showed that the recovered amounts of Salmeterol and Fluticasone Propionate from (b) (4) (Impactor) stages 6, 7 and 8 were atypically high, whilst lower than expected amounts were seen in stages 2, 3 and 4 when compared with the other inhalers from this batch of product.

The atypical APSD leads to lowest Salmeterol and Fluticasone Propionate ISM (Impactor Sized Mass - sum of stages 2 through stage 8) results seen for this batch of product. The preliminary investigation found that the distribution profile and low ISM indicated that a probable laboratory error occurred. It is most likely related to (b) (4) (b) (4) although the exact analytical error could not be determined.

All other results through life for this device for both Emitted Dose and (b) (4) were typical, indicating the atypical results were not product related.

An atypically high recovery for stage 3 obtained for both Salmeterol and Fluticasone Propionate, led to an investigation by (b) (4) which was opened for end of life (EoL) (b) (4) testing of Mylan unit number 221, (b) (4) unit number 39, Test Order 104 for lot 631-006. Solution verification was performed. The recapped original vials confirmed the original results, however, the retained duplicate vials did not match and had typical recovered amounts when compared to what is historically seen for these sample batches. The result of the preliminary investigation and solution verification concluded that no assignable analytical laboratory error had occurred. Solution verification results indicated that the original HPLC vial or cap used for analysis of Stage 3 for unit number 221 EoL was probably contaminated. All other results through life for this device for both Emitted Dose and (b) (4) were typical, indicating the atypical results were not product related.

Refer to [Bioequivalence question 16](#) and (b) (4) SOP (b) (4) [Laboratory Investigations, version 17](#) which was the (b) (4) Standard Operating Procedure for Laboratory Investigations effective at the time of these studies.

Reviewer's Comment:

- For unit #180 EOL 60 L/min (from reference batch # 5ZP8689), the applicant provided investigation report, and stated that recovered amounts of FP and SA from (b) (4) stages 6, 7 and 8 were atypically high, whilst lower than expected amounts were seen in stages 2, 3 and 4 when compared with the other inhalers from this batch of product. According to (b) (4)²⁷, the ISM obtained from this sample are the lowest observed for this batch of product, but not the lowest seen throughout testing of all devices for this study. The applicant suspected (b) (4) (b) (4), although the exact analytical error could not be determined.

²⁷ GS Review: ANDA 208891, Resubmission/After Action- Complete; Bioequivalence/Other, 8/28/2017 (Module 3.2.P.2) (b) (4), p. 4 of 9).

Additionally, according to (b) (4)²⁸, “[p]er client directive, a replacement device will not be collected” for this sample, “as a sufficient number of data points are generated for the purposes of this IVBE study.”

As mentioned in Section 4.16, SOP (b) (4) does not have objective criteria for aberrant or atypical results. Therefore, the reviewer disagrees with the applicant’s rejection of the original values, and the original values were used in the reviewer’s statistical analysis in Section 5.2.2.6.

- For Unit #221 EOL 60 L/min (from test batch #631-006), the applicant stated that an atypically high recovery for stage 3 obtained for both FP and SA. According to (b) (4)²⁹, based on results of solution verification, the recapped original vials confirmed the original results. However, the retained duplicate vials did not match and had typical recovered amounts when compared to what is historically seen for these sample batches. Therefore, the applicant considered that the original HPLC vial or cap used for analysis of Stage 3 for this unit was probably contaminated.

Additionally, according to (b) (4)³⁰, “there is no reportable result for cup 3 for this sample [Unit #221 EOL 60 L/min]. As a sufficient number of data points were generated for the purposes of this IVBE study, the original results for [Unit #221] EoL (b) (4) will be reported however, a statement will be added to the (b) (4) Results Summary Section of the report that due to this investigation and apparent sample contamination, the results are considered to be atypical.” However, it is noted that in addition to Stage 3 results, results from all other stages/mouthpiece/pre-separator of this unit was also not reported. The (b) (4) only had results for Stage 3. In the 3/22/2018 DRL response, the applicant provided original results of all stages/mouthpiece/pre-separator of this unit. As mentioned above, SOP (b) (4) does not have objective criteria for aberrant or atypical results. Therefore, the reviewer disagrees with the applicant’s rejection of the original values, and the original values were used in the reviewer’s statistical analysis in Section 5.2.2.6.

The applicant’s response is **acceptable**.

²⁸ GS Review: ANDA 208891, Resubmission/After Action- Complete; Bioequivalence/Other, 8/28/2017 (Module 3.2.P.2) (b) (4), p. 5 of 9).

²⁹ GS Review: ANDA 208891, Resubmission/After Action- Complete; Bioequivalence/Other, 8/28/2017 (Module 3.2.P (b) (4), p. 6 of 6).

³⁰ GS Review: ANDA 208891, Resubmission/After Action- Complete; Bioequivalence/Other, 8/28/2017 (Module 3.2.P.2) (b) (4), p. 6 of 6).

Deficiencies Related to Information Common to In Vitro Studies MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093 (4 kPa fixed pressure drop)

Both SAC and APSD Studies

4.31 Deficiency Comment #31

Each of the SAC and APSD studies at 4 kPa fixed pressure drop was conducted on 3 lots of test and 3 lots of RLD product. For each lot, 3 test and 3 RLD devices were tested, with 3 replicates of SAC (beginning, middle, and end lifestages), and 2 replicates of APSD (beginning and end lifestages) collected from each device. You then conducted statistical comparison of geometric mean ratios at 4 kPa vs. 60 L/min. Please repeat the study with 10 test and 10 RLD devices per lot, using 3 lots of test and 3 lots of unexpired RLD product. SAC study should be tested at beginning, middle and end lifestages, while APSD studies should be tested at beginning and end lifestages. Please conduct statistical comparison of test vs. RLD product at 4 kPa pressure drop using population bioequivalence (PBE) analysis. Please refer to *Draft Guidance on Budesonide Inhalation Suspension* for step-wise procedure of the PBE analysis.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf>

Please note that other deficiencies (deficiency #s 10-18, 22, 23, 32, and 33) related to the in vitro studies MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093 (4 kPa fixed pressure drop) are also identified and listed in the current section for IN VITRO STUDIES. Please take them into consideration when you repeat your in vitro studies (4 kPa fixed pressure drop).

Applicant's Response to Deficiency Comment #31:

Please refer to the Mylan's [Request for a Post Complete Response Scientific Meeting Sequence 0016](#) dated 03 April 2017, for a discussion on the applicability of the 4kPa studies submitted in ANDA 208891, Sequence 0000, Section 3.2.P.2.

The Agency has confirmed in their Response [Preliminary Meeting Comments](#) to Mylan's request for a Face-to-Face meeting dated 07 July 2017, that the in vitro studies at 4 kPa fixed pressure drop do not need to be repeated, provided that Bioequivalence questions 10-18, 22, 23 and 32 are addressed relating to studies MGR-REP-2015-092, MGR-PRO-REP-2015-103 and/or MGRREP-2015-093. Mylan confirms that the Bioequivalence questions cited have been addressed in this Complete Response Amendment.

Reviewer's Comment:

As detailed in the written response to the applicant's 4/3/2017 meeting request, the applicant will not be asked to repeat the in vitro studies at 4 kPa fixed pressure drop, provided that the applicant could adequately address deficiency #s 10-18, 22, 23, 32, and 33 in the 3/28/2017 CR letter that are related to the in vitro studies MGR-REP-2015-092,

MGR-PRO-REP-2015-103, and/or MGR-REP-2015-093 (4 kPa fixed pressure drop) in the CR response. The applicant has provided responses to the aforementioned deficiencies. Additional deficiencies are identified while reviewing the applicant's response (e.g. deficiency #10 in Section 4.10), and will be evaluated upon the applicant's submission of additional information. Currently, the applicant will not be asked to repeat the in vitro studies at 4 kPa fixed pressure drop.

The applicant's response is **acceptable**.

4.32 Deficiency Comment #32

You did not provide study results in SAS .xpt format for SAC and APSD studies at 4 kPa fixed pressure drop, and thus please provide such for your repeated studies. These SAS datasets should include % of label claim for the SAC study, mass balance (% of label claim) for the APSD study, and dose counter number for both SAC and APSD studies.

Applicant's Response to Deficiency Comment #32:

As requested, SAS.xpt data files for SAC and APSD studies (MGR-REP-2015-092, MGR-PROREP-2015-103 and MGR-REP-2015-093) at 4 kPa fixed pressure drop are provided.

Refer to Section 3.2.P.2:

- *sac-4kpa-transport*
- *define-sac-4kpa*
- *ngi-4kpa-transport*
- *define-ngi-4kpa*

Reviewer's Comment:

The applicant provided the requested SAS .xpt datasets. For details of the study results, please see Section 5.3.3.

The applicant's response is **acceptable**.

Deficiency Related to In Vitro Studies MGR-PRO-REP-2015-103 Only

APSD Study

4.33 Deficiency Comment #33

Based on chromatograms provided for the APSD study, it is noted that some runs had run time of 6.5 min while others had 3.5 min (9/22/2016 submission, Module 3.2.P.2\Attachment 3-7..., p. 131 of 238). Therefore, please explain why different run times were used.

Applicant’s Response to Deficiency Comment #33:

The analytical team responsible for testing MGR-PRO-2015-080, 90L/min APSD testing, unexpectedly identified that peaks were being eluted close to the fluticasone propionate peak during some of the analytical runs which made it difficult to quantify the fluticasone propionate area. These peaks were ‘carry over’ peaks eluting from a previous injection. In order to ensure high quality data was generated and reduce the chance of needing to replace results it was decided to extend the runtime from 3.5 minutes (as prescribed in MGR-METH-546069) to 6.5 minutes to ensure a clear baseline was obtained prior to moving on to the next injection. This extended run time was continued throughout the testing of this flow rate from period 3 to period 8. The longer run time was also implemented during MGR-PRO-2015-103. This method deviation was documented in the analytical packages.

This method deviation did not have any impact on the accuracy or validity of the analytical test results obtained.

Reviewer’s Comment:

Based on the applicant’s response provided above, the change in run time is not expected to affect the study outcome.

The applicant’s response is **acceptable**.

PK BE STUDIES

Deficiencies Related to Pre-Study Method Validation

4.34 Deficiency Comment #34

It is noted that you performed pre-study method validation on instruments (b) (4). However, additional instruments were used in the pivotal PK study (b) (4) was used in fasting study MGR001-1014; and (b) (4) was used in fasting studies MGR001-1005, MGR001-1006 and MGR001-1014). You did not provide detailed information of these additional instruments used. Therefore, please provide this information, and please be advised that according to *Guidance for Industry – Bioanalytical Method Validation* (draft guidance recommended September 2013), partial validation needs to be conducted for change(s) in instruments and/or software platforms.

Applicant’s Response to Deficiency Comment #34:

Two instrument platforms were utilized during assay validation and study sample analysis. (b) (4) model systems were utilized. Both systems operated under (b) (4). As this was anticipated, the validation, conducted using the (b) (4) model instrument, was supplemented with a partial validation of the (b) (4) model instrument. The partial validation was conducted in accordance with industry guidance through completion of an intra-day accuracy and precision run (see Table 2, Run 12 of Project 15-006 Fluticasone Validation Report and Attachment 6 of the

report). The QC summary data is provided for the reviewer's convenience in [Attachment 34.1](#) to this response.

It is acknowledged that the instrument platforms were not discernible from the provided instrument IDs. The following table (Table 34.1) provides traceability to the instrument model based on each system ID.



(b) (4)

In addition to the instrument platform validations, system qualifications are performed prior to analysis of study subject samples on a periodic basis. This is performed in accordance with Mylan SOP, MPI-SOP-BIO-GEN-0017 (Pre-Study Bioanalytical Method Qualification - [Attachment 34.2](#)). As described in the procedure, qualification of a validated instrument platform is done through the successful completion of either an intra-day accuracy and precision run or a simulated study run.

[Table 34-2](#) summarizes the qualification experiments conducted for each individual LCMS/MS system for each study. Please note that each mass spectrometer in question was qualified with the validated method prior to the analysis of unknown samples in accordance with Mylan's SOP. Run summary data for each of these runs is provided in [Attachment 34.3](#) to this response.

Table 34-2: Instrument Qualifications

Study ID	Instrument ID	(b) (4)	Location of Qualification Run	Run Type
MGR001-1006	(b) (4)	(b) (4)	Project 15-006 Validation Run 5	Accuracy and Precision
			Project 15-006 Validation Run 3	Accuracy and Precision
			Project 15-006 Validation Run 12	Accuracy and Precision
			MGR001-1006 Run 64	Accuracy and Precision
MGR001-1005	(b) (4)	(b) (4)	MGR001-1005 Run 4	Accuracy and Precision
			MGR001-1005 Run 2	Accuracy and Precision
			MGR001-1005 Run 30	Accuracy and Precision
			MGR001-1005 Run 20	Accuracy and Precision
MGR001-1014	(b) (4)	(b) (4)	MGR001-1014 Run 4	Accuracy and Precision
			MGR001-1014 Run 5	Accuracy and Precision
			MGR001-1014 Run 3	Simulated Study Run
			MGR001-1014 Run 6	Accuracy and Precision
			MGR001-1014 Run 2	Accuracy and Precision

Reviewer's Comment:

The applicant stated that the (b) (4) used (b) (4) model system, which is the same model system as used in the validated (b) (4). It is also noted that precision and accuracy of CCs and QCs in the PK studies are good. Therefore, the reviewer will not pursue the missing partial method validation issue further.

For the repeat PK study at 250/50 strength (MGR001-1016), the applicant used (b) (4) (b) (4), which are either validated (b) (4) or used the same instrument platform as those validated (b) (4). The precision and accuracy of CCs and QCs in the MGR001-1016 are good. Therefore, similarly, the reviewer will not pursue the missing partial method validation issue further.

The applicant's response is **acceptable**.

4.35 Deficiency Comment #35

You stated that assay selectivity was evaluated in 6 sources of human plasma (12/29/2015 submission, Module 5.3.1.4. 15-006 – Validation Study Tagging File\ Project 15-006 Validation Report, p. 6 of 16). However, you only provided representative chromatography to show selectivity. Please provide selectivity results for each of the 6 sources of human plasma.

Applicant's Response to Deficiency Comment #35:

Assay selectivity was assessed by evaluating six sources of human plasma, 3 male and 3 female. Any peak(s) in the matrix blanks at the retention time of Fluticasone or Salmeterol was considered non-interfering if its peak area was less than 20% of the peak area of the LLOQ standard in that analytical run. Peak(s) in the matrix blanks at the retention time of the internal standard were considered non-interfering if the peak area(s) were less than 5% of the mean internal standard peak area in the standards for that analytical run. At the reviewer's request, the Table 35.1 and Table 35.2 provide results for the selectivity experiments (i.e. Runs 4 and 26 of Project 15-006 Validation) to supplement the representative chromatography provided in the Project 15-006 Validation Report.

It should be noted, during validation a minor modification was made to the final reconstitution solvent composition following Run 18, whereby the mobile phase buffer (b) (4) was substituted for water to provide higher and more consistent recovery of Salmeterol (See Section 21 of the Validation Report). The aqueous:methanol ratio remained at 75:25. The selectivity experiment was analyzed prior to this modification in Run 4 and under the revised procedure in Run 26.

As can be viewed in the results table for each analyte, there were no detectable peaks for either analyte (i.e. FLUT or SALM) or internal standard (i.e. DFLUT or DSAL) in any of the sources evaluated. These experiments met the acceptance criteria set forth in

validation SOP MGWBIO-SOP-BIO-GEN-0016 (Module 5.3.1.4. Project 15-006 Validation Report, Attachment 3).

Table 35-1: Fluticasone Selectivity Results

Analytical Run ID	Plasma Lot ID	Sample ID	FLUT peak area	LS. (DFLUT) peak area
26	M12190P	RB 01 Male	0	0
	M12220P	RB 02 Male	0	0
	M12221P	RB 03 Male	0	0
	F12225P	RB 04 Female	0	0
	F12226P	RB 05 Female	0	0
	F12276P	RB 06 Female	0	0
4	M12190P	RB 01 Male	0	0
	M12220P	RB 02 Male	0	0
	M12221P	RB 03 Male	0	0
	F12225P	RB 04 Female	0	0
	F12226P	RB 05 Female	0	0
	F12276P	RB 06 Female	0	0

Table 35-2: Salmeterol Selectivity Results

Analytical Run ID	Plasma Lot ID	Sample ID	SALM peak area	LS. (DSAL) peak area
26	M12190P	RB 01 Male	0	0
	M12220P	RB 02 Male	0	0
	M12221P	RB 03 Male	0	0
	F12225P	RB 04 Female	0	0
	F12226P	RB 05 Female	0	0
	F12276P	RB 06 Female	0	0
4	M12190P	RB 01 Male	0	0
	M12220P	RB 02 Male	0	0
	M12221P	RB 03 Male	0	0
	F12225P	RB 04 Female	0	0
	F12226P	RB 05 Female	0	0
	F12276P	RB 06 Female	0	0

Reviewer’s Comment:

The applicant provided the selectivity results. The applicant also stated that during the validation study, a minor modification was made to the final reconstitution solvent composition whereby the mobile phase buffer (b) (4) was substituted for water in order to provide higher and more consistent recovery of SA. The applicant conducted the selectivity both prior to this modification and under the modified procedure. Under both procedures, no detectable peaks were noted in blank plasma samples for FP and SA.

The applicant’s response is **acceptable**.

4.36 Deficiency Comment #36

Since your proposed test product has two analytes (i.e., FP and SA), please provide evidence that one analyte does not interfere with analysis of the other analyte (e.g. LQC and HQC samples of FP fortified with SA show no effect on determination of FP, and vice versa).

Applicant's Response to Deficiency Comment #36:

The bioanalytical method used for the determination of fluticasone propionate (FLUT) and salmeterol (SALM) in human plasma employed high performance liquid chromatography (HPLC) with a triple quadrupole mass spectrometric (MS/MS) detection. The HPLC provides separation of FLUT from SALM using an analytical column. The retention time on the column is 3.2 min for FLUT and 1.2 min for SALM as shown in Figure 36-1. In this simultaneous assay, FLUT and SALM are physically separated by the HPLC column, meaning they are eluted into the mass spectrometric detector at different times. Because of this, they would not interfere with each other owing to the chromatographic separation.

Reviewer's Comment:

The applicant's response is **acceptable**.

Deficiency Related to Fasting Studies MGR001-1005 and MGR001-1014**4.37 Deficiency Comment #37**

For the 2 PK studies you conducted for the 250/50 mcg strength, it is noted that each of the MGR001-1005 and MGR001-1014 studies failed to meet the bioequivalence criteria of 80.00-125.00%. You conducted pooled analysis of these 2 PK studies, and stated that the pooled analysis met the BE criteria. Please be advised that your pooled analysis is not acceptable due to the following reasons:

- a) The pooled analysis consisted of only two studies with opposite findings. It is apparent that by pooling such data together, the differences between the two studies could be balanced out and therefore, yielding a result somewhere toward to the middle and making the pooled study pass bioequivalence.

- b) Study MGR001-1005 failed to show bioequivalence. Study MGR001-1014 also failed to show bioequivalence even though the batch of Advair Diskus® was selected to represent the Advair Diskus® population. Therefore, whether the pooled analysis results can truly represent all the 250/50 mcg strength data is questionable.
- c) The pooled analysis is a post-hoc analysis, not pre-specified in a protocol or a statistical analysis plan. Therefore, the finding from the pooled analysis is viewed as hypothesis generating and is not acceptable from the statistical point of view.
- d) Your statistical model for the pooled analysis included terms for study, subject within study, period within study, treatment, and study by treatment interaction, but did not take sequence-related effects such as sequence within study into consideration. In addition, the batch-to-batch variability was not addressed in the model. Even had the pooled analysis approach/concept been accepted, the suitability of the statistical model is still questionable.

Therefore, the fasting studies MGR001-1005 and MGR001-1014 is unacceptable. Please repeat the PK BE study for the 250/50 mcg strength.

Applicant's Response to Deficiency Comment #37:

Mylan acknowledges the Agency's position, that the pooled analysis presented in the original ANDA for the purposes of demonstrating BE for the 250/50 mcg strength is not acceptable.

Mylan also acknowledge the Agency's feedback provided in the Preliminary Meeting Comments and Meeting Minutes from the [July 13th, 2017 Meeting](#) that demonstration of PK BE within standard acceptance criteria for all primary endpoints in a single repeated PK BE study (utilizing a test batch with commercial device configuration) for the 250/50 mcg strength alone is adequate evidence to support bioequivalence of this strength (ie. without any need for any pooled analyses across studies).

In response to the request to repeat the PK BE study for the 250/50 mcg strength, an additional study (MGR001-1016) has been performed utilizing MGR001 in the commercial inhaler configuration (b) (4), manufactured (b) (4). Thus the MGR001 product tested in this study fully represents the proposed final commercial product. The study was identical in design to all the other PK BE studies conducted for MGR001 and the same clinical center was utilised.

The results of study MGR001-1016 are summarized briefly below and detail is provided in addenda to relevant sections of the ANDA, in particular [2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods Addendum](#) and [2.7.4 Summary of Clinical Pharmacology Addendum](#), with the Clinical Study Report provided

in *Module 5, Section 5.3.1.2* and SAS datasets (.xpt files) and define files for study MGR001-1016 are located in *Module 5, Section 5.3.1.2. CDISC datasets and Legacy*.

Mean plasma concentration-time profiles for FP and salmeterol were comparable following administration of the MGR001 test and Advair® Diskus® RLD products.

Statistical analyses of the log-transformed primary PK parameters C_{max} and AUC_{last} and the secondary PK parameter AUC_{inf} are presented for FP and salmeterol in Table 37-1 and Table 37-2, respectively. The geometric mean ratios between test (MGR001) and RLD (Advair® Diskus®) for C_{max}, AUC_{last} and AUC_{inf} were 100.92 %, 107.44 % and 109.25 %, respectively for FP and 93.34 %, 102.87 % and 101.68 %, respectively for salmeterol. The 90 % confidence intervals of the test/RLD ratios for C_{max}, AUC_{last} and AUC_{inf} were all within the acceptable bioequivalence range of 80.00 % and 125.00 % for both FP and salmeterol.

Table 37-1: Statistical Analysis of the Natural Log-Transformed Plasma Pharmacokinetic Parameters of FP Comparing MGR001 250/50 (3 Inhalations; Total Dose 750/150 mcg FP/Salmeterol; Test Product) to Advair® Diskus® 250/50 (3 Inhalations; Total Dose 750/150 mcg FP/Salmeterol; RLD Product) (n=66 Randomized), Study MGR001-1016

Parameter	MGR001 250/50 (Test Product)		Advair® Diskus® 250/50 (RLD Product)		Geometric Mean Ratio% (T/R)	90% Confidence Interval
	N	Adjusted Geometric Mean	N	Adjusted Geometric Mean		
C _{max} (pg/mL)	61	164.2	61	162.7	100.92	95.01 % - 107.20 %
AUC _{last} (pg•h/mL)	61	1251	61	1164	107.44	102.11 % - 113.06 %
AUC _{inf} (pg•h/mL)	59	1323	56	1211	109.25	103.62 % - 115.18 %

Source: MGR001-1016 Clinical Study Report, Table 11.2.1.1

Table 37-2: Statistical Analysis of the Natural Log-Transformed Systemic Exposure Parameters of Salmeterol Comparing MGR001 250/50 (3 Inhalations; Total Dose 750/150 mcg FP/Salmeterol; Test Product) to Advair® Diskus® 250/50 (3 Inhalations; Total Dose 750/150 mcg FP/Salmeterol; RLD Product), Study MGR001-1016

Parameter	MGR001 250/50 (Test Product)		Advair® Diskus® 250/50 (RLD Product)		Geometric Mean Ratio% (T/R)	90% Confidence Interval
	N	Adjusted Geometric Mean	N	Adjusted Geometric Mean		
C _{max} (pg/mL)	61	296.2	61	317.4	93.34	86.75 % - 100.43 %
AUC _{last} (pg•h/mL)	61	641.2	61	623.3	102.87	98.88 % - 107.02 %
AUC _{inf} (pg•h/mL)	61	672.4	60	661.2	101.68	98.12 % - 105.38 %

Source: MGR001-1016 Clinical Study Report, Table 11.2.1.2

Bioequivalence was therefore established between MGR001 250/50 (proposed commercial product and process) and Advair® Diskus® 250/50.

Thus, consistent with the Agency's request and feedback, the results of study MGR001-1016 have demonstrated BE for the 250/50 mcg strength across all primary (and secondary) PK endpoints based on standard acceptance criteria, providing adequate demonstration of PK BE for this product strength.

Reviewer's Comment:

The applicant repeated the PK study for the 250/50 strength, thus the applicant's response is **acceptable**.

Please see the reviewer's evaluation of these data in details in Section 5.1.1.

Comments for Future Submissions

4.38 Comment #38

Guidance for Industry - Bioanalytical Method Validation (posted September 2013) states that incurred sample reanalysis (ISR) sample selection should include "all study subjects". However, your ISR studies did not include all study subjects. For your future studies, please be advised to refer to the aforementioned Guidance for ISR sample selection.

Applicant's Response to Deficiency Comment #38:

It is acknowledged that the draft guidance posted September 2013 specifies that "In selecting samples for reanalysis, adequate coverage of the PK profile in its entirety should be provided and should include assessments around Cmax and in the elimination phase for all study subjects." In response to the comment and in anticipation of implementation of the draft guidance, as of April 2017 all study subjects are being included during incurred sample reanalysis.

Reviewer's Comment:

This was a comment for future submissions. The applicant's response is **acceptable**.

4.39 Comment #39

You submitted IND 118769 for the fasting study of the 250/50 mcg strength, but not for the 500/50 µg strength. Please be advised to submit a bio-IND prior to study commencement for your future study if the dose given in the PK study exceeds the maximum labeled single dose for the evaluation of safety.

Applicant's Response to Deficiency Comment #39:

Mylan would like to confirm that the following information (relating to the 500/50 mcg pivotal clinical study included in ANDA 208891) was filed to IND 118769:

- *Sequence 0015. New protocol and information amendment – chemistry, submitted 2nd June 2015 to support the conduct of study MGR001-1007 'An Open Label*

Randomized, Two Way Crossover Study To Determine Pharmacokinetic Bioequivalence Of Single Doses Of Fluticasone Propionate/Salmeterol Fixed Dose Combination (500/50 µg) Powder Administered By Oral Inhalation From MGR001 And Advair® Diskus® In Healthy Adult Subjects’.

- **Sequence 0016.** Protocol amendment – change in protocol, submitted 19th June 2015, to support a protocol amendment to study MGR001-1007 to increase the subject numbers.
- **Sequence 0021.** IND Annual Report, submitted 25th November, 2015. Study Synopsis for MGR001-1007 was included in the submission.

Mylan would also like to confirm that the clinical PK BE study conducted after receipt of the CRL, Study MGR001-1016, was filed to IND 118769:

- **Sequence 0023.** New protocol and information amendment – chemistry, submitted 17th May 2017, to support the conduct of study MGR001-1016 ‘An Open-Label Randomized, Two-Way Crossover Study To Determine Pharmacokinetic Bioequivalence Of Single Doses Of Fluticasone Propionate / Salmeterol Fixed Dose Combination (250/50 mcg) Powder Administered By Oral Inhalation From MGR001 And Advair® Diskus® In Healthy Adult Subjects’.

Reviewer’s Comment:

The applicant submitted the study protocol and amendments for PK study MGR001-1007 on 6/2/2015 and 6/19/2015 under IND 118769, which is before the dosing date of the aforementioned PK study (first dosing date: 7/14/2015). It is noted that DARRTS and GDRP does not have reviews associated with these 2 submissions.

The applicant also submitted the study protocol for PK study MGR001-1016 (the new repeat PK study for the 250/50 strength, please see Section 5.1.1) on 5/17/2017, which is before the dosing date of the aforementioned PK study (first dosing date: 6/20/2017). It is noted that DARRTS and GDRP does not have reviews associated with this submission.

The applicant’s response is **acceptable**.

FLOW PROFILING STUDY

Deficiencies Related to the Flow Profiling Study (MGR000-1003)

4.40 Deficiency Comment #40

According to p. 40 of 321 of the study report, the reference batch (batch # 547-046) used in this study is Accuhaler™. Therefore, the flow profiling study is unacceptable due to the use of non-US marketed RLD product. Please repeat the flow profiling study using US marketed RLD product.

It is also noted that in the clinical overview (12/29/2015 submission, Module 2.5\Clinical Overview, p. 7 of 21), you stated that “[t]he CRC749 device used in this study was identical in terms of the airway geometry (and therefore airflow paths and device resistance) and the drug-containing discs (and therefore the pharmaceutical performance) remained the same the CRC749 Clinical device used in the pivotal clinical endpoint BE study and PK BE studies with the 100/50 and 500/50 product strengths, and the Commercial device which was included in the pivotal PK BE studies with the 250/50 product strength.” Based on this statement, it appears that you used test device other than the clinical device (b) (4) and commercial device (b) (4). Please use the commercial device for the test product in your repeat flow profiling study.

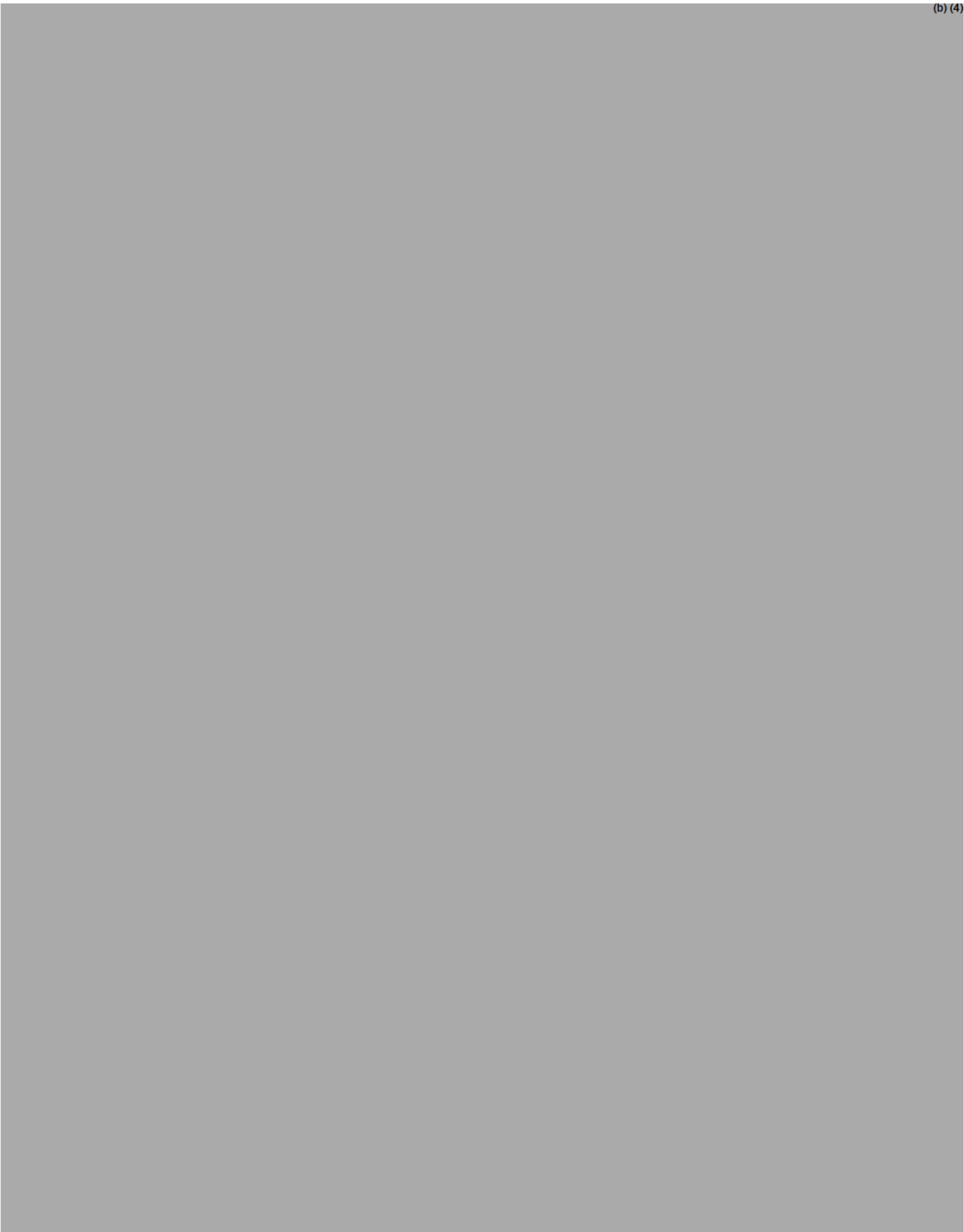
Please note that other deficiencies (deficiency #s 41-46) related to the flow profiling study are also identified and listed below. Please take them into consideration when you repeat the flow profiling study.

Applicant’s Response to Deficiency Comment #40:

Mylan recognizes the Agency’s questions raised upon review of the MGR000-1003 flow profile study leading to the Agency’s request for a repeat flow profiling study. Specifically, that the ‘reference’ device used in the study was the non-US RLD product (Accuhaler™ sourced from EU), rather than from the US RLD product (Diskus®), and that the configuration of CRC749 device used (b) (4) was not the clinical device used in the pivotal BE studies (with 100/50 and 500/50 product strengths; (b) (4) or, most importantly, the commercial inhaler (b) (4) (b) (4) which used in the pivotal BE studies for the 250/50 product strength.

Mylan also acknowledges the Agency’s further clarification, described in the preliminary comments from the Face to Face Meeting Minutes for July 13th, 2017, that Mylan may choose not to repeat the flow profiling study if adequate evidence is provided that the specific device resistance of the US and non-US RLD products are comparable (and that (b) (4) of the CRC-749 device are also comparable). In response to this clarification, Mylan presented the device specific airflow resistance data at the Face to Face meeting of July 13th and the Agency confirmed that an additional flow profiling study would not be required provided these data are included in the CR response. The Agency also requested that responses to deficiencies #41-46 were addressed, and these responses follow.

The “reference” devices used in study MGR000-1003 were from European commercial supplies, i.e., Accuhaler™. The Accuhaler™ and the Diskus® inhalers are covered by single patent, have the same presentation and only differ by trade name based on the region of marketing of the finished product (of note, some European countries use the name Diskus® to describe the inhaler). In vitro airflow characterisation studies confirming that the non-US RLD device used in study MGR000-1003 (Accuhaler™) and the US RLD device (GSK’s Diskus® device) have comparable device resistance are summarized in [Table 40-1](#).



In conclusion, given the compelling in-vitro bridge provided by these device specific airflow resistance data, the flow profile data obtained in study MGR000-1003 are representative of both the commercial CRC749 ((b) (4) and the US RLD inhaler (Diskus) and therefore, consistent with the Agency's feedback, Mylan have not conducted a repeat a flow profile study.

Whilst a flow profile study is not a requirement according to the Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate (2013), study MGR000-1003 has been provided by Mylan at the Agency's request. The flow rates (PIFR) measured in this study are representative of the to-be-marketed MGR001 and US RLD inhalers and demonstrate that all patient groups within the to-be-indicated population (pediatric asthma subjects age 4-7 years, pediatric asthma subjects age 8-11 years, adult asthma subjects and severe COPD subjects) were able to achieve PIFR >30 L/min. This information may be relevant to the determination of equivalence as 30L/min is the lowest flow rate at which in vitro equivalence was demonstrated for the MGR001 (test) and RLD product.

Reviewer's Comment:

As detailed in the written response to the applicant's 4/3/2017 meeting request, if the applicant chooses not to repeat the flow profiling study using US marketed product, the applicant is recommended to provide adequate evidence (e.g. data to confirm device resistance of the US market product is equivalent to the non-US version of the product used in MGR000-1003) to bridge the US market product with the non-US version product utilized in its Flow Profiling Study (MGR000-1003), in addition, adequate response should be provided to deficiency #s 41-46 in the 3/28/2017 CR letter that are related to the flow profiling study.

The applicant provided air flow resistance data for non-US RLD inhaler (Accuhaler™), which was used in the flow profiling study, as well as the air flow resistance data for US RLD inhaler (Diskus®) (please see table below). The air flow resistance of these 2 inhalers are considered comparable.

Therefore, the reviewer considers that the flow profile data from the flow profiling study with configuration (b) (4) of CRC749 and Accuhaler™ would be representative of the commercial test device (b) (4) and Diskus®.

The applicant's response is **acceptable**.

4.41 Deficiency Comment #41

According to the Information for Study Participants and Informed Consent Form (12/29/2015 submission, Module 5.3.4.1\IEC IRB Consent Form List, p. 26-27 of 95), both the test and reference devices were placed in the inhaler connecting box (ICB) in the horizontal orientation. Please specify how patients hold ICB for each device (e.g. which orientation). If same orientation was held between T and R devices, please justify the impact of device orientation on subject's flow profile.

Applicant's Response to Deficiency Comment #41:

During Study MGR000-1003 (an open study to measure the inhaled flow rates generated by healthy volunteers and patients inhaling through the CRC749 and Accuhaler®/Diskus® dry powder inhalers), participants were shown how to correctly hold the ICB (as per the study protocol). Participants held the ICB in the horizontal orientation for both devices.

(b) (4)

[Redacted]

[Redacted]

(b) (4)

the design of the airway geometry in Section 3.2.P.7.2.3 of the December 29, 2015 [ANDA 208891, Sequence 0000] submission). Hence the orientation of the device has no impact on the flow profile.

Reviewer's Comment:

The applicant's response is **acceptable**.

4.42 Deficiency Comment #42

According to Figure 3 in the aforementioned Information for Study Participants and Informed Consent Form (12/29/2015 submission, Module 5.3.4.1\IEC IRB Consent Form List, p. 26-27 of 95), you removed mouthpiece cover of the test device. Please justify its impact on device resistance.

Applicant's Response to Deficiency Comment #42:

[Redacted]

(b) (4)

The device resistance of the test device (i.e. the CRC749 inhaler) is determined by the design and geometry of the entire airway through the device from the air inlets, past the Disc and through to the

Mouthpiece (as described in Section 3.2.P.7.2.3.4 of the December 29, 2015 [ANDA 208891, Sequence 0000] submission). As the Mouthpiece Cover does not form part of the airway through the device it has no impact on the airflow through the device, and hence its removal has no impact on the device resistance.



Reviewer's Comment:

The applicant stated that the mouthpiece cover of the test product does not form part of the airway through the device, it has no impact on the airflow through the device, hence its removal has no impact on the device resistance.

The applicant's response is **acceptable**.

4.43 Deficiency Comment #43

In the study report (12/29/2015 submission, Module 5.3.4.1\Study Report Body\MGR000-1003 Study Report, p. 40 of 321), you stated that in order to ensure that the resistance of the dry powder inhaler (DPI) was not affected by enclosing it in the ICB, the resistance of the test and reference DPIs was determined before enclosure in the ICB.

This experiment was then repeated after enclosure in the ICB. The resistance of the enclosed DPI had to be $\pm 5\%$ of the resistance before the inhaler was put in the IDB; this was a key step in ensuring suitability of the enclosed DPI and the results were recorded in the batch records for the ICBs containing the inhalers. Please provide these results. In addition, please provide details of this study (e.g. study protocol/SOP and study report).

Applicant's Response to Deficiency Comment #43:

(b) (4)

These data confirm that the resistance of the enclosed DPI was within $\pm 5\%$ of the resistance before the inhaler was placed in the ICB.

Details of the study are provided with this response in Section 5.3.4.1 (MGR000-1003 report [MGR-REP-2017-078](#)).

Reviewer's Comment:

The applicant provided resistance data of the test and reference devices before and after enclosure in the ICB. Based on the data provided, the resistance of the enclosed devices is within $\pm 5\%$ of the resistance before the device was placed in the ICB, which met the acceptance criteria.

The applicant's response is **acceptable**.

4.44 Deficiency Comment #44

It is noted that the concomitant medication SAS .xpt dataset contained drug trade names but not generic names. In addition, route of administration (CM1_ROUT) and frequency was indicated by numbers (e.g. 3, 7, 17 for CM1_ROUT and 1, 5, 9 for CM1_FREQ), and it is unclear what these numbers stand for. Moreover, for start and end time of concomitant medications, you stated in your data definition file that your data format is DDMMYY10. However, values (e.g. 19029, 19640, 4565) listed in the SAS .xpt file does not match this format. It is also unclear what those numbers in CM1_STA2, CM1_STO2, CM1_ONGO (e.g. 0, 1, 2) stand for. Therefore, please clarify so. In addition, please list out the washout/withhold period between the concomitant medications and study procedures for each subject visit.

Applicant's Response to Deficiency Comment #44:

We note the request for clarification regarding the concomitant medication SAS .xpt dataset and provide the information for the coded terminology used in all datasets as well as a new dataset cm_atc.xpt mapping the generic names and levels of ATC coding for medications in one dataset [Module 5, Section 5.3.4.1 - Legacy]. We have also reviewed the data formats for the start and end times of concomitant medications (CM1_STAR and CM1_STOP) in cm.xpt using SAS v9.3 and SAS Universal Viewer and are unable to replicate the issue. The dates appear in the correct DDMMYY10. format.

As per the Clinical Protocol (26th July 2013), all medications taken within 28 days prior to the inhalation profiling testing were recorded as prior medications, and all medications taken after the first inspiratory profile testing procedure were recorded as concomitant medications; the washout/withhold period for concomitant medications is as follows:

Asthma Subjects (adult and pediatric): Prior to Screening (Visit 1) and Visit 2 (flow profiling visit), asthma subjects must abstain from using short acting β agonists (SABA) and sodium cromoglycate for a minimum of 6 hours; short acting antimuscarinics for a minimum of 8 hours; salmeterol, formoterol and aclidinium for a minimum of 12 hours; montelukast, glycopyrronium and indacaterol for a minimum of 24 hours; tiotropium for a minimum of 48 hours (subjects taking fixed dose combinations of β agonists and inhaled corticosteroids will need to withhold depending on the type of β agonists used).

Xolair must not have been administered in the previous 6 months. The Investigator may choose to restrict any other medication which he or she feels may affect the subject's pulmonary function.

COPD Subjects : Prior to Screening (Visit 1) and Visit 2 (inspiratory profile testing), COPD subjects abstained from using short acting β agonists (SABA) for a minimum of 6 hours and short acting anti-cholinergics for a minimum of 8 hours. Whilst short-acting (acute) bronchodilators were restricted, maintenance bronchodilators were not withheld for the COPD group as this was felt to be unethical for this patient population given their severe baseline airflow obstruction (post-bronchodilator FEV1 30-50% predicted).

All Subjects : In the event that any subject (asthma or COPD) needed to use a restricted bronchodilator during the withhold/washout phase (prior to screening or flow profile visits) they were instructed to do so and to inform the study center in order to reschedule the planned study visit.

All reported concomitant medications were ongoing at the time of the inspiratory profiling testing. The actual time of dosing of concomitant medications was not recorded in the CRF for the study, however medication restriction information was collected in the CRF as a Yes/No/Not Applicable; all entries were "No" or "Not Applicable", hence there would be no impact of these concomitant medications on the study assessments of inspiratory profile.

Reviewer's Comment:

The applicant stated that the actual time of concomitant medication dosing was not recorded in CRF for the study. Based on the "no" or "not applicable" answer to the medication restriction information in the CRF, the applicant stated that there would be no impact of concomitant medications on the study assessments of inspiratory profiles. Since this study is not a pivotal study, the reviewer will not pursue this issue further.

The applicant's response is **acceptable**.

4.45 Deficiency Comment #45

For pressure drop acceleration rate (kPa/sec), you excluded the multiple values from the summary statistics [e.g. Subject (b) (6) (healthy adult subject) / device: AccuhalerTM/Diskus[®] / manoeuver 8; Subject (b) (6) (healthy adult subject) / device: CRC749 / manoeuver 1]. Please provide your pre-specified acceptance criteria (e.g. in an SOP) for pressure drop acceleration rate data at the time of this study.

Applicant's Response to Deficiency Comment #45:

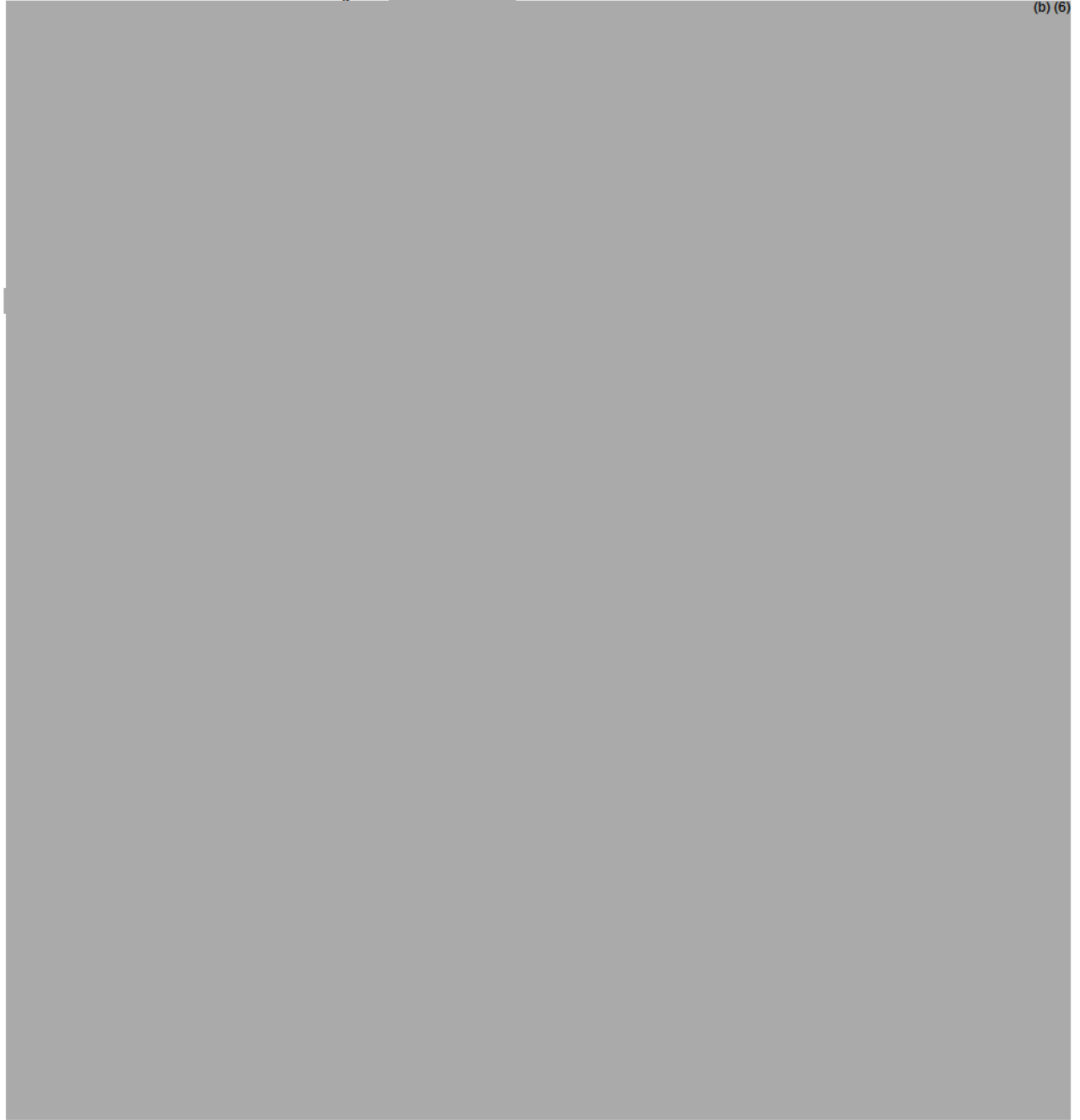
The pre-specified criterion for potentially excluding individual data points from the summary statistics was contained in documentation produced in order to use the Inhalation Profiling Analysis software (16.2.10 addendum - MGR000-1003 Working Instructions for Inhalation Profile Analyser).

The IPA Working Instructions stated in Section 5.4 “Check the r^2 value for the kPa/s slope parameter; ideally this should be > 0.995 ”. This check was to act as a “flag” to the team in order to review those flagged data and consider whether they should be included in the summary statistics.

The included and excluded pressure drop acceleration rate (PDAR) values for subject (b) (6) are detailed in Table 45-1.

Table 45-1: PDAR Values Subject (b) (6)

(b) (6)



It should be noted that only these 3 subjects of 78 subjects included in the flow profiling analysis set of study MGR00-1003 had PDAR values which were excluded from the summary statistics on the basis of the unblinded data review, and that in only 1 of these subjects (b) (6) was a PDAR value not reportable. Only 9 out of the total of 468 flow profiles (1.9%) collected during study MGR000-1003 had PDAR values which were excluded from the summary statistics, and the removal of these PDAR values had no impact on the primary endpoint for the study, that being PIFR.

Reviewer's Comment:

The applicant's response is **acceptable**.

4.46 Deficiency Comment #46

It is noted that although the use of rescue medicine is not mentioned in the study protocol or study report, you provided a SAS .xpt dataset "RESCUE", which, according to the data definition file, is about "Salbutamol Intake (Rescue Medication)". According to this dataset, multiple subjects took rescue medication. For each of these subjects, please list out the washout period between the rescue medication and study procedures for each visit. Please also justify the impact of rescue medication usage on inhalation profile of these subjects.

Applicant's Response to Deficiency Comment #46:

Mylan accept that the nomenclature for dataset RESCUE.XPT is misleading, as it contains the data for salbutamol administered prior to the post-bronchodilator pulmonary function testing conducted during screening, rather than detailing the use of salbutamol as rescue medication. As such, the v_element (visit)=1 (Visit 1 – Screening) in all records except for 2 subjects (b) (6) who had v_element=5 (Unscheduled Visit). Subjects (b) (6) both had salbutamol administered prior to post-bronchodilator pulmonary function testing assessments at unscheduled visits (b) (6) (b) (6) which occurred after Screening Visit 1 but prior to their Visit 2 date (b) (6). The post-bronchodilator pulmonary function testing was only performed at screening (Visit 1) in adult asthma or COPD subjects in order to ascertain

if their lung function met the inclusion criteria (all pediatric patients had historical data that was used), per listing 16.2.10.

The protocol stipulated that Visit 2 (the inspiratory profile testing visit) had to occur at least 24 hours after Visit 1 in adult asthma or COPD patients. The dates of Visit 1 (post-bronchodilator pulmonary function testing) and Visit 2 (inspiratory profile testing) for all subjects in “RESCUE.XPT” are detailed in [Table 46-1](#).

Therefore, all adult asthma and COPD subjects that had salbutamol administered prior to post-bronchodilator pulmonary function testing performed at screening (at Visit 1 or unscheduled Visit) had this at least one day prior to Visit 2, ensuring an appropriate washout of the bronchodilator occurred and preventing any impact on the inspiratory flow profiling at this visit.

The actual time of dosing of any other short acting bronchodilators (other than those associated with post-bronchodilator pulmonary function testing) was not recorded in the CRF for the study, however as there were withhold periods (see response to deficiency # 44) of at least 6 hours for short-acting bronchodilators in all subjects (and longer for maintenance bronchodilators in asthma subjects), and there were no Protocol Deviations associated with short acting bronchodilator use during the withhold periods prior to inspiratory profile testing, there was no impact of rescue bronchodilator use on the subjects’ inspiratory flow profiling data.

Table 46-1: Visit Dates For Subjects In RESCUE.XPT

Subject ID	Visit 1	Visit 2
		(b) (6)

	(b) (6)
* Subject (b) (6) had an unscheduled visit between V1 and V2 where the post-bronchodilator pulmonary function tests were repeated.	

Reviewer's Comment:

The applicant's response is **acceptable**.

Based on the applicant's responses to deficiencies related to the flow profiling study (please see Section 4.40-4.46), the flow profiling study is now considered **acceptable**. Please note that the flow profiling study is not a pivotal study.

4.47 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

PK BE Study MGR001-1016 (repeat PK study for the 250/50 mcg strength)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route), [Product ID]	Subjects Number (M/F), Type, Age (yrs.), Mean (Range)	Mean Parameters (SD)*							Study Report Location
					Treatment Group	C _{max} (pg/mL)	T _{max} (hr)	AUC _{last} (pg/mL•hr)	AUC _{inf} (pg/mL•hr)	T _{1/2} (hr)	K _{el} (hr ⁻¹)	
MGR001-1016	To confirm the systemic pharmacokinetic BE of both FP and salmeterol after oral inhalation of single doses of MGR001 (Test) vs Advair® Diskus® (Reference)	Open-label, Randomized 2-way crossover study	A=MGR001 Batch No. 60000354 250/50 mcg, (Single dose, 3 inhalations) [Test] B= Advair® Diskus® Lot No. 6ZP6787 250/50 mcg, (Single dose, 3 inhalations) [Reference]	66 Dosed 63 Completed (M:30/F:36) Healthy Subjects Mean Age**: 37.7 (18 to 55)	Fluticasone Propionate							Section 5.3.1.2
					A [Test]	170.0 (53.67)	1.003 (0.084-3.006)	1298 (417.7)	1371 (430.8)	11.237 (1.799)	0.0632 (0.0100)	
					B [Reference]	173.6 (56.36)	1.002 (0.334 – 3.010)	1237 (378.7)	1313 (387.3)	10.380 (1.707)	0.0685 (0.0107)	
					Salmeterol							
					A [Test]	319.5 (137.8)	0.083 (0.042-1.008)	700.0 (340.5)	733.4 (357.8)	11.552 (1.713)	0.0614 (0.0095)	
B [Reference]	352.8 (158.1)	0.083 (0.050-2.006)	685.7 (324.4)	728.0 (331.7)	11.664 (1.862)	0.0610 (0.0103)						

*Arithmetic mean (SD) for all parameters except median (range) for T_{max}

**Mean Age (Range) presented for all subjects (n=66).

4.48 Comments for Other OGD Disciplines

N/A

4.49 Pending Consults (Clinical, Statistical, Science Staff, Chemistry etc.)

N/A

APPEARS THIS WAY ON
ORIGINAL

5 APPENDIX

5.1 Individual Study Reviews

5.1.1 Single-dose Fasting Bioequivalence Study

Reviewer's note: For each of the fasting study, the applicant assigned each subject with both a subject number (b) (4)

(b) (4)

(b) (4) It appears that the applicant's clinical study reports prefer to refer to subjects using their subject numbers, whereas the bioanalytical report prefers to refer to subjects using their randomization numbers. Therefore, to be consistent with the applicant's report, the clinical portion of the review will refer to a subject mostly using subject number, whereas the analytical portion of the review will mostly use randomization number. For subjects with clinical-related issues that may impact PK analysis (e.g. protocol deviations), the reviewer will list out both subject number and randomization number in reviewer's comments. For details about each subject's subject number and randomization number, please refer to the randomization scheme in the Study Design section under each individual fasting study.

5.1.1.1 Study Design

5.1.1.1.1 Study Information

Study Number	MGR001-1016
Study Title	AN OPEN LABEL RANDOMIZED, TWO WAY CROSSOVER STUDY TO DETERMINE PHARMACOKINETIC BIOEQUIVALENCE OF SINGLE DOSES OF FLUTICASONE PROPIONATE / SALMETEROL FIXED DOSE COMBINATION (250/50 mcg) POWDER ADMINISTERED BY ORAL INHALATION FROM MGR001 AND ADVAIR® DISKUS® IN HEALTHY ADULT SUBJECTS
Clinical Site (Name & Address)	Worldwide Clinical Trials Early Phase Services, LLC 2455 NE Loop 410, Suite 150 San Antonio, Texas 78217
Principal Clinical Investigator	Dr Cynthia A. Zamora, MD
Dosing Dates ^	Group 1 Period 1: 6/20/2017 (Subject (b) (6) (b) (6) Group 1 Period 2: 6/27/2017 Group 2 Period 1: 6/21/2017 (Subject (b) (6) (b) (6) Group 2 Period 2: 6/28/2017 Group 3 Period 1: 6/22/2017 (Subject (b) (6) (b) (6) Group 3 Period 2: 6/29/2017
Analytical Site (Name & Address)	Mylan Pharmaceuticals Inc. Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505
Analysis Dates *	7/3/2017-7/10/2017

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Principal Analytical Investigator	Sandra Tarr Austria M.S.
Sample Storage : (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g., -20°C to -80°C)	FP: a) and b): Longest storage duration and condition: 20 days at -70°C±15°C SA: a) and b): Longest storage duration and condition: 20 days at -70°C±15°C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	FP: 132 days at -70°C±15°C SA: 132 days at -70°C±15°C

^ The applicant did not provide this information in the summary table or in the study report. The reviewer summarized this based on the case report forms (CRFs).

* The applicant did not provide this information in the summary table. The reviewer added this information based on the bioanalytical report.

5.1.1.1.2 Product (Bio-batch) Information

Product	Test	RLD
Treatment ID	Treatment A	Treatment B
Product Name	MGR001	Advair® Diskus®
Manufacturer	Mylan Dublin Respiratory	GlaxoSmithKline
Batch/Lot No.	60000354	6ZP6787
Manufacture Date	5/9/2016	
Expiration Date	11/8/2018	12/2017
Strength	250/50 mcg	250/50 mcg
Dosage Form	Inhalation Powder	Inhalation Powder
Bio-Batch Size	(b) (4)	
Production Batch Size		
Potency (Assay)	Emitted Dose as % of Target: Fluticasone Propionate 101 % Salmeterol 107 %	Emitted Dose as % of Target: Fluticasone Propionate 103 % Salmeterol 106 %
Content Uniformity (expressed as mean, % CV or per USP)	Fluticasone Propionate: Mean 103 % of Label Claim CV 3.0 % Salmeterol 103 % of Label Claim CV 2.5 %	
Dose Administered	Fluticasone Propionate 750 mcg Salmeterol 150 mcg	Fluticasone Propionate 750 mcg Salmeterol 150 mcg
Route of Administration	Inhalation	Inhalation

Are the test and reference products expired at the time of study? If Yes, please comment.	☐ Yes ☐ No

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Is same bio-batch used in the dissolution and all BE studies? If No, please comment.	☐ Yes ☐ No ☒ N/A (no dissolution studies)
Is the bio-batch size at least the recommended minimum of 100K or 10% of the production batch (whichever is greater) for oral solid dosage form? If No, please comment.	☒ Yes ☐ No
Is difference of the potency values for the Test and RLD within 5%? If No, please comment.	☒ Yes ☐ No

5.1.1.1.3 Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 66 Dosed: 66 Completed: 63 Samples Analyzed: 66 Statistically Analyzed: 61
No. of Sequences	2
No. of Periods	2
No. of Treatments	1
No. of Groups	3 Group 1: (b) (6) Group 2: (b) (6) Group 3: (b) (6)
Washout Period	7 days
Randomization	☒ Yes (please see details below) ☐ No
Blood Sampling Times	Pre-dose (0 hour) and at 2, 3, 4, 5, 10, 15, 20, 30, 45, 60, and 90 minutes, and 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours post dose.
IRB Approval	☒ Yes Date: 5/16/2017 (protocol Version 01), 5/22/2017 (Protocol Clarification Letter dated 5/17/2017 ³¹), 5/24/2017 (Protocol Clarification Letter dated 5/23/2017 ³²) ☐ No
Informed Consent	☒ Yes Date: 5/16/2017 ☐ No
Length of Fasting	8 hours prior and 4 hours post the start of pharmacokinetic sample collections on Day 1
Length of Confinement	From the day prior to dosing until 24 hours post-dose
Was the drug product administered per labeling for specialized dosage forms e.g. ODT?	☐ Yes ☐ No ☒ N/A

³¹ This protocol clarification dated 5/17/2017 was to correct errors in the Schedule of Activities in the protocol.

³² This protocol clarification dated 5/23/2017 was to modify the requirement that all procedures will be recorded to dd-mmm-yyyy, hh mmss. The time of procedures should be recorded per dd-mmm-yyyy, hh mmss for dosing times and PK blood samples; all other assessments can be recorded to the nearest minute. The format dd-mmm-yyyy must be used to record the date in the Clinical Database; whilst this format is not mandated for all source documentation, however, any source documentation that uses a format that could be open to interpretation will be checked prior to transfer to the Clinical Database.

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Safety Monitoring	☒ Yes ☐ No

Randomization Scheme

Randomization Number	Subject Number	Treatment received at Period 1	Treatment received at Period 2
	(b) (6)	A	B
		B	A
		A	B
		B	A
		B	A
		A	B
		A	B
		B	A
		B	A
		A	B
		B	A
		A	B
		B	A
		B	A
		A	B
		A	B
		B	A
		A	B
		B	A
		A	B
		B	A
		B	A
		A	B
		B	A
		B	A
		A	B
		B	A
		B	A
		A	B
		B	A
		B	A
		A	B
		B	A
		B	A
		A	B
		B	A
		B	A

Randomization Number	Subject Number	Treatment received at Period 1	Treatment received at Period 2
	(b) (6)	A	B
		B	A
		A	B
		A	B
		B	A
		B	A
		B	A
		A	B
		B	A
		A	B
		A	B
		A	B
		B	A
		B	A
		B	A
		A	B
		B	A
		B	A
		A	B
		A	B
		B	A
		B	A
		A	B
		A	B
		B	A
		B	A
		A	B
		B	A
		B	A

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Randomization Number	Subject Number	Treatment received at Period 1	Treatment received at Period 2
	(b) (6)	B	A
		A	B
		A	B
		A	B
		A	B
		A	B
		B	A
		B	A
		B	A
		B	A
		A	B
		B	A
		B	A
		A	B
		A	B

A = test

B = reference

Please note that Subjects (b) (6) were not dosed in Period 2 as they were dropped out prior to Period 2 dosing. Please see Section 5.3.1.2.2 for details.

Comments on Study Design: Adequate

- According to the 8/28/2017 cover letter³³ and the Clinical Summary Addendum 1³⁴, the test batch used in the current study utilized commercial inhaler configuration (b) (4) manufactured (b) (4).
- On Day -1 and Day 1 prior to dosing for both study periods, subjects were trained to achieve an appropriate inhalation maneuver for both the CRC749 and Diskus[®] inhalers.
- The research unit staff prepared (as per the instruction for use) each inhaler ready for dosing, before handing to the subject for dosing. The inhaler was re-prepared by the research unit staff following each inhalation and prior to the next inhalation. There was an interval of approximately 30 seconds between each inhalation.
- Subjects were instructed to rinse their mouths (without swallowing) with approximately 50 mL water after completing the three inhalations, and to spit the water out after rinsing. This is in line with the product-specific guidance, which states that “[s]ubjects should adhere to labeling as follows: ‘Rinse your mouth with water after breathing in the medicine. Spit the water out, do not swallow.’”

³³ GS Review: ANDA 208891, Resubmission/After Action- Complete; Bioequivalence/Other, 8/28/2017 (Module 1.2\Cover Letter – 0021 – Addendum5b – Bioequivalence (Clinical, Bioanalytical and Device), p. 10 of 52).

³⁴ GS Review: ANDA 208891, Resubmission/After Action- Complete; Bioequivalence/Other, 8/28/2017 (Module 2.7.2\MGR001-1016 – Summary of Clinical Pharmacology Studies, p. 2 of 9).

5.1.1.2 Clinical Results

5.1.1.2.1 Demographic Profile of Subjects

Study Number MGR001-1016			
		Treatment Groups	
		Test Product (MGR001 250/50mcg) N = 65	Reference Product (Advair® Diskus®) N = 64
Age (years)	Mean ± SD Range	37.9 ± 9.67 18 - 55	37.6 ± 9.91 18 - 55
Age Groups	<18 18-40 41-64 65-75 >75	0 (0%) 39 (60.0%) 26 (40.0%) 0 (0%) 0 (0%)	0 (0%) 39 (60.9%) 25 (39.1%) 0 (0%) 0 (0%)
Sex	Male Female	29 (44.6%) 36 (55.4%)	30 (46.9%) 34 (53.1%)
Race	White Black or African American American Indian or Alaska Native	50 (76.9%) 14 (21.5%) 1 (1.5%)	49 (76.6%) 14 (21.9%) 1 (1.6%)
BMI	Mean ± SD Range	26.2 ± 3.31 18.7 - 30.4	26.3 ± 3.34 18.7 - 30.4
Other Factors		N/A	N/A

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

5.1.1.2.2 Dropout Information

Subject No.	Randomization No.	Reason	Period	Replaced?
	(b) (6)	Subject was discontinued prior to Period 2 for deviation/noncompliance with the protocol (positive drug screen at admission) and did not receive Advair® Diskus® 250/50 mcg Date: (b) (6) Treatment: Prior to receiving Reference	1	No
	(b) (6)	Subject was withdrawn prior to Period 2 for an adverse event (sore throat) and did not receive Advair® Diskus® 250/50 mcg Date: (b) (6) Treatment: Prior to receiving Reference	1	No
	(b) (6)	Subject was withdrawn prior to Period 2 for an adverse event (viral upperrespiratory infection) and did not receive MGR001 250/50 mcg	1	No

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	Date: (b) (6) Treatment: Prior to receiving Test	

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

5.1.1.2.3 Study Adverse Events

System Organ Class/ Preferred Term	Reported Incidence by Treatment Groups	
	Study Number MGR001-1016*	
	Test Product (MGR001 250/50 mcg*) No. of Subjects n (%) N=65	Reference Product (Advair® Diskus® 250/50 mcg*) No. of Subjects n (%) N=64
Gastrointestinal disorders		
Abdominal Distension	1 (1.5%)	0 (0.0%)
General disorders and administration site conditions		
Vessel puncture site pain	3 (4.6%)	2 (3.1%)
Infections and infestations		
Viral upperrespiratory tract infection	0 (0.0%)	1 (1.6%)
Injury, poisoning and procedural complications		
Muscle strain	1 (1.5%)	0 (0.0%)
Musculoskeletal and connective tissue disorders		
Pain in extremity	0 (0.0%)	1 (1.6%)
Nervous system disorders		
Dizziness	1 (1.5%)	0 (0.0%)
Headache	0 (0.0%)	2 (3.1%)
Presyncope	3 (4.6%) [^]	0 (0.0%)
Respiratory, thoracic and mediastinal disorders		
Cough	1 (1.5%)	0 (0.0%)
Oropharyngeal pain	1 (1.5%)	0 (0.0%)
Vascular disorders		
Hot flush	1 (1.5%)	0 (0.0%)
Total	12 (18.5%) [^]	6 (9.4%)

[^] The applicant reported 2 incidences of presyncope in the Module 2.7 summary table. The reviewer corrected to 3 incidences based on the applicant's adverse event listing³⁵ as well as cross-checking with CRFs.

Subjects Experiencing Emesis (Include in eCTD)

N/A

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☒ No ☐ N/A

³⁵ GS Review: ANDA 208891, Resubmission/After Action- Complete; Bioequivalence/Other, 8/28/2017 (Module 5.3.1.2. mgr001-1016...\Adverse Event Listings\Adverse Events Listings, p. 3 and 8 of 20).

If yes, does the time of emesis exceed two times the median T _{max} value (IR products) or the labeled dosing interval (MR products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

5.1.1.2.4 Protocol Deviations

Study No. MGR001-1016		
Type	Subject #s (Test)	Subject #s (Ref.)
Study drug administration	(b) (6)	
Blood collection time deviations		
Non-compliance (positive drug screen at Period 2 check-in)		
Missed assessments (blood samples not collected per protocol)		
Inhalation training completed for both inhalers rather than just the inhaler to be used at Period 2		
Centrifugation settings not confirmed ³⁶		
Other ⁶		

¹ Subjects (b) (6) had inhalers where the dose counter did not decrement with the last dose administered, an investigation determined that only two dose pockets had been emptied and hence the subjects did not receive all three doses.

² Subject (b) (6) exhaled out of their mouth during the dosing.

³ Subject (b) (6) was reported to have exhaled through the inhaler with powder noted.

⁴ Subject (b) (6) was reported to have coughed on the third inhalation of study medication.

⁵ Subjects did not take study medication at 08:00 ±2 hours per protocol.

⁶ Other includes late or missing procedures not related to PK sampling or dosing. (The reviewer checked the protocol deviation listing, and the protocol deviation for these subjects are:

- Subject (b) (6), test treatment: 24 hour ECG performed after 24 hour vital signs due to technical difficulty
- Subject (b) (6), reference treatment: 24 hour ECG performed after 24 hour PK sample due to technical difficulty; 24 hour ECG performed after 24 hour vital signs due to technical difficulty
- Subject (b) (6), reference treatment: unable to verify 48 hour ECG was performed after 10 minute supine due to documentation error

³⁶ According to the protocol deviation listings, details of this protocol deviation related to centrifugation settings not confirmed is: 48 hour PK sample was not documented as having the centrifuge settings confirmed prior to the start of centrifugation.

Full listings of protocol deviations and additional dosing comments are provided in the [Clinical Study Report, Appendix 16.2.2, Module 5, Section 5.3.1.2](#) and [Clinical Study Report, Appendix 16.2.5.1, Module 5, Section 5.3.1.2](#) respectively.

If the applicant used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time.	☒ Actual ☐ Nominal
Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Comments on Clinical Results: Acceptable

Study Subjects and Dropouts

- Sixty-six (66) subjects were enrolled in the study (19 subjects dosed in each of Group 1 and Group 2, and 28 subjects dosed in Group 3) and 63 subjects completed the study. Subjects (b) (6) was dropped out from the study prior to Period 2 due to positive drug screen. Subjects (b) (6) were withdrawn prior to Period 2 due to adverse events (AEs). The reviewer verified from the case report forms (CRFs) of these 3 subjects that they were not dosed in Period 2. All of these 3 subjects were not replaced.
- Plasma from all 66 subjects were analyzed as per protocol³⁷, and plasma concentration from 61 subjects who completed the study [excluding Subjects (b) (6) whose inhaler dose counters did not decrement with the last dose administered, an Investigation determined that only two dose pockets had been emptied and hence the subjects did not receive all three doses. Please see reviewer's comments for protocol deviations for details] were used for statistical evaluation.

Adverse Events

- Sixteen (16) subjects (11 after the test product treatment and 5 after the reference product treatment) reported a total of 17 adverse events (AE). The most commonly reported AE was vessel puncture site pain, which was experienced by 3 subjects in the test treatment group and 2 subjects in the reference treatment group. The second and third most commonly reported AEs were presyncope (experienced by 3 subjects in the test treatment group) and headache (experienced by 2 subjects in the reference treatment group), respectively. The remaining AEs were reported by one subject in either treatment group.

³⁷ GS Review: ANDA 208891, Resubmission/After Action-Complete; Bioequivalence/Other, 8/28/2017 (Module 5.3.1.2. mgr001-1016...\Protocol or Amendment\MGR001-1016 Protocol and Protocol Amendments, p. 43 of 59).

- All AEs were considered mild in severity, except 3 incidences of presyncope, which were considered moderate in severity. All AEs were considered unrelated/not related to the study treatment, except abdominal distension, which were considered unlikely related to the study treatment, as well as dizziness and 1 incidence of headache, which were considered possibly related to the study treatment. All symptoms of AEs reported during the study were resolved/recovered.
- Two (2) subjects were discontinued from the study due to AE. Subject (b) (6) discontinued due to oropharyngeal pain after test treatment; and Subject (b) (6) was discontinued from the study due to viral upper respiratory tract infection following reference treatment.
- The applicant reported that there were no deaths, serious and significant adverse events in the study.

Concomitant Medications

- Concomitant medication 2 x Ibuprofen Tablets (strength not specified) were given to Subject (b) (6) who experienced headache in the reference drug treatment group. Since this subject was withdrawn from the study due to another AE (viral upper respiratory tract infection), this concomitant medication does not impact study outcome.
- The use of concomitant medication Mirena (levonorgestrel) intrauterine system as ongoing birth control in Subjects (b) (6) was also reported. The applicant evaluated the specificity of the analytical methods in the presence of levonorgestrel. Based on representative chromatograms provided, none of the tested compounds significantly interfere with the analysis of FP, SA and the internal standards.

The reviewer verified from Micromedex that there are no known drug-drug interactions between the aforementioned concomitant medications and the study drug FP/SX.³⁸

Protocol Deviations

- Ten (10) subjects had study drug administration deviation as detailed in table below.

³⁸ Micromedex:
<http://www.micromedexsolutions.com/micromedex2/librarian/PFDdefaultActionId/evidenceexpert.ShowDrugInteractionsResults> Last accessed: 1/12/2018.

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Subject	Randomization Code	Period	Treatment	Study Drug Administration Deviation
[REDACTED]	(b) (6)	1	T	Subject was likely only administered two of the three doses that should have been administered. After the dosing (Period 1) for this subject was complete, the dose counter on the inhaler (CRC749) read 58, this should have been 57 if all doses were administered correctly. Per device inspection report [REDACTED] (b) (4) the inhaler still had 58 doses remaining following investigation, confirming that the subject did not receive three doses.
		1	T	
		1	R	Subject was observed by the CRA to begin to exhale into the inhaler (Advair® Diskus®) with powder observed on the first inhalation; they were corrected by staff and inhaled correctly subsequently.
		2	T	Subject exhaled out of mouth during dosing.
		1	R	Subject coughed during the third inhalation.
		1	T	Subject did not dose within protocol specified window +/- 2 hours due to source template error
		2	R	
		1	T	
		2	R	
		2	T	
		1	R	
		1	T	
		2	R	
		2	T	
		1	R	
		2	T	
		1	R	

For the above subjects with study drug administration deviations, the applicant exclude Subjects [REDACTED] (b) (6) from statistical analysis since the subject did not receive 3 doses based on device inspection. All other subjects were included in the statistical analysis.

The reviewer agrees with the applicant's handling of the above subjects, with the exception of Subjects [REDACTED] (b) (6) as it is unclear whether the amount of dosing was impacted. Therefore, the reviewer will exclude these 2 subjects from statistical analysis as a conservative approach. In addition, the reviewer also informed Drug Product reviewer about the device issue for Subjects [REDACTED] (b) (6) and their device inspection report. And the device inspection report will be reviewed by Drug Product.

- Fourteen (14) subjects had missing blood sample collections for bio analysis {due to [needle] re-stick, technical difficulties, subject not showing up, being inadvertently discarded prior to shipping due to technician error [Subjects [REDACTED] (b) (6)]

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and [redacted] (b) (6) Period 1, 48 hrs], or unknown reason [Subject [redacted] (b) (6) Period 2, 0.33 hr}], and the applicant included all these subjects into the statistical analysis, except for Subject [redacted] (b) (6) due to study drug administration deviations (please see reviewer's comments above). However, the reviewer noticed that for the aforementioned 14 subjects, some of these missing sample blood collection time points are close to Tmax, thus may potentially affect Cmax of these subjects (please see table and representative plots of plasma concentration vs time below).

Subject	Randomization Code	Period	Treatment	Time of missing blood collection	Potentially affect Cmax for FP?	Potentially affect Cmax for SA?
[redacted] (b) (6)	[redacted] (b) (6)	1	R	2 min (0.03 hr)	No	Might (3 time points before current Tmax of 0.08 hr)
		1	T	4 min (0.07 hr)	No	Yes
		1	T	2 min (0.03 hr)	No	Might (2 time points before current Tmax of 0.07 hr)
		1	R	3 min (0.05 hr)	No	Yes
				10 min (0.17 hr)	No	Yes
		2	R	2 min (0.03 hr)	No	Might (2 time points before current Tmax of 0.07 hr)
		1	T	3 min (0.05 hr)	No	Yes
				48 hr	No	No
		2	R	3 min (0.05 hr)	No	Yes
		2	R	2 min (0.03 hr)	No	Might (3 time points before current Tmax of 0.08 hr)
		1	R	48 hr	No	No
		2	R	2 min (0.03 hr)	No	Might (2 time points before current

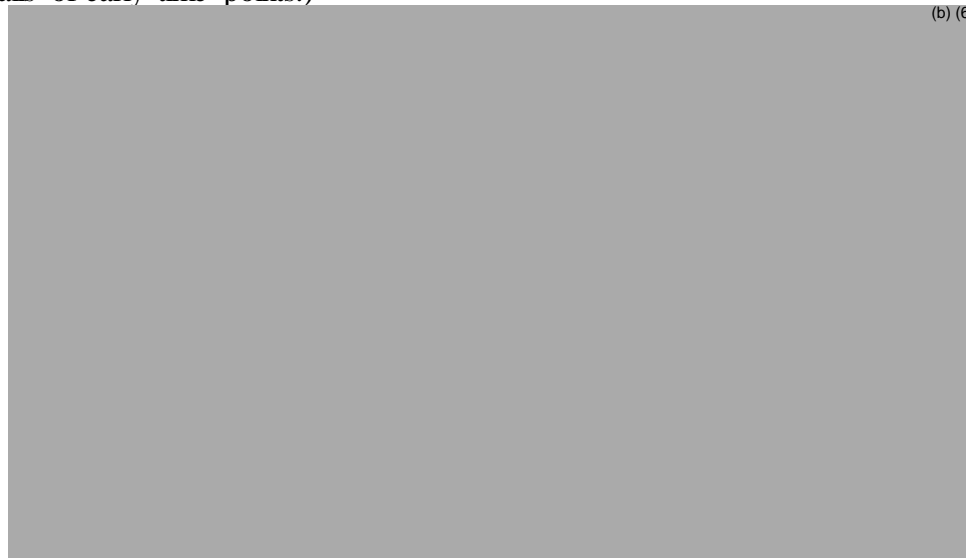
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						Tmax of 0.07 hr)
(b) (6)	1	R	2 min (0.03 hr)	No	Might (3 time points before current Tmax of 0.08 hr)	
	1	T	3 min (0.05 hr)	No	Might (2 time points before current Tmax of 0.08 hr)	
	2	R	20 min (0.33 hr)	No	No	
	1	R	3 min (0.05 hr)	No	Might (2 time points before current Tmax of 0.08 hr)	
	1	T	2 min (0.03 hr)	No	Might (2 time points before current Tmax of 0.08 hr)	

Representative plot of plasma concentration vs. time of subject with a missing time point that is very likely to impact C_{max} [Subject (b) (6) Period 1, 0.07 hr time point missing. AUC curve truncated at 0.8 hrs by the reviewer to show details of early time points]



Representative plot of plasma concentration vs. time of subject with a missing time point that might impact C_{max} [Subject (b) (6), Period 2, 0.03 hr time point missing. AUC curve truncated at 0.5 hr by the reviewer to show details of early time points.)



Representative plot of plasma concentration vs. time of subject with missing time points that is not likely to impact C_{max} [Subject (b) (6) Period 1, 0.33 hr time point missing. AUC curve truncated at 4 hrs by the reviewer to show details of early time points.]



The reviewer will **exclude** subjects with missing time point(s) that are **very likely to impact C_{max}**. For subjects with missing time point(s) that **might affect C_{max}**, the reviewer will also exclude them as a conservative approach. However, it should be noted that excluding the latter subjects does not change study outcome (please see tables below).

Excluding randomization #s (b) (6) (with missing samples that might affect C_{max}) [and excluding randomization (b) (6), (b) (6) (with missing samples that are very likely to impact C_{max})]

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
Group 1, 2 and 3 (trt*troupe = 2)					
LAUCT (hr *pg/ml)	677.89	659.47	1.03	98.59	107.17
LAUCI (hr *pg/ml)	710.94	694.03	1.02	98.38	106.66
LCMAX (pg/ml)	295.53	313.07	0.94	87.04	102.38

Note: The subjects were dosed in 3 groups, and the treatment*group interaction was not statistically significant (p>0.1) for LAUC_{0-t}, LAUC_{0-∞} and LC_{max}.

Not excluding randomization #s (b) (6) (with missing samples that might affect C_{max}) [but excluding randomization #s (b) (6) (with missing samples that are very likely to impact C_{max})]

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
Group 1, 2 and 3 (trt*troupe = 2)					
LAUCT (hr *pg/ml)	645.02	630.04	1.02	98.57	106.34
LAUCI (hr *pg/ml)	676.93	663.19	1.02	98.38	105.90
LCMAX (pg/ml)	290.75	309.14	0.94	87.16	101.49

Note: The subjects were dosed in 3 groups, and the treatment*group interaction was not statistically significant (p>0.1) for LAUC_{0-t}, LAUC_{0-∞} and LC_{max}.

- Subject (b) (6) had positive drug screen at Period 2 check-in. Since this subject was dropped out from the study, this protocol deviation does not impact study outcome.
- There were blood collection time deviations. Since the applicant used the actual sampling time points for the PK analysis, these deviations do not affect the study outcome.
- For the protocol deviation related to centrifugation settings not confirmed, according the protocol deviation listings, this protocol deviation is that 48 hour PK sample for randomization (b) (6), Period 2 was not documented as having the centrifuge settings confirmed prior to the start of centrifugation. The applicant further justified in the bioanalytical report that the centrifuge settings (1800g for 10 min at 4°C) for these 2 samples were verified 31 minutes and 15 minutes prior to centrifugation of these samples, respectively. The applicant stated that although the centrifuge settings were not verified specifically for these 2 samples, these settings were verified close in time to the centrifugation of these samples and multiple times prior to that. In addition, a plasma sample was received for analysis, thus the applicant considered it evident that the centrifuge settings were sufficient to separate the blood from the plasma. The applicant also stated that nothing abnormal was noted during the extraction of these samples and the chromatography was typical of the assay.

The reviewer will exclude these 48 hrs samples of these 2 subject periods as a conservative approach. Please note that these 2 samples are at the end of the elimination phase, and are not expected to affect C_{max}.

- Other protocol deviations mentioned above do not affect study outcome.

5.1.1.3 Bioanalytical Results

5.1.1.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
MPI-SOP-BIO-GEN-0018 (v. 4.0)	8/27/2015	Evaluation and Acceptance Criteria for Analytical Runs
MPI-SOP-BIO-GEN-0019 (v. 3.0)	2/3/2017	Chromatography Acceptance Criteria
MPI-SOP-BIO-GEN-0020 (v. 4.0)	8/27/2015	Re-assay or Re-injection of Clinical Samples
MPI-SOP-BIO-GEN-0023 (v. 4.0)	4/7/2016	Within-Study Incurred Sample Re-Analysis (ISR)

All necessary SOPs submitted?	☒ Yes ☐ No

5.1.1.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study MGR001-1016 FP										
Parameter	Standard Curve Samples									
Concentration (pg/mL)	1.000	2.000	3.000	10.00	30.00	100.0	300.0	400.0	500.0	600.0
Inter day Precision (% CV)	3.26	5.5	6.04	3.42	2.94	2.45	2.37	2.59	2.34	2.05
Inter day Accuracy (% Actual)	101.40	98.45	98.43	97.76	99.50	100.10	101.20	101.45	100.90	100.58
Linearity	0.9943 - 0.9999									
Linearity Range (pg/mL)	1.000 - 600.0									
Sensitivity/LOQ (pg/mL)	1.000									

Bioequivalence Study MGR001-1016 FP						
Parameter	Quality Control Samples					
Concentration (pg/mL)	3.000	15.00	90.00	240.0	450.0	450.0 Dilution=2
Inter day Precision (% CV)	8.34	4.45	4.31	3.85	3.55	3.12
Inter day Accuracy (% Actual)	97.03	102.33	101.61	101.13	101.47	99.6

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Bioequivalence Study MGR001-1016										
SA										
Parameter	Standard Curve Samples									
Concentration (pg/mL)	1.000	2.000	3.000	10.00	30.00	100.0	300.0	400.0	500.0	600.0
Inter day Precision (% CV)	2.54	4.51	4.18	2.65	3.19	2.11	2.22	2.23	2.19	2.15
Inter day Accuracy (% Actual)	102.70	97.90	96.03	96.45	98.53	100.30	102.67	102.38	101.46	101.52
Linearity	0.9934 - 0.9998 [^]									
Linearity Range (pg/mL)	1.000 - 600.0									
Sensitivity/LOQ (pg/mL)	1.000									

[^] The applicant reported the linearity as 0.9934 – 0.9995. The reviewer corrected the linearity based on the bioanalytical report.

Bioequivalence Study MGR001-1016						
SA						
Parameter	Quality Control Samples					
Concentration (pg/mL)	3.000	15.00	90.00	240.0	450.0	450.0 Dilution=2
Inter day Precision (% CV)	6.02	4.21	3.94	3.71	3.45	4.53
Inter day Accuracy (% Actual)	98.03	100.67	101.23	101.92	102.11	101.2

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☒ Yes (please see reviewer's comments below) ☐ No
Were 20% of chromatograms included?	☒ Yes ☐ No
Were chromatograms serially or randomly selected?	☒ serially (Run IDs 11-23, which includes subjects with randomization #s (b) (6) ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No
Were the chromatograms submitted by the applicant acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

5.1.1.3.3 Reanalysis of Study Samples

Study Number MGR001-1016 (Pivotal BE study with MGR001 250/50 mcg vs Advair® Diskus® 250/50 mcg)								
Repeat Analysis Results for FP								
Additional Information in Table 6A of Appendix 2 of the MGR001-1016 Bioanalytical Study Report								
Reason why assay was repeated ¹	Number of Samples Reanalyzed				Number of Recalculated Values used after Reanalysis			
	Actual Number		% of Total Assays		Actual Number		% of Total Assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Reason 1	2	4	0.07%	0.15%	2	4	0.07%	0.15%
Reason 2	2	0	0.07%	0.00%	2	0	0.07%	0.00%
Reason 3	1	2	0.04%	0.07%	1	2	0.04%	0.07%
Reason 4	0	2	0.00%	0.07%	0	2	0.07%	0.07%
Reason 5	1	0	0.04%	0.00%	0	0	0.00%	0.00%
Total	6	8	0.22%	0.30%	5	8	0.19%	0.30%

- ¹ Reason 1 = Abnormal Internal Standard (IS) Response
Reason 2 = Documented Sample Processing Error – lost during solid phase extraction procedure
Reason 3 = Documented Sample Processing Error – lost during assay procedure due to broken/cracked vial
Reason 4 = Documented Sample Processing Error – insuff. volume from single aliquot, aliquots combined for reassay
Reason 5 = Documented Sample Processing Error – insufficient volume to assay sample at full volume

Study Number MGR001-1016 (Pivotal BE study with MGR001 250/50 mcg vs Advair® Diskus® 250/50 mcg)								
Repeat Analysis Results for SA								
Additional Information in Table 6B of Appendix 2 of the MGR001-1016 Bioanalytical Study Report								
Reason why assay was repeated ¹	Number of Samples Reanalyzed				Number of Recalculated Values used after Reanalysis			
	Actual Number		% of Total Assays		Actual Number		% of Total Assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Reason 1	2	0	0.07%	0.00%	2	0	0.07%	0.00%
Reason 2	23	23	0.85%	0.85%	22	23	0.82%	0.85%
Reason 3	1	2	0.04%	0.07%	1	2	0.04%	0.07%
Reason 4	5	11	0.19%	0.41%	5	11	0.19%	0.41%
Reason 5	0	2	0.00%	0.07%	0	2	0.00%	0.07%
Reason 6	1	0	0.04%	0.00%	0	0	0.00%	0.00%
Total	32	38	1.19%	1.41%	30	38	1.11%	1.41%

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- ¹ Reason 1 = Documented Sample Processing Error – lost during solid phase extraction procedure
Reason 2 = Abnormal Internal Standard (IS) Response
Reason 3 = Documented Sample Processing Error – lost during assay procedure due to broken/cracked vial
Reason 4 = Sample Outside Limits of Curve Range (ALQ)
Reason 5 = Documented Sample Processing Error – insuff. volume from single aliquot, aliquots combined for reassay
Reason 6 = Documented Sample Processing Error – insufficient volume to assay sample at full volume

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	For a few repeat analysis, it is difficult to tell based on the raw data whether they are identified per SOP or not. However, they are not expected to affect the study outcome (please see details in the reviewer's comments below).
If no, is recalculation of PK parameters necessary?	No, as they are not expected to affect the study outcome (please see reviewer's comments below).
Did recalculation of PK parameters change the study outcome?	N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	N/A

Comments on Bioanalytical Results: Incomplete

General Comments

- Prior to biosample analysis, the applicant conducted 6 runs of qualification experiment accuracy and precision (Runs 1, 3, 5-8), 1 run of QC pool qualification (Run 2), 1 run of simulated study run (Run 4), and 1 run of qualification experiment accuracy and precision reinjection (Run 9). According to raw data provided, no biosamples were pre-analyzed in these runs.

Comments for **FP**

- The incurred sample reanalysis (ISR) was performed on 9.55% of the samples (257 out of 2692³⁹ total samples). For each subject period, the applicant selected at least one sample near C_{max} and one sample in the elimination phase, with exception of Subject (b) (6) Period 1, from whom no ISR sample was selected for near C_{max}. It is noted that 99.61% (256 out of 257) of the ISR were within 20% of the mean of original and repeat results. Therefore, even the if an additional ISR sample was included for the above mentioned subject period for near C_{max} at least 99.22% (256 out of 258) of the ISR samples would still be within the acceptance criteria. Therefore, the reviewer considers the ISR results acceptable.

Repeat Analysis

Abnormal Internal Standard (IS) Response

Three (3) samples were reassayed due to abnormal IS response. SOP MGWBIO-SOP-BIO-GEN-0020 states: “For each batch run, the mean internal standard peak area (or height) of all acceptable calibrators will be calculated. A clinical sample having an internal standard peak area (or height) < 40% or > 180% of this mean will be re-assayed due to abnormal internal standard response.” Additionally, according to the aforementioned SOP, samples reassayed due to abnormal IS response should be reassayed in singlet. The reviewer verified that reassay and final reporting of all samples were in accordance with SOP.

Documented Sample Processing Error – lost during solid phase extraction procedure

Two (2) samples were reassayed due to documented sample processing error – lost during solid phase extraction procedure. SOP MGWBIO-SOP-BIO-GEN-0020 states that “documented sample processing error or analyst error” should be reassayed in singlet, but did not specify detailed conditions that could be classified as sample processing error. According to the numerical raw data, both samples [Subject (b) (6) Period 2, 3 minutes and 1 hr] had 0 response for both analyte and IS. Therefore, the reviewer considers these samples identified per SOP. The reviewer also verified that final reporting of these samples were in accordance with SOP.

³⁹ According to the bioanalytical report, 1 sample (Subject (b) (6) Period 1, 2 minutes) did not have sufficient volume to be analyzed at full assay volume (800 µL). Consequently, it was not analyzed and does not have reported value. The reviewer verified from the SAS .xpt dataset that this sample was reported as missing value.

Documented Sample Processing Error – lost during assay procedure due to broken/cracked vial

Three (3) samples were reassayed due to documented sample processing error – lost during assay procedure due to broken/cracked vial. According to the numerical raw data, all of these 3 samples either had 0 response for both analyte and IS [Subject (b) (6), Period 2, 15 minutes; and Subject (b) (6) Period 2, 2 minutes], or had 0 response for IS and <1% analyte response as compared to adjacent samples [Subject (b) (6) Period 2, 2 hrs]. Therefore, the reviewer considers these samples identified per SOP. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Documented Sample Processing Error – insufficient volume from single aliquot, aliquots combined for reassay

Two (2) samples were reassayed due to documented sample processing error – insufficient volume from single aliquot, aliquots combined for reassay. According to the numerical raw data, one [Subject (b) (6) Period 1, 2 minutes] of these 2 samples had 0 response for both analyte and IS. Therefore, the reviewer considers this sample identified per SOP. The reviewer also verified that final reporting of this sample was in accordance with SOP.

However, for Subject (b) (6) Period 1, 2 minutes, according to the numerical raw data, the IS response was acceptable (within 40%-180% of mean IS of its run), and the analyte response is 227 [analyte response for the immediate precedent sample (pre-dose sample) is 0, and for the succeeding sample (4 minutes sample, please note that the 3 minutes sample of this period is missing) is 47172]. Since this sample is at the absorption phase, it is difficult to tell based on the raw data whether this sample was identified per SOP.

However, since this sample is at the early absorption phase [the applicant considered original concentration not reportable, but according to the reviewer's calculation based on the raw data, the original concentration is BLOQ (0.1578 pg/mL). The reassay concentration is 5.938 pg/mL. Both of these values are markedly smaller than C_{max} (147.1 pg/mL) of the corresponding subject period], and the study is not marginal, this sample reassay is not expected to affect the study outcome. Therefore, the reviewer will not pursue this issue further. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Documented Sample Processing Error – insufficient volume to assay sample at full volume

One (1) sample [Subject (b) (6) Period 1, 2 minutes] was reassayed due to documented sample processing error – insufficient volume to assay sample at full volume. According to the numerical raw data, this sample had 0 analyte response, and its IS response was acceptable (within 40%-180% of mean IS of its run). The applicant stated that the reassay value is also not reportable due to insufficient volume to reassay

sample at full volume. Therefore, the final concentration of this sample is reported as “.” in the SAS .xpt file.

Based on the plasma concentration vs time plot of this subject, this sample is not expected to affect C_{max}. In addition, the study is not marginal. Therefore, reporting of this sample as “.” is not expected to affect the study outcome, hence the reviewer will not pursue this issue further.

Comments for SA

- For reassay of samples above ULOQ, the applicant used 2-fold dilution, which was covered by the dilution integrity study in pre-study method validation. It is noted that the applicant did not include dilution QCs (DQCs) in the analytical run. Instead, they diluted high QCs (450 pg/mL) 2-fold with K2EDTA human plasma according to SOP MGWBIO-SOP-BIO-GEN-0020. However, since the method validation guidance did not require DQC in the reassay run, the reviewer will not pursue this issue further.
- ISR was performed on 9.55% of the samples (257 out of 2692⁴⁰ total samples). For each subject period, the applicant selected at least one sample near C_{max} and one sample in the elimination phase, with exception of Subject (b) (6), Period 1, from whom no ISR sample was selected for near C_{max}. It is noted that 99.61% (256 out of 257) of the ISR were within 20% of the mean of original and repeat results. Therefore, even the if an additional ISR sample was included for the above mentioned subject period for near C_{max} at least 99.22% (256 out of 258) of the ISR samples would still be within the acceptance criteria. Therefore, the reviewer considers the ISR results acceptable.

Repeat Analysis

Documented Sample Processing Error – lost during solid phase extraction procedure

Two (2) samples were reassayed due to documented sample processing error – lost during solid phase extraction procedure. According to the numerical raw data, both samples [Subject (b) (6) Period 2, 3 minutes and 1 hr] had 0 response for both analyte and IS. Therefore, the reviewer considers these samples identified per SOP. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Abnormal Internal Standard (IS) Response

Forty-six (46) samples were reassayed due to abnormal IS response. The reviewer verified that reassay and final reporting of all samples were in accordance with SOP.

⁴⁰ According to the bioanalytical report, 1 sample (Subject (b) (6) Period 1, 2 minutes) did not have sufficient volume to be analyzed at full assay volume (800 µL). Consequently, it was not analyzed and does not have reported value. The reviewer verified from the SAS .xpt dataset that this sample was reported as missing value.

Documented Sample Processing Error – lost during assay procedure due to broken/cracked vial

Three (3) samples were reassayed due to documented sample processing error – lost during assay procedure due to broken/cracked vial. According to the numerical raw data, all of these 3 samples [Subject (b) (6) Period 2, 15 minutes; Subject (b) (6) Period 2, 2 minutes; and Subject (b) (6) Period 2, 2 hrs] had 0 response for both analyte and IS. Therefore, the reviewer considers these samples identified per SOP. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Sample Outside Limits of Curve Range (ALQ)

Sixteen (16) samples were reassayed due to ALQ. Based on the 3/22/2018 DRL response, these samples were correctly identified based on pre-established criterion in the SOP. The reviewer verified that after adjusting for dilution factor, all reassayed values of these samples were either higher than the highest CS (600.0 pg/mL) (all 16 samples except 2 samples as detailed below), or higher than 85% of the highest CS [Subject (b) (6) Period 1, 5 minutes (594.4 pg/mL); and Subject (b) (6) Period 2, 3 minutes (591.9 pg/mL)]. Final reporting of these samples were in accordance with SOP.

Documented Sample Processing Error – insufficient volume from single aliquot, aliquots combined for reassay

Two (2) samples were reassayed due to documented sample processing error – insufficient volume from single aliquot, aliquots combined for reassay. According to the numerical raw data, one [Subject (b) (6), Period 1, 2 minutes] of these 2 samples had 0 response for both analyte and IS. Therefore, the reviewer considers this sample identified per SOP. The reviewer also verified that final reporting of this sample was in accordance with SOP.

However, for Subject (b) (6) Period 1, 2 minutes, according to the numerical raw data, the IS response was acceptable (within 40%-180% of mean IS of its run), and the analyte response is 0 [analyte response for the immediate precedent sample (pre-dose sample) is 0, and for the succeeding sample (4 minutes sample, please note that the 3 minutes sample of this period is missing) is 1472457]. Since this sample is at the absorption phase, it is difficult to tell based on the raw data whether this sample was identified per SOP. It is also noted that this sample is 3 time points before current Tmax of 5 minutes, thus it might affect Cmax. However, since this subject is excluded from the reviewer's statistical analysis due to a missing sample [Subject (b) (6) Period 1, 3 minutes] that might affect Cmax, and the study outcome is not affected (please see details in Section 5.1.1.2.4), the reviewer will not pursue this issue further.

Documented Sample Processing Error – insufficient volume to assay sample at full volume

One (1) sample [Subject (b) (6) Period 1, 2 minutes] was reassayed due to documented sample processing error – insufficient volume to assay sample at full volume. According to the numerical raw data, this sample had 0 analyte response, and its IS response was acceptable (within 40%-180% of mean IS of its run). Since this sample is at the absorption phase, it is difficult to tell based on the raw data whether this sample was identified per SOP. The applicant stated that the reassay value is also not reportable due to insufficient volume to reassay sample at full volume. Therefore, the final concentration of this sample is reported as “.” in the SAS .xpt file. It is noted that this sample is 3 time points before current Tmax of 5 minutes, thus it might affect Cmax. However, since this subject is excluded from the reviewer’s statistical analysis due to missing samples [Subject (b) (6) Period 1, 3 minutes] that might affect Cmax, and the study outcome is not affected (please see details in Section 5.1.1.2.4), the reviewer will not pursue this issue further.

5.1.1.4 Pharmacokinetic Results

5.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters – Reviewer’s Results

Fasting Bioequivalence Study, Study No. MGR001-1016									
Parameter (units)	Test				Reference				T/R
	Mean	% CV	Min	Max	Mean	% CV	Min	Max	
FP									
AUC _{0-t} (hr *pg/ml)	1351.092	32.40	631.71	2574.04	1256.763	30.16	364.07	2070.23	1.08
AUC _∞ (hr *pg/ml)	1412.413	32.20	651.41	2639.63	1309.047	30.11	377.02	2192.68	1.08
C _{max} (pg/ml)	172.347	31.29	79.96	308.80	172.245	30.48	64.39	292.20	1.00
T _{max} * (hr)	1.003	.	0.08	3.01	1.001	.	0.33	3.01	1.00
K _{el} (hr ⁻¹)	0.060	15.77	0.04	0.08	0.063	17.60	0.04	0.09	0.95
T _{1/2} (hr)	11.873	16.35	8.50	17.58	11.309	18.51	7.86	17.33	1.05
SA									
AUC _{0-t} (hr *pg/ml)	734.232	47.12	207.57	2130.38	723.700	47.49	111.13	2035.82	1.01
AUC _∞ (hr *pg/ml)	769.372	47.25	234.14	2262.66	759.195	47.34	131.51	2167.46	1.01
C _{max} (pg/ml)	326.339	44.17	109.70	740.80	350.393	44.70	65.75	879.80	0.93
T _{max} * (hr)	0.083	.	0.05	1.01	0.083	.	0.05	2.01	1.00
K _{el} (hr ⁻¹)	0.059	16.09	0.04	0.09	0.059	16.91	0.04	0.09	1.00
T _{1/2} (hr)	11.999	14.58	8.08	16.67	11.980	15.21	7.30	16.30	1.00

* T_{max} values are presented as median, range

5.1.1.4.2 Geometric Means and 90% Confidence Intervals - Applicant Calculated

MGR001 250/50 MCG AND ADVAIR® DISKUS® 250/50 MCG						
Dose: 3 Inhalations; Total Dose 750/150 mcg FP/salmeterol						
Number of Subjects Completed = 63						
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study Number MGR001-1016): Fluticasone Propionate						
Parameter	Test	N	Reference	N	Ratio*	90% C.I.**
AUClast (pg h/mL)	1251	61	1164	61	1.0744	102.11% - 113.06%
AUCinf (pg.h/mL)	1323	59	1211	56	1.0925	103.62% - 115.18%
C _{max} (pg/mL)	164.2	61	162.7	61	1.0092	95.01% - 107.20%
Fasting Bioequivalence Study (Study Number MGR001-1016): Salmeterol						
Parameter	Test	N	Reference	N	Ratio*	90% C.I.**
AUClast (pg h/mL)	641.2	61	623.3	61	1.0287	98.88% - 107.02%
AUCinf (pg.h/mL)	672.4	61	661.2	60	1.0168	98.12% - 105.38%
C _{max} (pg/mL)	296.2	61	317.4	61	0.9334	86.75% - 100.43%

*Ratio (A/B) = e^[LSMEAN of LNA - LSMEAN of LNB]; **Used Natural Log Transformed Parameter

5.1.1.4.3 Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder							
3 x 250/50 mcg							
Fasting Bioequivalence Study, Study No. MGR001-1016, N=63 (Male=29 and Female=34)							
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
FP							
Parameter (units)	Test	N	Reference	N	Ratio	90% C.I.	
Group 1, 2 and 3 (trt*troupe = 2)							
LAUCT (hr *pg/ml)	1278.49	59*	1190.68	59*#	1.07	101.85	113.20
LAUCI (hr *pg/ml)	1338.01	59*	1240.91	59*#	1.08	102.37	113.58
LCMAX (pg/ml)	165.06	59*	163.92	59*#	1.01	94.76	107.00
SA							
Parameter (units)	Test	N	Reference	N	Ratio	90% C.I.	
Group 1, 2 and 3 (trt*troupe = 2)							
LAUCT (hr *pg/ml)	677.89	49*^	659.47	49*^#	1.03	98.59	107.17
LAUCI (hr *pg/ml)	710.94	49*^	694.03	49*^#	1.02	98.38	106.66
LCMAX (pg/ml)	295.53	49*^	313.07	49*^#	0.94	87.04	102.38

* Subjects (b) (6) were excluded by the reviewer due to dosing deviations.

^ Subjects (b) (6) were excluded by the reviewer due to missing samples that potentially affect C_{max}.

The last time point (48 hrs) for Subjects (b) (6) Period 2 (reference treatment) were treated as missing by the reviewer due to protocol deviations related to centrifugation settings.

5.1.1.4.4 Additional Information for the Study

FP

Root Mean Square Error	AUCt: 0.1711 AUCi: 0.1683 Cmax: 0.1967
Is there a Tmax difference between Test and Reference? If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).	☐ Yes ☒ No
Were the subjects dosed in groups? If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?	☒ Yes ☐ No
Are there measurable drug concentrations at 0 hr? If yes, please comment (and take necessary action, if needed).	☐ Yes ☒ No
Are there first measurable drug concentration as Cmax? If yes, please comment.	☐ Yes ☒ No
Are there Cmax at the first time point? If yes, is the study (sample) design adequate?	☐ Yes ☒ No

Ratio of AUC0-t/AUC∞				
Treatment	n	Mean	Minimum	Maximum
Test	59	0.96	0.89	0.99
Reference	59	0.96	0.90	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.				N/A

Group Analysis Consideration

Is the drug product highly variable drug? If yes, please check the current DB policy to evaluate group effect: \\cdsnas\ogds11\firmnz^{(b) (4)}controls\98-392a.doc	☐ Yes ☒ No
If no, is the group*treatment interaction term statistically significant at alpha=0.1 (i.e., p < 0.1)? If p ≥ 0.1, no need to consider group effect.	☐ Yes ☒ No ☐ N/A
If yes, did you use the statistical model with group effect included?	☐ Yes ☐ No ☒ N/A
If yes, specify which PK parameter(s).	N/A
If yes (i.e. group*treatment term is significant), was each group analyzed separately?	☐ Yes ☐ No ☒ N/A
If each group was analyzed, did any individual	☐ Yes ☐ No ☒ N/A

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group meet BE criteria?	
If none of individual group meets the BE criteria, did you have other justifications for accepting the data? If yes, please provide justifications.	☐ Yes ☐ No ☒ N/A

SA

Root Mean Square Error	AUCt: 0.1221 AUCi: 0.1181 Cmax: 0.2375
Is there a Tmax difference between Test and Reference? If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).	☐ Yes ☒ No
Were the subjects dosed in groups? If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?	☒ Yes ☐ No
Are there measurable drug concentrations at 0 hr? If yes, please comment (and take necessary action, if needed).	☐ Yes ☒ No
Are there first measurable drug concentration as Cmax? If yes, please comment.	☒ Yes [Subject (b) (6) Period 1, reference treatment, Cmax at the 1 st post dose actual time point of 2.5 minutes. Please see reviewer's comments below] ☐ No
Are there Cmax at the first time point? If yes, is the study (sample) design adequate?	☒ Yes (same as the subject above. Please see reviewer's comments below) ☐ No

Ratio of AUC _{0-t} /AUC _∞				
Treatment	n	Mean	Minimum	Maximum
Test	49	0.95	0.89	0.99
Reference	49	0.95	0.85	0.98
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.			N/A	

Group Analysis Consideration

Is the drug product highly variable drug? If yes, please check the current DB policy to evaluate group effect: \cdsnas\logds11\firmnz (b) (4) controls\98-392a.doc	☐ Yes ☒ No
If no, is the group*treatment interaction term statistically significant at alpha=0.1 (i.e., p < 0.1)? If p ≥ 0.1, no need to consider group effect.	☐ Yes ☒ No ☐ N/A
If yes, did you use the statistical model with group	☐ Yes ☐ No ☒ N/A

effect included?	
If yes, specify which PK parameter(s).	N/A
If yes (i.e. group*treatment term is significant), was each group analyzed separately?	☐ Yes ☐ No ☒ N/A
If each group was analyzed, did any individual group meet BE criteria?	☐ Yes ☐ No ☒ N/A
If none of individual group meets the BE criteria, did you have other justifications for accepting the data? If yes, please provide justifications.	☐ Yes ☐ No ☒ N/A

Comments on PK results: Adequate

- The reviewer specified linear range used to calculate Kel; therefore, SAS code CALKE was used for statistical analysis.
- The subjects were dosed in 3 groups; therefore, analysis of variance was performed with the group effect incorporated in the model.

For FP and SA, there was no statistically significant difference ($p > 0.1$) in terms of treatment*group for LnAUC_t ($p = 0.7971$ for FP, $p = 0.3402$ for SA), LnAUC_i ($p = 0.7312$ for FP, $p = 0.3603$ for SA), LnC_{max} ($p = 0.1982$ for FP, $p = 0.2732$ for SA). All of the subjects in this study were recruited from the same geographic region and were dosed at the same clinical facility within 3 days. Accordingly, the reviewer combined three groups for statistical analysis as per current DB practice⁴¹.

- There are differences between the applicant and the reviewer calculated geometric means and 90% confidence intervals for AUC_{0-t}, AUC_∞ and C_{max} (Sections 5.1.1.4.2 and 5.1.1.4.3). It should be noted that the reviewer excluded subjects that experienced dosing error, had missing samples that could potentially affect C_{max}, and samples with protocol deviations in centrifugation settings. In addition, according to the study report, the applicant's AUC was calculated by the linear-log trapezoidal method, whereas the Agency's SAS code used the linear trapezoidal method. Moreover, the reviewer also suspects that the applicant did not incorporate group effect in their calculation, as leaving out the group effect (let trtgroup=" " instead of "2" in SAS code) using the applicant's dataset leads to exactly the same results as applicant-calculated C_{max} (verified by the reviewer, results not shown).

⁴¹ V:\FIRMSNZ (b) (4)\CONTROLS\98-392A.doc

- The study still meet BE acceptance criteria after statistical analysis was completed under the assumption that all groups are homogenous and can therefore be treated as a single group for statistical analysis purposes⁴² (please see table below).

trtgroup=null

Parameter	Least Squares	Geometric Mean	Ratio	90% Confidence Intervals	
	Test	Reference	(T/R)	Lower	Upper
FP					
LAUCT (hr *pg/ml)	1278.82	1194.00	1.07	101.62	112.88
LAUCI (hr *pg/ml)	1337.94	1243.86	1.08	102.16	113.26
LCMAX (pg/ml)	164.35	163.61	1.00	94.47	106.81
SA					
LAUCT (hr *pg/ml)	672.67	653.68	1.03	98.58	107.42
LAUCI (hr *pg/ml)	705.47	687.95	1.03	98.38	106.89
LCMAX (pg/ml)	296.58	315.51	0.94	86.38	102.29

- For SA, 1 subject from the reference treatment group had the first measurable drug concentration as C_{max} as well as first post-dose time point as C_{max}. However, it should be noted that the applicant included sufficient PK sampling times to cover the expected T_{max} range per the RLD labeling (i.e. about 5 min for SA and 1 to 2 hrs for FP). The applicant included early time points (2, 3, 4, 5, 10, 15 min) in addition to 4 more time points within the first hour. This time point selection is in line with *Draft Guidance for Industry – Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted under an ANDA* (posted Dec 2013).
- T_{max} (hr) for the test and reference product are provided below:

FP

	Test	Reference	Ratio
Median	1.003	1.001	1.00
Min	0.08	0.33	0.24
Max	3.01	3.01	1.00

SA

	Test	Reference	Ratio
Median	0.083	0.083	1.00
Min	0.05	0.05	1.00
Max	1.01	2.01	0.50

As shown in the stick plot below, the T_{max} values for the test and reference products are considered comparable for FP and SA.

⁴² Because the study met the following criteria, it is not necessary to include group*treatment interaction in the statistical model: 1) the clinical study took place at once site; 2) all subjects were recruited from the same enrollment pool; 3) all of the subjects had similar demographics and; 4) all enrolled subjects were randomly assigned to treatment groups at study outset. Therefore, statistical analysis was performed with the group*treatment interaction set to null.



- The 90% confidence intervals for FP and SA are within the acceptable limits of 80%-125%.

5.1.1.5 Overall Comment

Was the fasting bioequivalence study acceptable? Acceptable.

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

FP					
Time (hr)	Test (n= 59)		Reference (n= 59)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.03	27.08	108.96	26.05	105.00	1.04
0.05	35.11	103.93	35.66	95.46	0.98
0.07	45.90	112.35	49.64	76.44	0.92
0.08	54.37	95.63	61.58	76.00	0.88
0.17	68.16	53.07	69.88	50.44	0.98
0.25	89.88	49.65	96.30	50.72	0.93
0.33	116.38	44.58	117.54	42.95	0.99
0.50	135.92	32.99	132.23	41.11	1.03
0.75	150.69	31.28	149.78	35.45	1.01
1.00	155.06	33.17	155.89	33.65	0.99
1.50	151.57	33.16	147.09	30.56	1.03
2.00	138.43	33.98	134.41	30.80	1.03
3.00	119.89	33.69	114.97	31.18	1.04
4.00	101.63	36.41	97.25	31.84	1.05
6.00	64.04	35.83	59.89	31.98	1.07
8.00	49.43	38.97	45.96	34.52	1.08
12.00	29.56	39.87	26.83	35.93	1.10
24.00	11.73	39.51	9.97	41.32	1.18
36.00	5.64	41.11	4.78	41.43	1.18
48.00	3.48	43.18	2.97	46.48	1.17

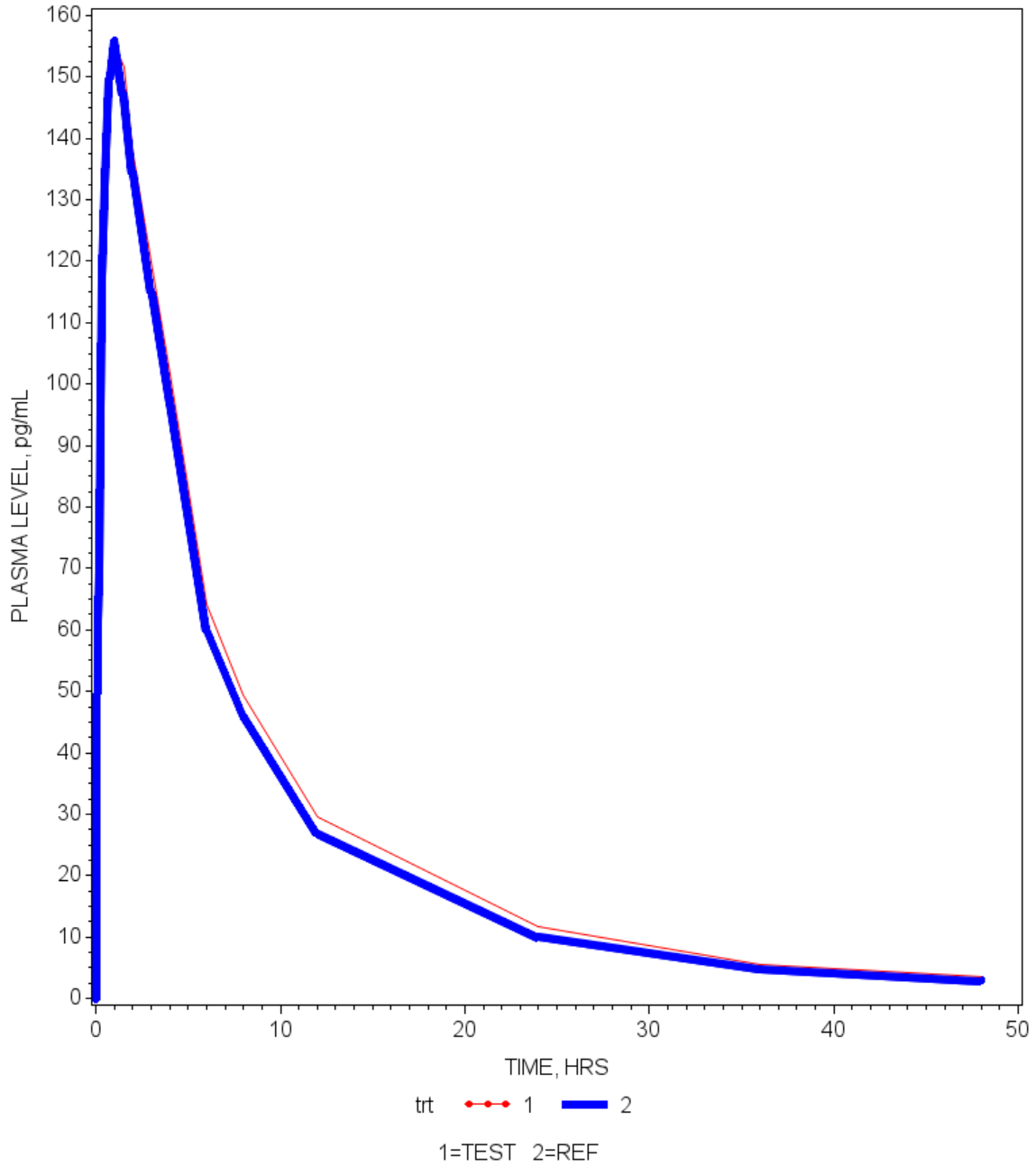
ANDA 208891
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SA					
Time (hr)	Test (n= 49)		Reference (n= 49)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.03	189.30	51.27	220.82	61.83	0.86
0.05	267.78	51.10	293.31	50.81	0.91
0.07	305.33	48.53	332.15	45.38	0.92
0.08	317.41	43.81	337.92	44.94	0.94
0.17	203.53	36.66	212.74	37.44	0.96
0.25	154.05	34.36	152.45	36.01	1.01
0.33	128.28	31.66	126.54	32.61	1.01
0.50	104.30	31.19	105.70	35.33	0.99
0.75	91.80	34.98	89.43	37.33	1.03
1.00	89.44	40.49	86.96	43.11	1.03
1.50	82.54	49.10	78.09	47.08	1.06
2.00	71.19	50.38	69.39	51.14	1.03
3.00	52.80	54.38	50.81	53.20	1.04
4.00	40.22	58.25	39.45	56.25	1.02
6.00	29.59	58.18	28.36	53.51	1.04
8.00	21.77	53.66	21.66	55.07	1.00
12.00	14.26	60.10	14.15	58.75	1.01
24.00	7.16	54.93	7.12	56.46	1.01
36.00	3.08	61.34	3.09	65.14	1.00
48.00	1.80	72.82	1.80	72.08	1.00

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

FP

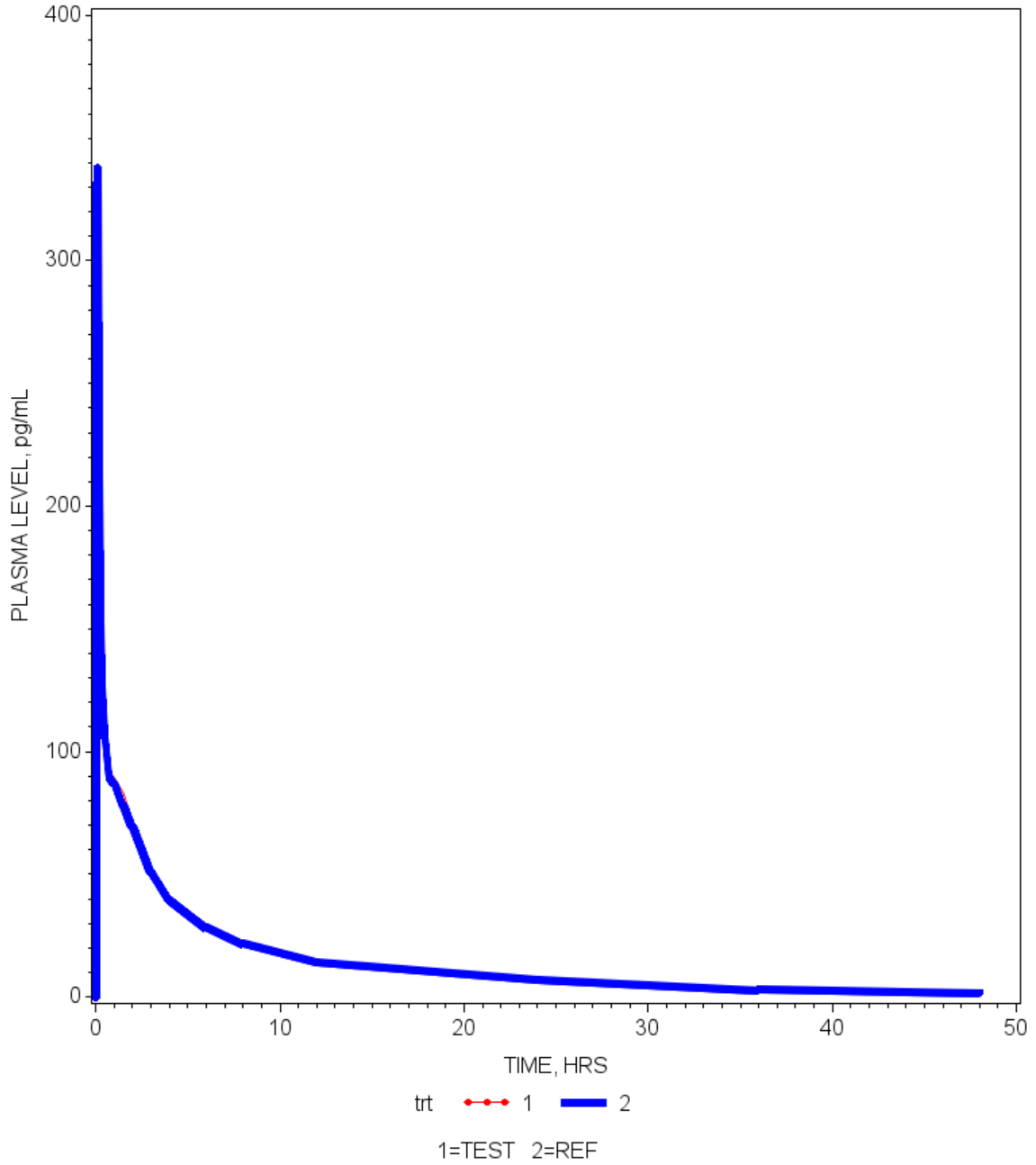
PLASMA Fluticasone Propionate LEVELS
Fluticasone Propionate and Salmeterol Xinafoate DPI, ANDA 208891
UNDER Fasting CONDITIONS
DOSE= 3 x 250/50 MCG



ANDA 208891
Single-Dose Fasting Bioequivalence Study Review

SA

PLASMA Salmeterol LEVELS
Fluticasone Propionate and Salmeterol Xinafoate DPI, ANDA 208891
UNDER Fasting CONDITIONS
DOSE= 3 x 250/50 MCG



Comments:

- In addition to the studies reviewed in the original submission, the applicant submitted additional studies (i.e. in vitro bridging studies to support (b) (4), and repeat PK BE study for the 250/50 mcg strength). These studies used new test

⁴⁵ According to the firm's 1/12/2017 ECD response [GS Review: ANDA 208891, Response to ECD/Bioequivalence, 1/12/2017 (Module 1.2\Cover Letter..., p. 17 of 21)], the emitted dose values reported in the COA of 102.0% for FP and 101.0% for SA contained a minor rounding error. The correct values are 101.6% for FP and 100.9% for SA.

and reference batches (**bolded** in the table above), and their batch information is added to the batch information table above, together with other batches that was used in studies submitted in the original submission.

The reviewer's comments below only talks about these new batches. For information regarding batches used in the original submission, please refer to the original BE review.

- According to CC13-0422⁴⁶, the Agency recommends the applicant to use same batches of the reference and the test for their proposed clinical program and for in vitro BE studies, whenever feasible.

For the repeat PK BE study for the 250/50 mcg strength (MGR001-1016), the test lot (lot #60000354) used in this study was not tested in in vitro bridging or pivotal in vitro BE studies. The acceptability of this test batch being used in the PK BE study is deferred to Drug Product.

The reference lot (lot #6ZP6787) used in the repeat PK BE study was used in in vitro bridging studies.



⁴⁶ <\\cdsnas\OGDS6\CONTROLS\2013-docs\13-0422.pdf>, p. 18 of 28.

⁴⁷ V:\Science Group\Master Files BE Posting\Fluticasone Propionate_Salmeterol Xinafoate_021077\ Fluticasone Propionate_Salmeterol Xinafoate_21077_RC09-13.doc, p. 12 of 62.



⁴⁸ GS Review: ANDA 208891, Quality/Response To Information Request, 3/23/2018 (Module 1.2\Cover Letter – 0034..., p. 56 of 66).

5.2.1.2 Device Comparability

Reviewer's Comments:

1. As mentioned in the original BE review, the device resistance for the test device is almost (b) (4)% higher than that of RLD (please see table below).



To support the device resistance difference, the applicant provided the following studies based on pre-ANDA communications with the Agency (CC12-0731⁴⁹ and CC13-0422⁵⁰):

- i) Justification/data (e.g., comparisons of inspiratory flow rates or profiles generated by relevant patients for the test and reference DPIs) to support that this difference in the device resistance does not impact therapeutic equivalence of the proposed generic and the RLD.

In CC12-0731⁵¹, the Agency stated that data from patients (or from BE studies in healthy volunteers) showing similarity of flow rates would be helpful in the Agency's evaluation. The applicant was also advised to consider flow rate dependency of product performance. If there is little flow rate dependency, this mitigates impact of difference in device resistance.

- ii) The SAC and APSD results for MGR001 and RLD measured at flow rates that produce 4 kPa pressure drop⁵² across the corresponding inhalers.
- iii) Justification that the airflow resistance difference between MGR001 and RLD does not impact the usability of their proposed generic product. This was achieved by conduct of a patient survey as part of the clinical endpoint BE study to evaluate/capture patients' experience with the use of MGR001.

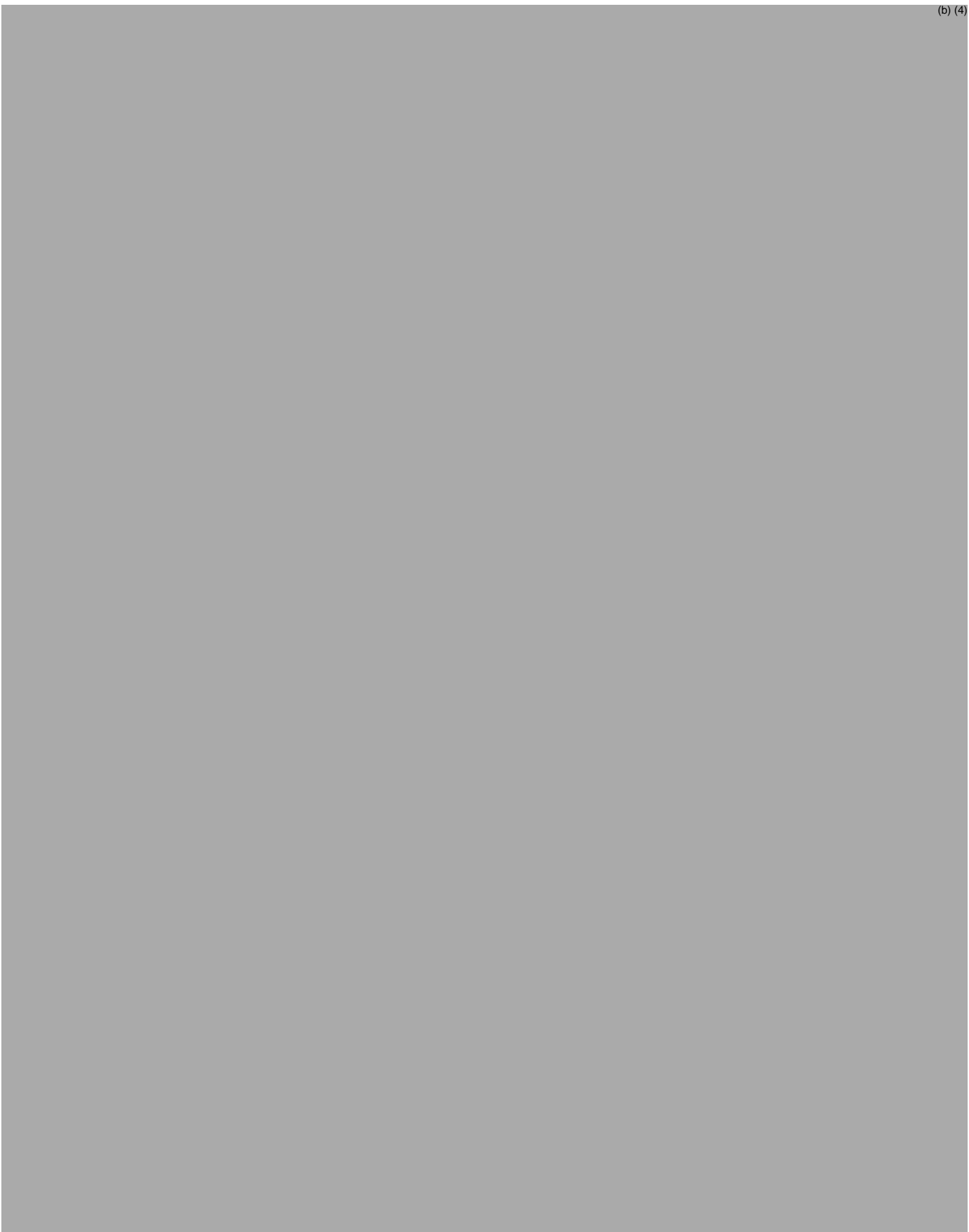


⁴⁹ [\\cdsnas\OGDS6\CONTROLS\2012-docs\12-0731.pdf](#), p. 13 of 34 (Question 3a).

⁵⁰ [\\cdsnas\OGDS6\CONTROLS\2013-docs\13-0422.pdf](#) p. 28 of 28.

⁵¹ [\\cdsnas\OGDS6\CONTROLS\2012-docs\12-0731.pdf](#), p. 33 of 34 (Question 8).

⁵² According to CC13-0422 (p. 21 of 28), "[i]n literature, it has been reported that patients produce around 4 kPa pressure drop across the inhaler when inhale against resistances typical for the marketed DPIs. Comparable emitted dose and fine particle mass measured at 4kPa pressure drop for both the devices can provide additional confirmation that resistance difference between the RLD and MGR001 is acceptable."



2. As mentioned in the executive summary and Section 3.2, the threshold analysis and the acceptability of the device orientation difference is evaluated by DCR.
3. As mentioned in the original BE review, according to Clinical Overview [Error! Bookmark not defined.](#), the CRC749 design development program resulted in the *clinical device* that was used in the in vivo flow profiling study and the majority of the pivotal clinical studies (i.e., pivotal PK BE studies MGR001-1006 and MGR001-1007 and pivotal clinical endpoint BE study MGR001-3001).

(b) (4)

the final *commercial device* which was used in the pivotal PK BE studies MGR001-1005, MGR001-1014, MGR001-1016 and the device robustness study MGR001-1010. It should be also noted that similar to pivotal PK BE studies and the clinical endpoint study, pivotal in vitro studies (as evaluated in Section 5.2.2) were using clinical device for the 100/50 mcg and 500/50 mcg strengths, and commercial device for the 250/50 mcg strength. The in vitro bridging studies (as evaluated in Section 5.2.4) were using commercial devices for all 3 strengths, according to the applicant's 3/23/2018 Information Request response to CMC.

(b) (4)

. According to internal communication with Drug Product reviewer, there is no concern regarding difference between the clinical and commercial devices.

The applicant's device comparability is **acceptable**.

5.2.2 Individual In Vitro-Test Reviews – Pivotal Studies

Reviewer’s note: Instead of recording actuation numbers, the applicant recorded “dose counter number” for each of their in vitro BE studies. Please note that dose counter number starts with 60, and counts down by 1 following each adequate actuation. Test performed on dose counter # 60 corresponds to actuation #1, and test performed on dose counter #59 corresponds to actuation #2, and so on. To be consistent with the applicant, the reviewer will refer to dose counter number instead of actuation number in this Section 5.2.2.

5.2.2.1 Single Actuation Content through Container Life – 100/50 mcg strength

5.2.2.1.1 Results Summary

Applicant’s results

Flow Rate (L/min)	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
30	FP	BoL	95.23	66.14	1.44	4.34	22.64	0.19
		EoL	95.11	88.74	1.07	4.34	12.88	0.34
		MoL	95.93	92.93	1.03	5.48	8.02	0.68
	Sal	BoL	47.52	32.16	1.48	1.79	11.08	0.16
		EoL	47.73	43.17	1.11	2.15	6.22	0.34
		MoL	47.93	45.19	1.06	2.59	4.01	0.65
60	FP	BoL	97.46	89.67	1.09	3.43	3.04	1.13
		EoL	99.30	99.74	1.00	4.08	5.28	0.77
		MoL	99.91	96.34	1.04	6.02	3.29	1.83
	Sal	BoL	48.70	43.73	1.11	1.74	1.55	1.12
		EoL	49.39	48.48	1.02	1.93	2.54	0.76
		MoL	49.51	46.78	1.06	2.70	1.53	1.76
90	FP	BoL	96.72	90.76	1.07	4.05	3.26	1.24
		EoL	97.73	101.42	0.96	4.14	3.97	1.04
		MoL	99.29	95.99	1.03	5.30	3.41	1.55
	Sal	BoL	48.50	44.36	1.09	1.94	1.50	1.29
		EoL	48.83	49.37	0.99	2.04	1.61	1.27
		MoL	49.43	46.76	1.06	2.37	1.54	1.55

Reviewer's Results – 30 L/min

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE													
		Dose Counter #	Mean				Variability (% CV)					Mean Ratio (I/R)	
			Drug Mass		% label claim		Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)	Geo (n=60)
			Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3				
FP													
BEG	Test	60	95.12	95.01	102.27	102.16	3.90	5.34	4.02	2.32	4.80	1.31	1.46
	Ref	60	72.78	65.27	78.26	70.18	20.54	6.15	50.50	22.09	31.69		
MID	Test	30	95.97	95.82	103.20	103.03	2.96	3.97	3.51	5.62	5.69	1.03	1.03
	Ref	30	93.16	92.79	100.17	99.78	5.02	5.07	13.43	0.94	8.76		
END	Test	1	94.96	94.86	102.11	102.00	3.90	3.16	4.82	3.23	4.70	1.06	1.07
	Ref	1	89.66	88.63	96.41	95.30	14.55	6.31	17.53	8.04	14.57		
SA													
BEG	Test	60	47.46	47.42	105.46	105.38	4.02	2.61	3.72	2.50	3.98	1.34	1.49
	Ref	60	35.46	31.76	78.80	70.57	20.90	5.98	50.83	22.10	31.85		
MID	Test	30	47.87	47.80	106.38	106.23	2.79	3.75	3.81	5.17	5.40	1.06	1.06
	Ref	30	45.24	45.06	100.53	100.13	4.95	4.69	13.91	1.07	8.94		
END	Test	1	47.55	47.50	105.67	105.56	3.93	2.87	4.62	3.00	4.49	1.09	1.10
	Ref	1	43.59	43.09	96.86	95.75	14.67	6.39	16.76	8.41	14.47		

Reviewer's Results – 60 L/min

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE													
		Dose Counter #	Mean				Variability (% CV)					Mean Ratio (T/R)	
			Drug Mass		% label claim		Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)	Geo (n=60)
			Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3				
FP													
BEG	Test	60	97.52	97.46	104.86	104.80	2.27	2.37	4.14	2.17	3.52	1.09	1.09
	Ref	60	89.73	89.67	96.48	96.42	2.22	3.06	3.81	1.92	3.45		
MID	Test	30	100.08	99.91	107.62	107.43	4.04	4.79	3.31	5.46	6.01	1.04	1.04
	Ref	30	96.28	96.23	103.53	103.47	3.51	2.34	3.04	1.90	3.34		
END	Test	1	99.39	99.30	106.87	106.78	2.96	2.50	4.39	2.87	4.11	1.00	1.00
	Ref	1	99.72	99.58	107.23	107.07	5.42	2.88	4.84	3.80	5.38		
SA													
BEG	Test	60	48.73	48.70	108.29	108.22	2.53	2.36	3.46	2.69	3.57	1.11	1.11
	Ref	60	43.76	43.74	97.25	97.19	2.22	3.22	3.93	2.08	3.60		
MID	Test	30	49.59	49.51	110.19	110.03	3.74	2.35	3.14	5.44	5.44	1.06	1.06
	Ref	30	46.73	46.71	103.85	103.80	3.47	2.48	2.30	1.97	3.18		
END	Test	1	49.43	49.39	109.84	109.76	3.03	2.32	3.44	3.13	3.91	1.02	1.02
	Ref	1	48.46	48.39	107.68	107.53	5.41	3.09	4.92	3.52	5.32		

Reviewer's Results – 90 L/min

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE													
		Dose Counter #	Mean				Variability (% CV)					Mean Ratio (I/R)	
			Drug Mass		% label claim		Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)	Geo (n=60)
			Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3				
FP													
BEG	Test	60	96.81	96.72	104.09	104.00	5.28	2.80	3.81	1.41	4.18	1.07	1.07
	Ref	60	90.82	90.76	97.65	97.59	2.84	2.60	3.61	2.39	3.59		
MID	Test	30	99.42	99.29	106.91	106.76	3.87	3.89	3.58	4.65	5.33	1.04	1.03
	Ref	30	96.05	95.99	103.28	103.22	2.70	3.78	2.61	2.26	3.55		
END	Test	1	97.82	97.73	105.18	105.09	4.14	3.60	4.38	1.72	4.23	0.96	0.96
	Ref	1	101.50	101.42	109.14	109.06	4.46	3.55	2.72	1.89	3.91		
SA													
BEG	Test	60	48.53	48.50	107.85	107.77	4.63	3.56	3.13	1.65	3.99	1.09	1.09
	Ref	60	44.39	44.36	98.64	98.58	2.37	2.22	3.26	2.57	3.38		
MID	Test	30	49.49	49.43	109.97	109.85	2.69	3.87	2.98	4.39	4.80	1.06	1.06
	Ref	30	46.79	46.76	103.97	103.91	2.08	3.49	2.08	2.45	3.28		
END	Test	1	48.87	48.83	108.61	108.52	3.60	4.12	4.26	1.69	4.18	0.99	0.99
	Ref	1	49.39	49.37	109.76	109.70	3.93	2.51	2.40	1.62	3.26		

Reviewer's Comments:

- As mentioned in the original BE review, the applicant repeated 14 samples using new devices, and each of these 14 samples were repeated for both FP and SA (please see table below). As detailed in the original BE review (for sample #s 1-13) or in Section 4.24 (for sample #14), the reviewer considers the applicant's reason for original sample rejection acceptable. However, it should be noted that the applicant only repeated the sample at the end lifestage in the above replacement devices. Therefore, these 2 samples containing lifestage data from diff

- erent devices were excluded from the reviewer’s statistical evaluation.

Number	Product	Batch number	Original inhaler number	Replacement inhaler number	Flow rate (L/min)	Reason for replacement
1	MGR001	631-003	9	112	30	Leak in sample collection tube, analysis halted.
2	Advair	4ZP3863	2	117	30	For ten instances of SAC, tested in the same chromatography run there were bracketing standard agreement failures and a standard preparation error. Hence no original analytical data was generated for these replicates.
3	MGR001	631-001	19	115	30	
4	MGR001	631-002	10	112	30	
5	MGR001	631-001	15	114	30	
6	MGR001	631-001	5	116	30	
7	MGR001	631-003	10	115	30	
8	Advair	4ZP3863	5	118	30	
9	MGR001	631-003	20	113	30	
10	Advair	5ZP8178	17	116	30	
11	MGR001	631-003	7	114	30	
12	Advair	5ZP8178	38	111	60	Leak in sample collection tube, analysis halted.
13	Advair	4ZP3863	39	111	60	
14	Advair	5ZP8397	40	180	60	

- The applicant’s and the reviewer’s results are not the same due to the reviewer’s exclusion of the above samples.
- Based on the applicant’s and reviewer’s results, the reference product had lower FP and SA emitted dose as compared to the test product at beginning lifestages at 30 L/min flow rate. It is also noted that RLD had high variability for FP under this condition. As mentioned in the original BE review, the applicant also noted the same observation, and considered it to reflect a considerable number of actuations with low dose emission from the RLD at this flow rate.⁵⁴ The reviewer checked study data for each individual unit, and found that RLD batch #5ZP8397 had multiple samples that had very low emitted dose for FP (b) (4) at beginning lifestages at 30 L/min flow rate.

5.2.2.1.2 In Vitro PBE Analysis

5.2.2.1.2.1 FP – 30 L/min

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 208891 SAC Test:

I. Summary

⁵⁴ GS Review: ANDA 208891, 12/29/2015 (Module 3.2.P.2)Pharmaceutical Development, p. 341 of 676).

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.4361
	CI:	-0.3648
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.1434
	CI:	-0.1145
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0 , PASS. For linearized theta P, if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	95.23	Mean: 81.27	Ratio: 117.18
		90% CI for ratio:	(111.5, 123.2)
(log scale) Mean:	4.56	Mean: 4.40	Diff: 0.16
(log scale) CV:	1.11	CV: 8.81	
(log scale) σ_{BT} :	0.039	σ_{BR} : 0.000	Ratio: -
(log scale) σ_{WT} :	0.032	σ_{WR} : 0.387	Ratio: 0.084
(log scale) σ_T :	0.051	σ_R : 0.387	Ratio: 0.131

5.2.2.1.2.2 FP – 60 L/min

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for

ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0075

CI: -0.0054
 Pass/Fail: PASS
 Constant-scaled: Point estimate: -0.0208
 CI: -0.0195
 Pass/Fail: PASS
 Overall Test Outcome: Pass/Fail: **PASS**

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (θ_P) of 2.0891. For linearized θ_P , if the upper bound of the confidence interval is < 0 , PASS. For linearized θ_P , if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	98.88	Mean: 95.07	Ratio: 104.01
		90% CI for ratio: (102.9,105.2)	
(log scale) Mean:	4.59	Mean: 4.55	Diff: 0.04
(log scale) CV:	1.03	CV: 1.33	
(log scale) σ_{BT} :	0.033	σ_{BR} : 0.000	Ratio: -
(log scale) σ_{WT} :	0.034	σ_{WR} : 0.060	Ratio: 0.558
(log scale) σ_T :	0.047	σ_R : 0.060	Ratio: 0.782

5.2.2.1.2.3 FP – 90 L/min

In Vitro PBE Analysis - Approximate Confidence Interval
 Using Moment-Based Simplified Parameter Estimates
 for

ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
 MIXED SCALING APPROACH
 Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled: Point estimate: -0.0078
 CI: -0.0061
 Pass/Fail: PASS
 Constant-scaled: Point estimate: -0.0216
 CI: -0.0207
 Pass/Fail: PASS
 Overall Test Outcome: Pass/Fail: **PASS**

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0 , PASS. For linearized theta P, if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	97.91	Mean: 95.96	Ratio: 102.03
		90% CI for ratio: (100.9,103.1)	
(log scale) Mean:	4.58	Mean: 4.56	Diff: 0.02
(log scale) CV:	1.04	CV: 1.28	
(log scale) SigmaBT:	0.030	SigmaBR: 0.000	Ratio: -
(log scale) SigmaWT:	0.036	SigmaWR: 0.058	Ratio: 0.624
(log scale) SigmaT:	0.047	SigmaR: 0.058	Ratio: 0.814

5.2.2.1.2.4 SA – 30 L/min

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled: Point estimate: -0.4304
CI: -0.3578
Pass/Fail: PASS

Constant-scaled: Point estimate: -0.1354
CI: -0.1045
Pass/Fail: PASS

Overall Test Outcome: Pass/Fail: **PASS**

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0 , PASS. For linearized theta P, if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$,

use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	47.58	Mean: 39.50	Ratio: 120.43
		90% CI for ratio: (114.5,126.6)	
(log scale) Mean:	3.86	Mean: 3.68	Diff: 0.19
(log scale) CV:	1.20	CV: 10.58	
(log scale) SigmaBT:	0.039	SigmaBR: 0.000	Ratio: -
(log scale) SigmaWT:	0.025	SigmaWR: 0.389	Ratio: 0.065
(log scale) SigmaT:	0.046	SigmaR: 0.389	Ratio: 0.120

5.2.2.1.2.5 SA – 60 L/min

In Vitro PBE Analysis - Approximate Confidence Interval
 Using Moment-Based Simplified Parameter Estimates
 for
 ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
 MIXED SCALING APPROACH
 Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0050
	CI:	-0.0027
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0186
	CI:	-0.0169
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0 , PASS. For linearized theta P, if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	49.20	Mean: 46.24	Ratio: 106.41
		90% CI for	ratio: (105.3,107.6)
(log scale) Mean:	3.90	Mean: 3.83	Diff: 0.06
(log scale) CV:	1.13	CV: 1.54	
(log scale) SigmaBT:	0.034	SigmaBR: 0.000	Ratio: -
(log scale) SigmaWT:	0.028	SigmaWR: 0.059	Ratio: 0.478
(log scale) SigmaT:	0.044	SigmaR: 0.059	Ratio: 0.746

5.2.2.1.2.6 SA – 90 L/min

In Vitro PBE Analysis - Approximate Confidence Interval
 Using Moment-Based Simplified Parameter Estimates
 for
 ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
 MIXED SCALING APPROACH
 Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0053
	CI:	-0.0036
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0199
	CI:	-0.0187
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0 , PASS. For linearized theta P, if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	48.92	Mean: 46.78	Ratio: 104.56
		90% CI for	ratio: (103.5,105.6)
(log scale) Mean:	3.89	Mean: 3.85	Diff: 0.04

(log scale)	CV:	1.14	CV:	1.42		
(log scale)	SigmaBT:	0.030	SigmaBR:	0.000	Ratio:	-
(log scale)	SigmaWT:	0.032	SigmaWR:	0.055	Ratio:	0.591
(log scale)	SigmaT:	0.044	SigmaR:	0.055	Ratio:	0.807

5.2.2.1.3 Conclusions

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE				
REVIEW OF TESTING METHODS:				
Is the testing method validated?			Yes	
Is the Quantitative Analytical Method Validated? (e.g., HPLC)			Yes	
Is testing performed as per RLD labeling?			Yes	
If yes, what is the actuation number tested?			Study protocol states that dose counter #s 60 (beginning), 30 (middle) and 1 (end) were to be used. The actual dose counter# used were 60 or 59 (beginning), 30 or 29 (middle) and 1 (end).	
Are the testing methods acceptable?			ACCEPTABLE	
If not, why?			N/A	
STUDY RESULTS:				
Are data expressed as actual amount and % of label claim?			Yes	
Is the geo-mean of the test product (% of label claim) within 95-105% ?	Beginning		FP	SA
		30 L/min	Yes (102.16%)	No (105.38%)
		60 L/min	Yes (104.80%)	No (108.22%)
	Middle	90 L/min	Yes (104.00%)	No (107.77%)
		30 L/min	Yes (103.03%)	No (106.23%)
		60 L/min	No (107.43%)	No (110.03%)
	End	90 L/min	No (106.76%)	No (109.85%)
		30 L/min	Yes (102.00%)	No (105.56%)
		60 L/min	No (106.78%)	No (109.76%)
		90 L/min	No (105.09%)	No (108.52%)
Are the PBE results acceptable?			Acceptable	
If not, why?			N/A	

Comments:

- The geo-mean of the test product is within 95-105% of label claim for FP for each of the 3 lifestages at each of the 3 flow rates, except for BOL and EOL at 60 and 90 L/min. For SA, geo-mean of the test product is within 95-105% of label claim for none of the testing conditions (please see highlighted in the table above).

However, since the PBE analysis of both FP and SA met BE criteria, the reviewer will not pursue this issue further.

The applicant's pivotal SAC study for the 100/50 mcg strength is **acceptable**.

5.2.2.1.4 Deficiencies / Recommendations

N/A

APPEARS THIS WAY ON
ORIGINAL

5.2.2.2 Aerodynamic Particle Size Distribution (APSD) – 100/50 mcg strength

5.2.2.2.1 Results Summary – Aerodynamic Particle Size Distribution

Applicant's results - ISM

Flow Rate (L/min)	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
30	FP	BoL						(b) (4)
		EoL						
	Sal	BoL						
		EoL						
60	FP	BoL						
		EoL						
	Sal	BoL						
		EoL						
90	FP	BoL						
		EoL						
	Sal	BoL						
		EoL						

Reviewer's Results – 30 L/min

Aerodynamic Particle Size Distribution										
		Mean Drug Deposition (µg)		Variability (% CV)					Mean Ratio (I/R)	
				Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)	Geo (n=60)
		Arithm	Geo	Lot 1	Lot 2	Lot 3				
FP										
Delivered Dose (µg)	Test	(b) (4)								
	Ref									
Fine Particle Mass (µg)	Test									
	Ref									
Impactor-Sized Mass (µg)	Test									
	Ref									
SA										
Delivered Dose (µg)	Test	(b) (4)								
	Ref									
Fine Particle Mass (µg)	Test									
	Ref									
Impactor-Sized Mass (µg)	Test									
	Ref									

Reviewer's Results – 60 L/min

Aerodynamic Particle Size Distribution										
		Mean Drug Deposition (μg)		Variability (% CV)				Mean Ratio (T/R)		
				Within Lot (n=20)			Between Lot (n=3)	Total (n=60)		
		Arithm	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=60)	Geo (n=60)
FP										
Delivered Dose (μg)	Test								(b) (4)	
	Ref									
Fine Particle Mass (μg)	Test									
	Ref									
Impactor-Sized Mass (μg)	Test									
	Ref									
SA										
Delivered Dose (μg)	Test								(b) (4)	
	Ref									
Fine Particle Mass (μg)	Test									
	Ref									
Impactor-Sized Mass (μg)	Test									
	Ref									

Reviewer's Results – 90 L/min

Aerodynamic Particle Size Distribution									
		Mean Drug Deposition (µg)		Variability (% CV)				Mean Ratio (I/R)	
				Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	
		Arithm	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=60)
FP									
Delivered Dose (µg)	Test	(b) (4)							
	Ref								
Fine Particle Mass (µg)	Test								
	Ref								
Impactor-Sized Mass (µg)	Test								
	Ref								
SA									
Delivered Dose (µg)	Test	(b) (4)							
	Ref								
Fine Particle Mass (µg)	Test								
	Ref								
Impactor-Sized Mass (µg)	Test								
	Ref								

(b) (4)

Reviewer’s Comments:

- As mentioned in the original BE review, the applicant repeated 15 samples using new devices, and each of these 15 samples were repeated for both FP and SA.
 - Among the 15 samples, the applicant stated that the following 12 samples did not have the original data generated due to analysis being stopped prior to data generation. As mentioned in the original BE review, the reviewer considers the applicant’s reason for original sample rejection (please see details in the table below) acceptable. However, it should be noted that the applicant only repeated the sample at the end lifestage in the above replacement devices. Therefore, these 12 samples containing lifestage data from different devices will be excluded from the reviewer’s statistical evaluation.

Number	Product	Batch number	Original inhaler number	Replacement inhaler number	Flow rate (L/min)	Reason for replacement
1	Advair	4ZP3863	10	116	30	For 10 instances of APSD at end of life the mouth and throat samples were stored at ambient rather than 5°C prior to analysis in error. Hence the original preparations were not tested and new replacement inhalers were tested.
2	MGR001	631-002	7	111	30	
3	Advair	5ZP8178	18	115	30	
4	Advair	5ZP8397	2	112	30	
5	Advair	5ZP8178	1	113	30	
6	MGR001	631-001	8	112	30	
7	MGR001	631-001	20	113	30	
8	MGR001	631-003	5	111	30	
9	Advair	5ZP8178	7	114	30	
10	Advair	4ZP3863	1	115	30	
11	MGR001	631-001	57	111	90	Pipetting error into cup 4 observed during preparation; analysis halted
12	Advair	4ZP3863	53	114	90	Incorrect volume pipetted into cup 6; analysis halted.

- As mentioned in the original BE review, for the remaining 3 samples, the applicant stated that the original data was generated, and the applicant provided reason for original sample rejection below:

Number	Product	Batch number	Original inhaler number	Replacement inhaler number	Flow rate (L/min)	Reason for replacement
13	Advair	4ZP3863	21	112	60	Very low results for mouth and throat stage for both APIs. (b) (4) investigation (b) (4), concluded lab error and replacement device was tested.
14	Advair	5ZP8178	32	112	60	High Fluticasone propionate result for mouth and throat sample. Salmeterol value as expected. (b) (4) investigation (b) (4) concluded lab error and replacement device was tested.
15	Advair	4ZP3863	25	113	60	Poor chromatography (broad peaks) in mouth and throat test sample. (b) (4) investigation (b) (4) concluded lab error and replacement device tested.

- For sample # 13 above, the applicant rejected the original sample since certain stages had very low or high values. As mentioned in Section 4.16, SOP (b) (4) Laboratory Investigations does not have objective criteria for aberrant or atypical values. Therefore, the reviewer considers rejection of the original sample not acceptable. Thus the reviewer will use original values of this sample in statistical analysis.
- For sample # 14 above, the applicant rejected the original sample due to high FP result for mouth and throat sample. The reviewer checked the raw data, and noticed that the mouth and throat value is remarkably higher than that of other samples, making the mass balance 206.57%. Therefore, the reviewer considers it reasonable to reject the original sample. However, it should be noted that the applicant only repeated the sample at the beginning lifestage in the above replacement devices. Therefore, this sample containing lifestage data from different devices will be excluded from the reviewer's statistical evaluation. Please note that using original values of this sample in statistical analysis does not affect the study outcome.
- For sample #15 that was repeated due to poor chromatograms (board peaks), as detailed in the original BE review, the reviewer considers the original sample rejection acceptable. However, it should be noted that the applicant only repeated the sample at the

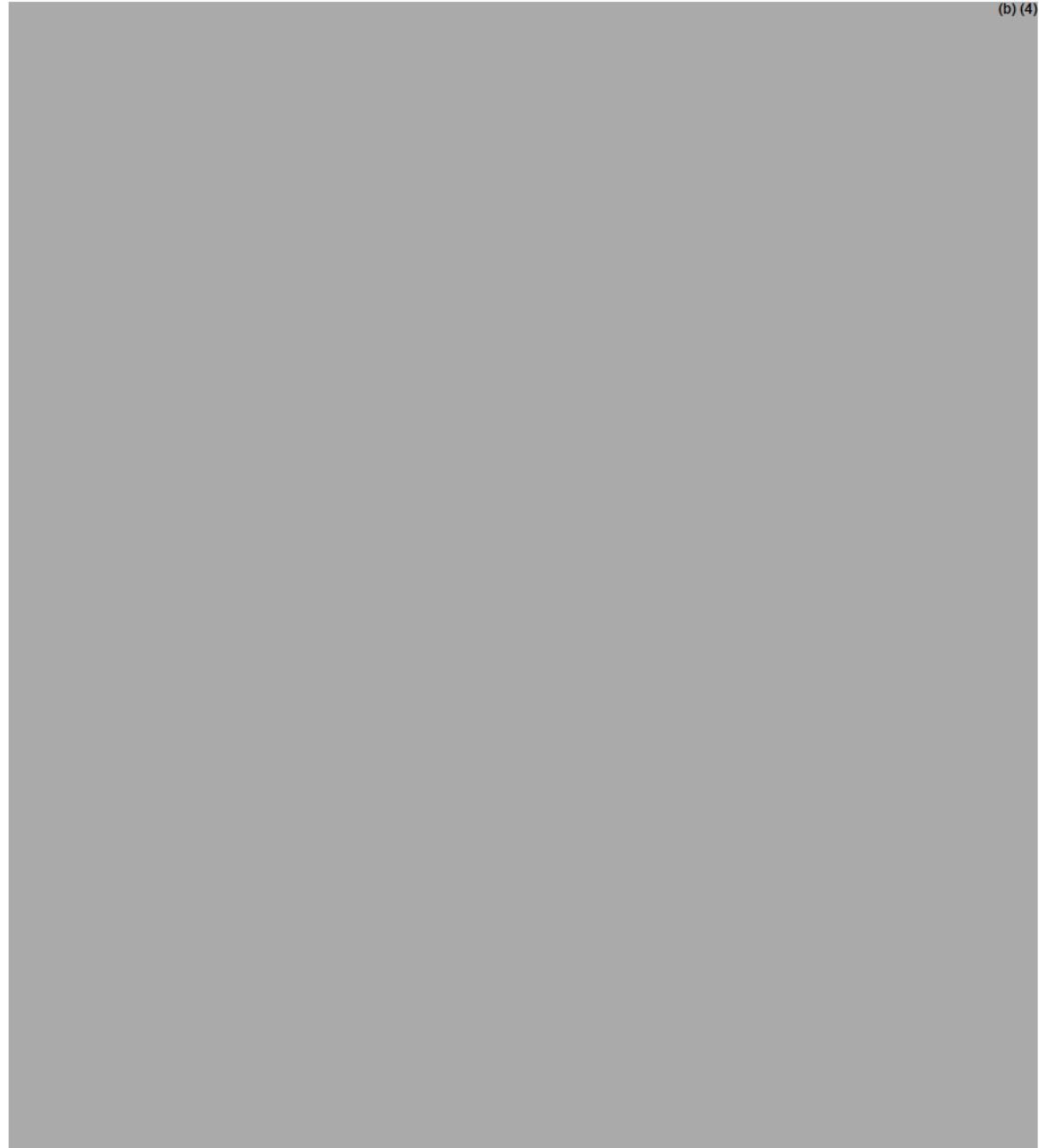
beginning lifestage in the above replacement devices. Therefore, this sample containing lifestage data from different devices will be excluded from the reviewer's statistical evaluation.

- As mentioned in the original BE review, the applicant stated that “*No acceptable data generated for both FP and Sal*” for the following sample, and the applicant was asked to provide the data obtained as well as supporting document for why this data was not acceptable. As detailed in Section 4.25, the reviewer does not agree with the applicant's rejection of the original data, hence the original value of this sample will be used in the reviewer's statistical analysis.

Product	Batch Number	(b) (4) Unit	Mylan Unit	Flow Rate (L/min)	Lifestage
REF	5ZP8178	39	159	60	BOL



⁵⁵ GS Review: ANDA 208891, Resubmission/After Action-Complete; Bioequivalence/Other, 8/28/2017 (Module 3.2.P.2\Study 057755-02-04 (P20987) – APSD – 100/50mcg – 30 L/min – Chromatograms, p. 916 of 2029).



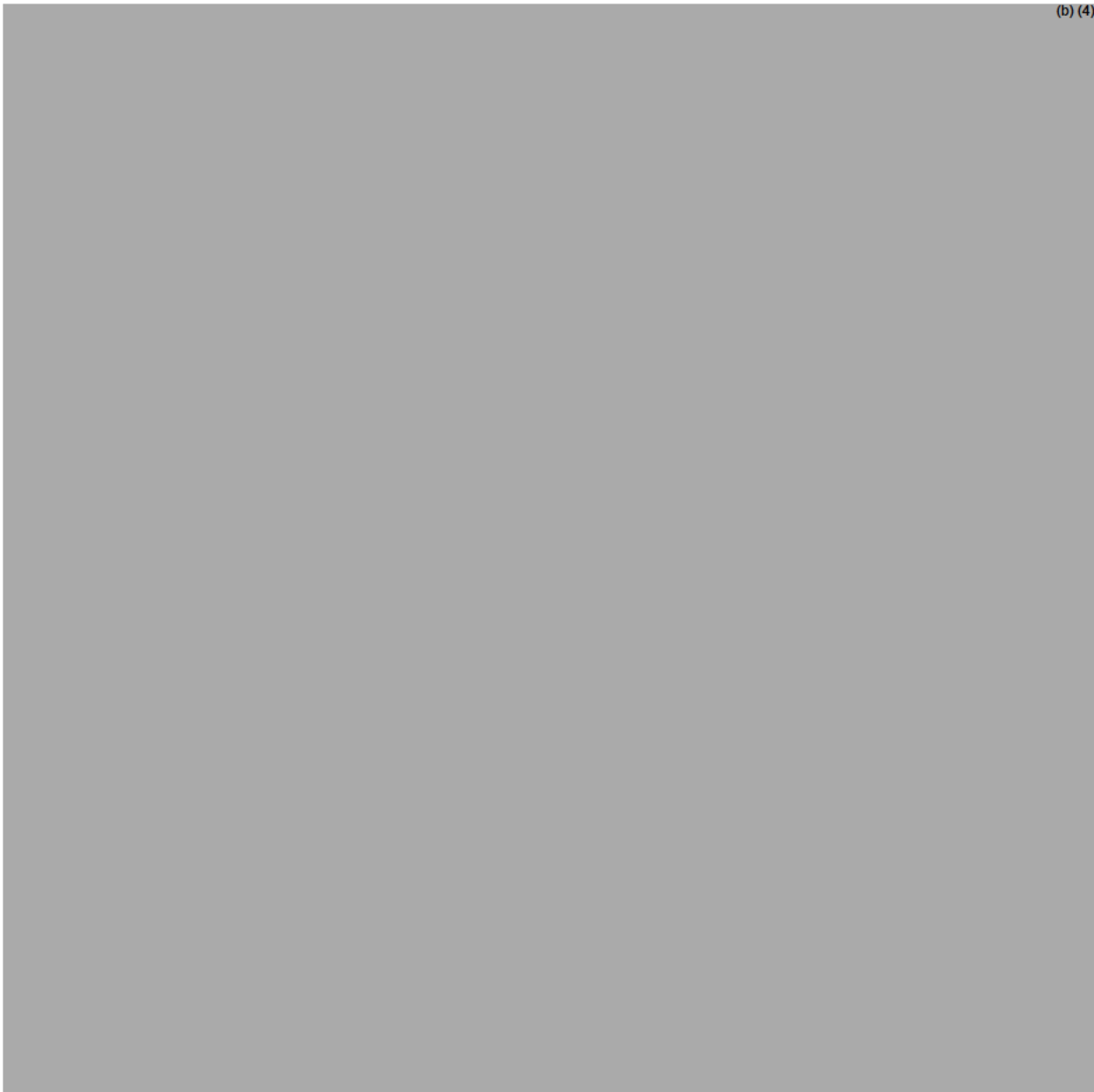
- As mentioned in the original BE review, the applicant stated that in all APSD studies, test sample solutions were stored at 5°C for periods up to 5 days, except that one set of APSD test solutions generated from a single test sample (test lot #631-003, beginning lifestage testing, (b) (4) Test Order 24, Unit #240, 60 L/min) was injected up to 4 hrs beyond the 6-day period.⁵⁶ The reviewer excluded this set of data from statistical analysis due to this stability issue.

⁵⁶ GS Review: ANDA 208891, Response to ECD/Bioequivalence, 1/12/2017 (Module 1.2\Cover Letter..., p. 15 of 21)



The reviewer checked the raw data, and noted that for each of the above conditions, 1 or 2 test samples had mass balance (%LC) above 115% or below 85%. All other samples had mass balance (%LC) between 85-115%. Since only 1 or 2 samples out of 60 test samples are not within 85-115% of LC, and the mass balance passed PBE analysis, the reviewer will not pursue this issue further.

In addition, the mass balance of reference product (% LC) at the 30 L/min flow rate has ranges outside of 85-115%, with multiple samples below 85% for FP and SA. This is consistent with the observation that the emitted dose of the reference product is highly variable and had multiple samples with low SAC values at 30 L/min flow rate of the SAC study. In addition, the mass balance passed PBE analysis. Therefore, the reviewer will not pursue this issue further.



5.2.2.2.3 Conclusions

AERODYNAMIC PARTICLE SIZE DISTRIBUTION	
REVIEW OF TESTING METHODS:	
Is the testing method for CI test validated?	Yes
Is the analytical method (e.g. HPLC) validated?	Yes
Is testing conducted as per RLD labeling?	Yes
Are the testing methods acceptable?	ACCEPTABLE
If not, why?	N/A
STUDY RESULTS:	

AERODYNAMIC PARTICLE SIZE DISTRIBUTION		
Results	Does Impactor Size Mass data pass PBE?	Yes
	Does ISM data pass modified chi-square ratio test?	Yes for FP and SA at 30 and 90 L/min No for FP and SA at 60 L/min
	Do mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle dose (FPD) pass PBE?	Yes
Mass Balance	Is the mean range for Total B between 85-115% of the label claim? (on a per actuation basis)	Yes for the test product at 30 L/min flow rate for FP and for the reference product at 90 L/min for SA, and no for rest of conditions.
	Is PBE acceptable?	Yes
If not, why?		N/A

Comments:

- The test product passes PBE analysis for ISM and mass balance. In addition, it passes the modified chi-square test using acceptance criteria of 25% difference for FP and SA at 30 and 90 L/min flow rates. For FP and SA at 60 L/min flow rate, the test product does not pass the modified chi-square test using acceptance criteria of 25% or 30% difference. However, it is noted that 1) modified chi-square test is not one of the BE tests in the product-specific guidance, and 2) the same strength of test product manufactured (b) (4) (please note that the test product used in the current in vitro BE study was manufactured (b) (4) pass the modified chi-square test using acceptance criteria of 25% difference for both FP and SA at 60 L/min (please see details in Section 5.2.4.4). Therefore, the reviewer will not pursue this issue further.

It is noted that in BE review of ANDA 209959 (Albuterol Inhalation Aerosol), the modified chi-square analysis also passes at the 30% difference but failed at the 25% difference for the APSD study. The BE reviewer of ANDA 209959 considers it acceptable since “this data is considered supportive only at this time

(b) (5) 64

- It is noted that the mass balance of the drug product (% LC) ranges outside of 85-115% for all conditions other than test product at 30 L/min flow rate for FP and for the reference product at 90 L/min for SA. As detailed in Section 5.2.2.2.1, the reviewer will not pursue this issue further.

⁶⁴ GDRP: ANDA-209959-ORIG-1, Bioequivalence Review, A209959N000DB-Review01-11032016, 12/26/2017.

The applicant's pivotal APSD study for the 100/50 mcg strength is **acceptable**.

5.2.2.2.4 Deficiencies / Recommendations

N/A

5.2.2.3 Single Actuation Content through Container Life – 250/50 mcg strength

5.2.2.3.1 Results Summary

Applicant's results

Flow Rate (L/min)	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
30	FP	BoL	231.06	195.91	1.18	8.51	39.73	0.21
		EoL	235.25	229.26	1.03	8.14	20.73	0.39
		MoL	236.66	239.46	0.99	9.75	11.87	0.82
	Sal	BoL	46.76	38.61	1.21	1.44	7.86	0.18
		EoL	47.47	45.11	1.05	1.23	4.07	0.30
		MoL	47.47	47.10	1.01	1.53	2.36	0.65
60	FP	BoL	240.25	229.60	1.05	11.98	7.12	1.68
		EoL	241.73	246.77	0.98	9.61	9.90	0.97
		MoL	244.18	240.70	1.01	13.11	8.73	1.50
	Sal	BoL	48.21	45.37	1.06	1.66	1.48	1.12
		EoL	48.61	48.51	1.00	1.53	1.93	0.79
		MoL	48.90	47.30	1.03	2.23	1.78	1.26
90	FP	BoL	242.21	232.07	1.04	8.85	8.15	1.09
		EoL	245.03	249.79	0.98	8.36	5.49	1.52
		MoL	249.78	242.85	1.03	10.60	7.89	1.34
	Sal	BoL	48.65	45.73	1.06	1.60	1.69	0.95
		EoL	49.06	49.07	1.00	1.52	1.10	1.39
		MoL	49.61	47.64	1.04	1.98	1.56	1.27

Reviewer's Results – 30 L/min

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE													
		Dose Counter #	Mean				Variability (% CV)					Mean Ratio (I/R)	
			Drug Mass		% label claim		Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)	Geo (n=60)
			Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3				
FP													
BEG	Test	60	231.22	231.06	99.23	99.17	3.80	3.81	3.43	0.79	3.68	1.14	1.18
	Ref	60	202.35	195.91	86.85	84.08	30.43	8.45	14.21	6.26	19.64		
MID	Test	30	236.86	236.66	101.66	101.57	3.31	3.94	4.06	2.15	4.12	0.99	0.99
	Ref	30	239.75	239.46	102.90	102.77	1.98	4.73	5.74	2.87	4.95		
END	Test	1	235.38	235.25	101.02	100.97	3.93	3.35	2.94	0.96	3.46	1.02	1.03
	Ref	1	230.27	229.26	98.83	98.39	2.09	5.49	12.48	6.18	9.00		
SA													
BEG	Test	60	46.78	46.76	103.95	103.90	2.29	3.07	3.55	1.01	3.07	1.17	1.21
	Ref	60	39.89	38.61	88.64	85.79	14.25	8.36	30.41	6.70	19.71		
MID	Test	30	47.50	47.47	105.55	105.49	2.85	3.14	2.92	1.64	3.22	1.01	1.01
	Ref	30	47.16	47.10	104.80	104.67	5.37	4.48	1.66	3.57	5.01		
END	Test	1	47.48	47.47	105.52	105.49	2.12	2.98	2.34	0.93	2.58	1.05	1.05
	Ref	1	45.31	45.11	100.68	100.24	12.23	5.55	1.52	6.41	8.98		

Reviewer's Results – 60 L/min

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE													
		Dose Counter #	Mean				Variability (% CV)					Mean Ratio (I/R)	
			Drug Mass		% label claim		Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)	Geo (n=60)
			Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3				
FP													
BEG	Test	60	240.53	240.25	103.23	103.11	5.78	3.88	4.89	1.40	4.98	1.05	1.05
	Ref	60	229.71	229.60	98.59	98.54	2.77	2.49	2.33	2.25	3.10		
MID	Test	30	244.52	244.18	104.94	104.80	4.58	5.98	5.25	1.59	5.36	1.02	1.01
	Ref	30	240.86	240.70	103.37	103.31	3.81	2.86	2.09	2.60	3.63		
END	Test	1	241.92	241.73	103.83	103.75	3.27	3.93	4.63	0.88	3.97	0.98	0.98
	Ref	1	246.98	246.77	106.00	105.91	6.55	1.75	1.90	0.35	4.01		
SA													
BEG	Test	60	48.24	48.21	107.20	107.14	2.60	3.05	4.34	0.99	3.44	1.06	1.06
	Ref	60	45.39	45.37	100.88	100.82	2.49	2.42	2.47	2.64	3.25		
MID	Test	30	48.95	48.90	108.79	108.68	3.77	4.61	4.96	1.48	4.56	1.03	1.03
	Ref	30	47.34	47.30	105.19	105.12	3.84	2.82	1.96	2.89	3.75		
END	Test	1	48.63	48.61	108.06	108.01	2.43	2.90	3.88	0.79	3.14	1.00	1.00
	Ref	1	48.55	48.51	107.90	107.81	6.43	1.80	1.93	0.61	3.97		

Reviewer's Results – 90 L/min

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE													
		Dose Counter #	Mean				Variability (% CV)					Mean Ratio (I/R)	
			Drug Mass		% label claim		Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)	Geo (n=60)
			Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3				
FP													
BEG	Test	60	242.61	242.46	104.12	104.06	2.94	4.23	3.44	0.90	3.59	1.04	1.04
	Ref	60	232.21	232.07	99.66	99.60	3.44	3.17	2.04	2.44	3.51		
MID	Test	30	250.08	249.85	107.33	107.23	3.14	4.22	4.92	1.56	4.27	1.03	1.03
	Ref	30	242.98	242.85	104.28	104.23	4.01	2.90	1.96	1.50	3.25		
END	Test	1	245.08	244.94	105.19	105.12	3.01	3.23	3.85	1.08	3.43	0.98	0.98
	Ref	1	249.85	249.79	107.23	107.20	1.94	2.07	2.09	1.11	2.20		
SA													
BEG	Test	60	48.73	48.70	108.29	108.23	2.82	3.43	3.27	0.95	3.22	1.06	1.06
	Ref	60	45.76	45.73	101.70	101.63	3.39	3.37	2.06	2.71	3.69		
MID	Test	30	49.65	49.61	110.33	110.25	3.12	3.87	4.45	1.66	4.02	1.04	1.04
	Ref	30	47.66	47.64	105.91	105.86	3.72	3.09	1.86	1.75	3.26		
END	Test	1	49.06	49.04	109.03	108.98	2.69	2.58	3.83	0.99	3.12	1.00	1.00
	Ref	1	49.08	49.07	109.07	109.05	2.10	2.08	2.29	0.85	2.23		

Reviewer's Comments:

- As mentioned in the original BE review, the applicant repeated the following sample using a new device, and this sample was repeated for both FP and SA (please see table below). The applicant stated that this sample did not have the original data generated due to analysis being stopped prior to data generation. It should be noted that the applicant only repeated the sample at the end lifestage in the above replacement devices. Therefore, this sample containing lifestage data from different devices were excluded from the reviewer's statistical evaluation.

Number	Product	Batch Number	Unit	Flow Rate (L/min)	Lifestage	Reason for replacement
1	TEST	631-009	293R	90	EOL	Incorrect actuation time for initial replicate.

- The applicant's and the reviewer's results are not the same due to the reviewer's exclusion of the above samples.

- Based on the reviewer's results, the reference product had lower FP and SA emitted dose as compared to the test product at beginning lifestages at 30 L/min flow rate. It is also noted that reference product had high variability for FP and SA at beginning and end lifestages at 30 L/min flow rate. As mentioned in the original BE review, the reviewer checked study data for each individual unit, and found that reference batches had multiple samples that had low emitted dose for FP and SA at beginning lifestages at 30 L/min flow rate.

5.2.2.3.2 In Vitro PBE Analysis

5.2.2.3.2.1 FP – 30 L/min

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval
Linearized Theta P

Reference-scaled:	Point estimate:	-0.1190	
	CI:	-0.1005	
	Pass/Fail:	PASS	
Constant-scaled:	Point estimate:	-0.0560	
	CI:	-0.0491	
	Pass/Fail:	PASS	
Overall Test Outcome:	Pass/Fail:		PASS

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0 , PASS. For linearized theta P, if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	234.31	Mean: 220.74	Ratio: 106.15
		90% CI for	ratio: (103.5, 108.9)
(log scale) Mean:	5.46	Mean: 5.40	Diff: 0.06

(log scale)	CV:	0.71	CV:	3.71		
(log scale)	SigmaBT:	0.023	SigmaBR:	0.000	Ratio:	-
(log scale)	SigmaWT:	0.031	SigmaWR:	0.200	Ratio:	0.156
(log scale)	SigmaT:	0.039	SigmaR:	0.200	Ratio:	0.194

5.2.2.3.2.2 FP – 60 L/min

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for

ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0046
	CI:	-0.0033
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0207
	CI:	-0.0199
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0 , PASS. For linearized theta P, if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	242.05	Mean: 238.92	Ratio: 101.31
		90% CI for	ratio: (100.3, 102.3)
(log scale) Mean:	5.49	Mean: 5.48	Diff: 0.01
(log scale) CV:	0.87	CV: 0.87	
(log scale) SigmaBT:	0.032	SigmaBR: 0.000	Ratio: -
(log scale) SigmaWT:	0.035	SigmaWR: 0.048	Ratio: 0.740
(log scale) SigmaT:	0.048	SigmaR: 0.048	Ratio: 1.003

5.2.2.3.2.3 FP – 90 L/min

In Vitro PBE Analysis - Approximate Confidence Interval

Using Moment-Based Simplified Parameter Estimates
for
ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0038
	CI:	-0.0029
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0209
	CI:	-0.0203
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0 , PASS. For linearized theta P, if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	245.73	Mean: 241.46	Ratio: 101.77
		90% CI for	ratio: (100.9, 102.6)
(log scale) Mean:	5.50	Mean: 5.49	Diff: 0.02
(log scale) CV:	0.72	CV: 0.78	
(log scale) SigmaBT:	0.024	SigmaBR: 0.000	Ratio: -
(log scale) SigmaWT:	0.032	SigmaWR: 0.043	Ratio: 0.733
(log scale) SigmaT:	0.040	SigmaR: 0.043	Ratio: 0.921

5.2.2.3.2.4 SA – 30 L/min

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for

ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA

MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.1165
	CI:	-0.0977
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0533
	CI:	-0.0457
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0 , PASS. For linearized theta P, if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	47.23	Mean: 43.45	Ratio: 108.70
		90% CI for ratio:	(106.0, 111.5)
(log scale) Mean:	3.86	Mean: 3.77	Diff: 0.08
(log scale) CV:	0.79	CV: 5.32	
(log scale) SigmaBT:	0.016	SigmaBR: 0.000	Ratio: -
(log scale) SigmaWT:	0.026	SigmaWR: 0.201	Ratio: 0.130
(log scale) SigmaT:	0.030	SigmaR: 0.201	Ratio: 0.152

5.2.2.3.2.5 SA – 60 L/min

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for

ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0043
	CI:	-0.0031
	Pass/Fail:	PASS

Constant-scaled: Point estimate: -0.0206
 CI: -0.0198
 Pass/Fail: PASS

Overall Test Outcome: Pass/Fail: **PASS**

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (θ_P) of 2.0891. For linearized θ_P , if the upper bound of the confidence interval is < 0 , PASS. For linearized θ_P , if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	48.57	Mean: 47.04	Ratio: 103.25
		90% CI for ratio: (102.4, 104.1)	
(log scale) Mean:	3.88	Mean: 3.85	Diff: 0.03
(log scale) CV:	0.98	CV: 1.21	
(log scale) σ_{BT} :	0.024	σ_{BR} : 0.000	Ratio: -
(log scale) σ_{WT} :	0.029	σ_{WR} : 0.047	Ratio: 0.626
(log scale) σ_T :	0.038	σ_R : 0.047	Ratio: 0.810

5.2.2.3.2.6 SA – 90 L/min

In Vitro PBE Analysis - Approximate Confidence Interval
 Using Moment-Based Simplified Parameter Estimates
 for

ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA MIXED SCALING APPROACH

Point Estimate and Upper Bound of 95% Confidence Interval

Linearized θ_P

Reference-scaled: Point estimate: -0.0032
 CI: -0.0021
 Pass/Fail: PASS

Constant-scaled: Point estimate: -0.0203
 CI: -0.0196
 Pass/Fail: PASS

Overall Test Outcome: Pass/Fail: **PASS**

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (θ_P) of 2.0891. For linearized θ_P , if the upper bound of the confidence interval is < 0 , PASS. For linearized θ_P , if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	49.12	Mean: 47.46	Ratio: 103.49
		90% CI for	ratio: (102.7, 104.3)
(log scale) Mean:	3.89	Mean: 3.86	Diff: 0.03
(log scale) CV:	0.91	CV: 1.11	
(log scale) σ_{BT} :	0.020	σ_{BR} : 0.000	Ratio: -
(log scale) σ_{WT} :	0.029	σ_{WR} : 0.043	Ratio: 0.681
(log scale) σ_T :	0.036	σ_R : 0.043	Ratio: 0.832

5.2.2.3.3 Conclusions

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE				
REVIEW OF TESTING METHODS:				
Is the testing method validated?		Yes		
Is the Quantitative Analytical Method Validated? (e.g., HPLC)		Yes		
Is testing performed as per RLD labeling?		Yes		
If yes, what is the actuation number tested?		Study protocol states that dose counter #s 60 (beginning), 30 (middle) and 1 (end) were to be used. The actual dose counter# used were 60 or 59 (beginning), 30 or 29 (middle) and 1 (end)		
Are the testing methods acceptable?		ACCEPTABLE		
If not, why?		N/A		
STUDY RESULTS:				
Are data expressed as actual amount and % of label claim?		Yes		
Is the geo-mean of the test product (% of label claim) within 95-105%?		FP	SA	
	Beginning	30 L/min	Yes (103.11%)	Yes (103.90%)
		60 L/min	Yes (103.11%)	No (107.14%)
		90 L/min	Yes (104.06%)	No (108.23%)
	Middle	30 L/min	Yes (104.80%)	No (105.49%)

		60 L/min	Yes (104.80%)	No (108.68%)
		90 L/min	No (107.23%)	No (110.25%)
	End	30 L/min	Yes (103.75%)	No (105.49%)
		60 L/min	Yes (103.75%)	No (108.01%)
		90 L/min	No (105.12%)	No (108.98%)
Are the PBE results acceptable?			Acceptable	
If not, why?			N/A	

Comments:

- The geo-mean of the test product is within 95-105% of label claim for FP for each of the 3 lifestages at each of the 3 flow rates, except MOL and EOL at 90 L/min flow rate. For SA, geo-mean of the test product is within 95-105% of label claim for BOL at 30 L/min flow rate, but is not within 95-105% of label claim for the rest of the conditions (please see **highlighted** in the table above). However, since the PBE analysis of both FP and SA met BE criteria, the reviewer will not pursue this issue further.

The applicant's pivotal SAC study for the 250/50 mcg strength is **acceptable**.

5.2.2.3.4 Deficiencies / Recommendations

N/A

5.2.2.4 Aerodynamic Particle Size Distribution (APSD) – 250/50 mcg strength

5.2.2.4.1 Results Summary – Aerodynamic Particle Size Distribution

Applicant's results - ISM

Flow Rate (L/min)	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
30	FP	BoL						(b) (4)
		EoL						
	Sal	BoL						
		EoL						
60	FP	BoL						
		EoL						
	Sal	BoL						
		EoL						
90	FP	BoL						
		EoL						
	Sal	BoL						
		EoL						

Reviewer's Results – 30 L/min

Aerodynamic Particle Size Distribution									
		Mean Drug Deposition (µg)		Variability (% CV)				Mean Ratio (I/R)	
				Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)
		Arithm	Geo	Lot 1	Lot 2	Lot 3			
FP									
Delivered Dose (µg)	Test	(b) (4)							
	Ref								
Fine Particle Mass (µg)	Test								
	Ref								
Impactor-Sized Mass (µg)	Test								
	Ref								
SA									
Delivered Dose (µg)	Test	(b) (4)							
	Ref								
Fine Particle Mass (µg)	Test								
	Ref								
Impactor-Sized Mass (µg)	Test								
	Ref								

Reviewer's Results – 60 L/min

Aerodynamic Particle Size Distribution									
		Mean Drug Deposition (µg)		Variability (% CV)				Mean Ratio (I/R)	
				Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)
		Arithm	Geo	Lot 1	Lot 2	Lot 3			
FP									
Delivered Dose (µg)	Test	(b) (4)							
	Ref								
Fine Particle Mass (µg)	Test								
	Ref								
Impactor-Sized Mass (µg)	Test								
	Ref								
SA									
Delivered Dose (µg)	Test	(b) (4)							
	Ref								
Fine Particle Mass (µg)	Test								
	Ref								
Impactor-Sized Mass (µg)	Test								
	Ref								

Reviewer's Results – 90 L/min

Aerodynamic Particle Size Distribution									
		Mean Drug Deposition (µg)		Variability (% CV)				Mean Ratio (T/R)	
				Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)
		Arithm	Geo	Lot 1	Lot 2	Lot 3			
FP									
Delivered Dose (µg)	Test	(b) (4)							
	Ref								
Fine Particle Mass (µg)	Test								
	Ref								
Impactor-Sized Mass (µg)	Test								
	Ref								
SA									
Delivered Dose (µg)	Test	(b) (4)							
	Ref								
Fine Particle Mass (µg)	Test								
	Ref								
Impactor-Sized Mass (µg)	Test								
	Ref								



Reviewer’s Comments:

- As mentioned in the original BE review, for the 90 L/min flow rate, the applicant stated that after completion of the initial testing for this study, it was discovered that the flow meter used for the APSD testing at 90 L/min failed its calibration and was subsequently reading incorrect flow values. Therefore, the APSD testing was repeated for the 90 L/min flow rate (MGR-PRO-2015-080 v3.0). As detailed in the original BE review, the reviewer agrees with the repeat of this study at 90 L/min flow rate.
- As mentioned in the original BE review, the applicant repeated 9 samples using new devices, and each of these 9 samples were repeated for both FP and SA. Out of these 9 samples, 6 are from the 30 L/min, 60 L/min and repeat 90 L/min flow rate.
 - Among the 6 samples, the applicant stated that the following 2 samples did not have the original data generated due to analysis being stopped prior to data generation. As mentioned in Section 4.28, the reviewer agrees with the rejection of the original samples. However, it should be noted that the applicant only repeated the sample at the beginning lifestage in the replacement devices. Therefore, these 2 samples containing lifestage data from different devices were excluded from the reviewer’s statistical evaluation.

Number	Product	Batch Number	Unit	Flow Rate (L/min)	Lifestage	Reason for replacement
1	REF	5ZP0114	91R	30	BOL	Error during sampling. Mouth and throat samples were washed into the same volumetric flask.
2	TEST	631-008	37R	30	BOL	

- For the following 3 samples, the applicant stated that the original data was generated, and provided reason for original sample rejection below:

Number	Product	Batch Number	Unit	Flow Rate (L/min)	Lifestage	Reason for replacement
1	REF	5ZP9304	198R	60	BOL	Poor chromatography affecting integration. Samples reached expiry therefore could not be re-injected
2	REF	5ZP9882	240R	60	BOL	Stage 5 being sampled instead of stage 4.
3	TEST	631-007	367R	90 (repeat)	BOL	Poor chromatography (broad peaks)
4	REF	5ZP9304	433R	90 (repeat)	EOL	Aberrant chromatography (no FP or SA peaks) was obtained for the mouthpiece and throat test sample

- For samples #s 1 and 3 above, as mentioned in the original BE review, the reviewer verified that the original samples had poor chromatography, and agrees that these samples be repeated. However, it should be noted that the applicant only repeated the sample at the beginning lifestage in the replacement devices. Therefore, this sample containing lifestage data from different devices was excluded from the reviewer's statistical evaluation.
- For sample #2 above, as detailed in Section 4.28, since SOP (b) (4) Laboratory Investigations does not have objective criteria for "aberrant" or "atypical", the reviewer disagrees with the applicant's rejection of the original data. Therefore, the reviewer used original value of this sample in the statistical analysis.
- For sample #4 above, as detailed in Section 4.29, the reviewer considers the rejection of the original sample reasonable. However, it should be noted that the applicant only repeated the sample at the beginning lifestage in the replacement devices. Therefore, this sample containing lifestage data from different devices was excluded from the reviewer's statistical evaluation.



The reviewer checked the raw data, and noted that for each of the above conditions, 1 or 2 test samples had mass balance (%LC) above 115%. All other samples had mass balance (%LC) between 85-115%. Since only 1 sample out of 60 test or reference samples are not within 85-115% of LC, and the mass balance passed PBE analysis, the reviewer will not pursue this issue further.

In addition, the mass balance of reference product (% LC) at the 30 L/min flow rate has ranges outside of 85-115% for both FP and SA. This is consistent with

the observation that the emitted dose of the reference product may be highly variable at 30 L/min flow rate of the SAC study. In addition, the mass balance passed PBE analysis. Therefore, the reviewer will not pursue this issue further.

- The average APSD data is listed in the table below

(b) (4)



⁶⁵ Input cutoff diameters as provided by Applicant based on Apparatus used in the study.

⁶⁶ Input cutoff diameters as provided by Applicant based on Apparatus used in the study.



5.2.2.4.3 Conclusions

AERODYNAMIC PARTICLE SIZE DISTRIBUTION	
REVIEW OF TESTING METHODS:	
Is the testing method for CI test validated?	Yes
Is the analytical method (e.g. HPLC) validated?	Yes
Is testing conducted as per RLD labeling?	Yes
Are the testing methods acceptable?	Acceptable
If not, why?	N/A
STUDY RESULTS:	

AERODYNAMIC PARTICLE SIZE DISTRIBUTION		
Results	Does Impactor Size Mass data pass PBE?	Yes
	Does ISM data pass modified chi-square ratio test?	Yes
	Do mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle dose (FPD) pass PBE?	Yes, except FPD for SA at 30 L/min flow rate
Mass Balance	Is the mean range for Total B between 85-115% of the label claim? (on a per actuation basis)	Yes, except for FP (test and reference) and SA (reference only) at 30 L/min flow rate, and for SA (test and reference) at 90 L/min flow rate.
	Is PBE acceptable?	Yes
If not, why?		N/A

Comments:

- The test product passes PBE analysis for ISM and mass balance. In addition, it passes the modified chi-square test using acceptance criteria of 25% difference.
- The test product passes PBE analysis for MMAD, GSD and FPM for FP and SA at each flow rate, except FPD for SA at 30 L/min. However, since FPD is not one of the BE criteria in the product-specific guidance, the reviewer will not pursue this issue further.

It is noted that the mass balance of the drug product (% LC) ranges outside of 85-115% for FP (test and reference) and SA (reference only) at 30 L/min flow rate, and for SA (test and reference) at 90 L/min flow rate. As detailed in Section 5.2.2.4.1, the reviewer will not pursue this issue further.

The applicant's pivotal APSD study for the 250/50 mcg strength is **acceptable**.

5.2.2.4.4 Deficiencies / Recommendations

N/A

5.2.2.5 Single Actuation Content through Container Life – 500/50 mcg strength

5.2.2.5.1 Results Summary

Applicant's results

Flow Rate (L/min)	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
30	FP	BoL	458.99	104.24	4.40	18.06	162.57	0.11
		EoL	470.36	481.88	0.98	19.97	55.44	0.36
		MoL	452.55	445.30	1.02	20.27	76.15	0.27
	Sal	BoL	46.20	10.40	4.44	1.47	16.02	0.09
		EoL	47.38	47.41	1.00	1.72	5.38	0.32
		MoL	45.55	43.75	1.04	1.68	7.42	0.23
60	FP	BoL	474.46	445.78	1.06	20.66	16.31	1.27
		EoL	478.71	497.77	0.96	19.08	12.20	1.56
		MoL	468.53	479.82	0.98	22.19	15.37	1.44
	Sal	BoL	47.37	44.04	1.08	1.80	1.67	1.07
		EoL	48.16	48.92	0.98	1.96	1.22	1.60
		MoL	46.65	47.13	0.99	1.90	1.48	1.29
90	FP	BoL	481.70	451.22	1.07	21.78	11.25	1.94
		EoL	487.98	498.22	0.98	18.97	13.51	1.40
		MoL	476.63	477.05	1.00	20.90	15.82	1.32
	Sal	BoL	47.97	44.53	1.08	1.84	1.12	1.64
		EoL	48.89	48.88	1.00	1.70	1.28	1.33
		MoL	47.55	47.01	1.01	1.76	1.53	1.15

Reviewer's Results – 30 L/min

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE													
		Dose Counter #	Mean				Variability (% CV)					Mean Ratio (T/R)	
			Drug Mass		% label claim		Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)	Geo (n=60)
			Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3				
FP													
BEG	Test	60	459.34	458.99	98.78	98.71	3.36	2.35	3.45	3.03	3.93	2.58	4.40
	Ref	60	178.12	104.24	38.30	22.42	73.62	83.97	111.20	41.75	91.27		
MID	Test	30	452.99	452.55	97.42	97.32	2.63	4.12	4.11	3.14	4.48	1.00	1.02
	Ref	30	453.81	445.30	97.59	95.76	14.25	9.52	24.32	1.90	16.78		
END	Test	1	470.78	470.36	101.24	101.15	2.96	3.40	2.59	3.71	4.24	0.97	0.98
	Ref	1	485.82	481.88	104.48	103.63	8.14	9.25	14.48	4.59	11.41		
SA													
BEG	Test	60	46.23	46.20	102.73	102.68	3.00	2.10	2.98	2.10	3.19	2.62	4.44
	Ref	60	17.66	10.40	39.24	23.10	73.14	83.60	110.27	41.51	90.71		
MID	Test	30	45.58	45.55	101.29	101.22	2.49	3.84	3.42	2.10	3.69	1.02	1.04
	Ref	30	44.56	43.75	99.02	97.21	14.03	9.48	24.16	1.42	16.65		
END	Test	1	47.41	47.38	105.35	105.28	2.59	3.09	2.52	2.93	3.62	0.99	1.00
	Ref	1	47.79	47.41	106.20	105.36	8.09	9.13	14.41	4.29	11.26		

Reviewer's Results – 60 L/min

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE													
		Dose Counter #	Mean				Variability (% CV)					Mean Ratio (I/R)	
			Drug Mass		% label claim		Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)	Geo (n=60)
			Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3				
FP													
BEG	Test	60	474.90	474.46	102.13	102.03	2.76	4.18	2.25	3.70	4.35	1.06	1.06
	Ref	60	446.28	445.96	95.98	95.91	2.52	5.54	1.81	0.87	3.67		
MID	Test	30	469.04	468.53	100.87	100.76	4.46	5.27	4.12	1.51	4.73	0.98	0.98
	Ref	30	480.00	479.75	103.23	103.17	1.53	1.54	4.15	2.28	3.23		
END	Test	1	479.09	478.71	103.03	102.95	2.78	4.01	3.30	2.62	3.98	0.96	0.96
	Ref	1	497.88	497.73	107.07	107.04	2.63	2.29	2.50	0.53	2.47		
SA													
BEG	Test	60	47.40	47.37	105.34	105.26	2.31	3.73	2.64	2.97	3.80	1.08	1.08
	Ref	60	44.08	44.05	97.96	97.88	2.57	5.69	2.16	0.98	3.83		
MID	Test	30	46.69	46.65	103.75	103.67	3.22	5.11	3.40	1.21	4.07	0.99	0.99
	Ref	30	47.17	47.15	104.82	104.77	1.58	1.54	4.09	2.15	3.15		
END	Test	1	48.20	48.16	107.11	107.02	3.10	4.74	3.27	2.00	4.06	0.99	0.98
	Ref	1	48.93	48.91	108.73	108.70	2.61	2.41	2.54	0.58	2.52		

Reviewer's Results – 90 L/min

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE													
		Dose Counter #	Mean				Variability (% CV)					Mean Ratio (T/R)	
			Drug Mass		% label claim		Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)	Geo (n=60)
			Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3				
FP													
BEG	Test	60	482.18	481.70	103.70	103.59	4.54	3.55	2.93	3.26	4.52	1.07	1.07
	Ref	60	451.37	451.23	97.07	97.04	2.82	2.49	1.86	0.99	2.51		
MID	Test	30	477.07	476.63	102.60	102.50	3.87	4.00	4.09	2.38	4.38	1.00	1.00
	Ref	30	477.54	477.28	102.70	102.64	3.06	1.54	4.15	1.58	3.32		
END	Test	1	488.34	487.98	105.02	104.94	3.55	3.48	2.34	2.84	3.88	0.98	0.98
	Ref	1	498.59	498.41	107.22	107.18	3.53	2.52	1.48	0.98	2.72		
SA													
BEG	Test	60	48.01	47.97	106.68	106.60	4.02	3.64	1.87	2.52	3.83	1.08	1.08
	Ref	60	44.55	44.54	99.01	98.98	2.82	2.51	1.95	0.97	2.54		
MID	Test	30	47.58	47.55	105.74	105.67	3.63	3.57	3.64	1.23	3.70	1.01	1.01
	Ref	30	47.06	47.03	104.57	104.52	2.98	2.23	3.92	1.32	3.26		
END	Test	1	48.91	48.89	108.70	108.63	3.37	3.45	2.17	2.17	3.48	1.00	1.00
	Ref	1	48.91	48.90	108.69	108.66	2.81	2.83	1.69	1.18	2.63		

Reviewer's Comments:

- As mentioned in the original BE review, the applicant repeated the following 2 samples using new devices, and each of these 2 samples were repeated for both FP and SA. The applicant also stated that these samples did not have the original data generated due to analysis being stopped prior to data generation. As mentioned in the original BE review, the reviewer considers the applicant's reason for original sample rejection acceptable. However, it should be noted that the applicant only repeated the sample at the end lifestage in the above replacement devices. Therefore, these 2 samples containing lifestage data from different devices were excluded from the reviewer's statistical evaluation.

Sample	Product	Batch number	Original inhaler number	Replacement inhaler number	Flow rate (L/min)	Reason for replacement
1	Advair	4ZP5917	40	111	60	Leak in sample collection tube, analysis halted.
2	Advair	4ZP7022	53	112	90	

5.2.2.5.2 In Vitro PBE Analysis

5.2.2.5.2.1 FP – 30 L/min

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for

ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-2.7684
	CI:	-2.3100
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.7524
	CI:	-0.5568
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0 , PASS. For linearized theta P, if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	460.58	Mean: 281.75	Ratio: 163.47
		90% CI for ratio:	(144.7, 184.7)
(log scale) Mean:	6.13	Mean: 5.64	Diff: 0.49
(log scale) CV:	0.73	CV: 17.50	
(log scale) SigmaBT:	0.027	SigmaBR: 0.000	Ratio: -
(log scale) SigmaWT:	0.036	SigmaWR: 0.987	Ratio: 0.037
(log scale) SigmaT:	0.045	SigmaR: 0.987	Ratio: 0.046

5.2.2.5.2.2 FP – 60 L/min

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for

ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

```

Reference-scaled:      Point estimate:  -0.0078
                      CI:                -0.0062
                      Pass/Fail:         PASS

Constant-scaled:     Point estimate:  -0.0221
                      CI:                -0.0214
                      Pass/Fail:         PASS

Overall Test Outcome: Pass/Fail:        PASS

```

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0 , PASS. For linearized theta P, if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	473.88	Mean: 473.99	Ratio: 99.98
		90% CI for ratio: (98.9,101.0)	
(log scale) Mean:	6.16	Mean: 6.16	Diff: -0.00
(log scale) CV:	0.72	CV: 0.91	
(log scale) SigmaBT:	0.033	SigmaBR: 0.000	Ratio: -
(log scale) SigmaWT:	0.029	SigmaWR: 0.056	Ratio: 0.521
(log scale) SigmaT:	0.044	SigmaR: 0.056	Ratio: 0.787

5.2.2.5.2.3 FP – 90 L/min

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for

ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

```

Reference-scaled:      Point estimate:  -0.0056
                      CI:                -0.0043
                      Pass/Fail:         PASS

Constant-scaled:     Point estimate:  -0.0213
                      CI:                -0.0205
                      Pass/Fail:         PASS

```

Overall Test Outcome: Pass/Fail: **PASS**

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0 , PASS. For linearized theta P, if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	482.08	Mean: 475.25	Ratio: 101.44
		90% CI for ratio: (100.4, 102.4)	
(log scale) Mean:	6.18	Mean: 6.16	Diff: 0.01
(log scale) CV:	0.71	CV: 0.81	
(log scale) SigmaBT:	0.032	SigmaBR: 0.000	Ratio: -
(log scale) SigmaWT:	0.030	SigmaWR: 0.050	Ratio: 0.596
(log scale) SigmaT:	0.044	SigmaR: 0.050	Ratio: 0.878

5.2.2.5.2.4 SA – 30 L/min

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for

ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled: Point estimate: -2.7094
CI: -2.2556
Pass/Fail: PASS

Constant-scaled: Point estimate: -0.7208
CI: -0.5241
Pass/Fail: PASS

Overall Test Outcome: Pass/Fail: **PASS**

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0 , PASS. For linearized theta P, if the upper bound of the confidence interval is > 0 , FAIL. If the estimate

of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	46.37	Mean: 27.83	Ratio: 166.60
		90% CI for ratio: (147.6, 188.0)	
(log scale) Mean:	3.84	Mean: 3.33	Diff: 0.51
(log scale) CV:	1.00	CV: 29.49	
(log scale) SigmaBT:	0.018	SigmaBR: 0.000	Ratio: -
(log scale) SigmaWT:	0.034	SigmaWR: 0.981	Ratio: 0.035
(log scale) SigmaT:	0.038	SigmaR: 0.981	Ratio: 0.039

5.2.2.5.2.5 SA – 60 L/min

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for

ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled: Point estimate: -0.0073
CI: -0.0058
Pass/Fail: PASS

Constant-scaled: Point estimate: -0.0219
CI: -0.0212
Pass/Fail: PASS

Overall Test Outcome: Pass/Fail: **PASS**

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0 , PASS. For linearized theta P, if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	47.39	Mean: 46.66	Ratio: 101.57
		90% CI for ratio: (100.6,102.6)	
(log scale) Mean:	3.86	Mean: 3.84	Diff: 0.02
(log scale) CV:	1.07	CV: 1.42	
(log scale) SigmaBT:	0.029	SigmaBR: 0.000	Ratio: -
(log scale) SigmaWT:	0.030	SigmaWR: 0.055	Ratio: 0.546
(log scale) SigmaT:	0.041	SigmaR: 0.055	Ratio: 0.758

5.2.2.5.2.6 SA – 90 L/min

In Vitro PBE Analysis - Approximate Confidence Interval
 Using Moment-Based Simplified Parameter Estimates
 for
 ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
 MIXED SCALING APPROACH
 Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0047
	CI:	-0.0035
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0209
	CI:	-0.0201
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0 , PASS. For linearized theta P, if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	48.13	Mean: 46.79	Ratio: 102.87
		90% CI for ratio: (102.0,103.8)	

(log scale)	Mean:	3.87	Mean:	3.85	Diff:	0.03
(log scale)	CV:	0.99	CV:	1.24		
(log scale)	SigmaBT:	0.025	SigmaBR:	0.000	Ratio:	-
(log scale)	SigmaWT:	0.029	SigmaWR:	0.048	Ratio:	0.614
(log scale)	SigmaT:	0.038	SigmaR:	0.048	Ratio:	0.808

5.2.2.5.3 Conclusions

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE				
REVIEW OF TESTING METHODS:				
Is the testing method validated?		Yes, but with deficiencies in method transfer		
Is the Quantitative Analytical Method Validated? (e.g., HPLC)		Yes		
Is testing performed as per RLD labeling?		Yes		
If yes, what is the actuation number tested?		Study protocol states that dose counter # 60 (beginning), 30 (middle) and 1 (end) were to be used. The actual dose counter# used were 60 or 59 (beginning), 30 or 29 (middle) and 1 (end).		
Are the testing methods acceptable?		ACCEPTABLE		
If not, why?		N/A		
STUDY RESULTS:				
Are data expressed as actual amount and % of label claim?		Yes		
Is the geo-mean of the test product (% of label claim) within 95-105%?			FP	SA
	Beginning	30 L/min	Yes (98.71%)	Yes (102.68%)
		60 L/min	Yes (102.03%)	No (105.26%)
		90 L/min	Yes (103.59%)	No (106.60%)
	Middle	30 L/min	Yes (97.32%)	Yes (101.22%)
		60 L/min	Yes (100.76%)	Yes (103.67%)
		90 L/min	Yes (102.50%)	No (105.67%)
	End	30 L/min	Yes (101.15%)	No (105.28%)
		60 L/min	Yes (102.95%)	No (107.02%)
		90 L/min	Yes (104.94%)	No (108.63%)
Are the PBE results acceptable?		Acceptable		
If not, why?		N/A		

Comments:

- The geo-mean of the test product is within 95-105% of label claim for FP for each of the 3 lifestages at each of the 3 flow rates. For SA, geo-mean of the test product is within 95-105% of label claim for BOL at 30 L/min flow rate, and for

MOL at 30 and 60 L/min flow rates, but is not within 95-105% of label claim for the rest of the conditions (please see **highlighted** in the table above). However, since the PBE analysis of both FP and SA met BE criteria, the reviewer will not pursue this issue further.

The applicant's pivotal SAC study for the 500/50 mcg strength is **acceptable**.

5.2.2.5.4 Deficiencies / Recommendations

N/A

5.2.2.6 Aerodynamic Particle Size Distribution (APSD) – 500/50 mcg strength

5.2.2.6.1 Results Summary – Aerodynamic Particle Size Distribution

Applicant's results - ISM

Flow Rate (L/min)	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
30	FP	BoL	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	(b) (4)
		EoL						
	Sal	BoL						
		EoL						
60	FP	BoL						
		EoL						
	Sal	BoL						
		EoL						
90	FP	BoL						
		EoL						
	Sal	BoL						
		EoL						

Reviewer's Results – 30 L/min

Aerodynamic Particle Size Distribution										
		Mean Drug Deposition (µg)		Variability (% CV)					Mean Ratio (I/R)	
				Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)	Geo (n=60)
		Arithm	Geo	Lot 1	Lot 2	Lot 3				
FP										
Delivered Dose (µg)	Test	(b) (4)								
	Ref									
Fine Particle Mass (µg)	Test									
	Ref									
Impactor-Sized Mass (µg)	Test									
	Ref									
SA										
Delivered Dose (µg)	Test	(b) (4)								
	Ref									
Fine Particle Mass (µg)	Test									
	Ref									
Impactor-Sized Mass (µg)	Test									
	Ref									

Reviewer's Results – 60 L/min

Aerodynamic Particle Size Distribution									
		Mean Drug Deposition (µg)		Variability (% CV)				Mean Ratio (I/R)	
				Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)
		Arithm	Geo	Lot 1	Lot 2	Lot 3			
FP									
Delivered Dose (µg)	Test	(b) (4)							
	Ref								
Fine Particle Mass (µg)	Test								
	Ref								
Impactor-Sized Mass (µg)	Test								
	Ref								
SA									
Delivered Dose (µg)	Test	(b) (4)							
	Ref								
Fine Particle Mass (µg)	Test								
	Ref								
Impactor-Sized Mass (µg)	Test								
	Ref								

Reviewer's Results – 90 L/min

Aerodynamic Particle Size Distribution									
		Mean Drug Deposition (µg)		Variability (% CV)				Mean Ratio (I/R)	
				Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	
		Arithm	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=60)
FP									
Delivered Dose (µg)	Test	(b) (4)							
	Ref								
Fine Particle Mass (µg)	Test								
	Ref								
Impactor-Sized Mass (µg)	Test								
	Ref								
SA									
Delivered Dose (µg)	Test	(b) (4)							
	Ref								
Fine Particle Mass (µg)	Test								
	Ref								
Impactor-Sized Mass (µg)	Test								
	Ref								

(b) (4)

Reviewer’s Comments:

- As mentioned in the original BE review, the applicant repeated 2 samples using new devices (please see table below), and each of these 2 samples were repeated for both FP and SA. The applicant also stated that these samples did not have the original data generated due to analysis being stopped prior to data generation. As detailed in the original BE review, the reviewer considers the applicant’s reason for original sample rejection acceptable. However, it should be noted that the applicant only repeated the sample at the end lifestage in the replacement devices. Therefore, these 2 samples containing lifestage data from different devices were excluded from the reviewer’s statistical evaluation.

Sample	Product	Batch number	Original inhaler number	Replacement inhaler number	Flow rate (L/min)	Reason for replacement
1	Advair	4ZP7022	7	111	30	Leak occurred while recovering preseparator, analysis halted.
2	MGR001	631-006	9	111	30	Collection cup insufficiently dry, analysis halted.

- As mentioned in the original BE review, in the study report MGR-REP-2015-097 (version 1.0, p. 13 of 178), the applicant stated that “for units 180 and 221 EOL 60 L/min, no acceptable data will be reported for FP and SA”. As detailed in Section 4.30, the reviewer disagrees with the rejection of these 2 original samples. Therefore, the reviewer used original data of these 2 samples.
- It is noted that the mass balance of reference product (% LC) at the 30 L/min flow rate has ranges outside of 85-115%, with multiple samples below 85% for FP and SA. This is consistent with the observation that the emitted dose of the reference product is highly variable and had multiple samples with low SAC values at 30 L/min flow rate of the SAC study. In addition, the mass balance passed PBE analysis. Therefore, the reviewer will not pursue this issue further.



5.2.2.6.3 Conclusions

AERODYNAMIC PARTICLE SIZE DISTRIBUTION	
REVIEW OF TESTING METHODS:	
Is the testing method for CI test validated?	Yes
Is the analytical method (e.g. HPLC) validated?	Yes
Is testing conducted as per RLD labeling?	Yes
Are the testing methods acceptable?	ACCEPTABLE
If not, why?	N/A
STUDY RESULTS:	

AERODYNAMIC PARTICLE SIZE DISTRIBUTION		
Results	Does Impactor Size Mass data pass PBE?	YES
	Does ISM data pass modified chi-square ratio test?	Yes for FP at 30, 60 and 90 L/min and SA at 30 L/min No for SA at 60 and 90 L/min
	Do mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle dose (FPD) pass PBE?	YES
Mass Balance	Is the mean range for Total B between 85-115% of the label claim? (on a per actuation basis)	YES, except for reference product at 30 L/min for both FP and SA
	Is PBE acceptable?	YES
If not, why?		N/A

Comments:

- The test product passes PBE analysis for ISM and mass balance. In addition, it passes the modified chi-square test using acceptance criteria of 25% difference for FP at 30, 60 and 90 L/min and SA at 30 L/min flow rates.

For SA at 60 L/min flow rate, the test product does not pass the modified chi-square test using acceptance criteria of 25% or 30% difference. However, it is noted that 1) modified chi-square test is not one of the BE tests in the product-specific guidance, and 2) the applicant conducted APSD study using the same strength of test product manufactured (b) (4) (please note that the test product used in the current in vitro BE study was manufactured (b) (4) (please see details in Section 5.2.4.6). Therefore, the reviewer will not pursue this issue further.

For SA at 90 L/min flow rate, the test product does not pass the modified chi-square test using acceptance criteria of 25% difference, but passes using acceptance criteria of 30% difference. DBI consulted ORS (which is the office who recommends conducting modified chi-square test for APSD study) on the acceptability of the APSD study based on this observation. ORS consult reviewer evaluated 1) the role of modified chi-square test under the current weight-of-evidence approach recommended in the product-specific guidance, 2) availability of in vivo BE information, and 3) impact of low deposition sites on modified chi-square test outcome, and considers that the current APSD study is acceptable.⁷⁹ Therefore, the reviewer will not pursue this issue further.

It is noted that in BE review of ANDA 209959 (Albuterol Inhalation Aerosol), the modified chi-square analysis also passed at the 30% difference but failed at the

⁷⁹ GDRP: ANDA-208891-ORIG-1-AMEND-22, Respond to Consult Request, 23136539_Conult response_ORs.doc, 5/25/2018.

25% difference for the APSD study. The BE reviewer of ANDA 209959 considered it acceptable since “this data is considered supportive only at this time

(b) (5)

(b) (5) ⁸⁰

- It is noted that the mass balance of reference product (% LC) at the 30 L/min flow rate has ranges outside of 85-115% for both FP and SA. As detailed in Section 5.2.2.6.1, the reviewer will not pursue this issue further.

The applicant’s pivotal APSD study for the 500/50 mcg strength is **acceptable**.

5.2.2.6.4 Deficiencies / Recommendations

N/A

⁸⁰ GDRP: ANDA-209959-ORIG-1, Bioequivalence Review, A209959N000DB-Review01-11032016, 12/26/2017.

5.2.3 Individual In Vitro-Test Reviews – Studies with 4 kPa Fixed Pressure Drop

Reviewer’s note: Instead of recording actuation numbers, the applicant recorded “dose counter number” for each of their in vitro BE studies. Please note that dose counter number starts with 60, and counts down by 1 following each adequate actuation. Test performed on dose counter # 60 corresponds to actuation #1, and test performed on dose counter #59 corresponds to actuation #2, and so on. To be consistent with the applicant, the reviewer will refer to dose counter number instead of actuation number in this Section 5.2.3.

5.2.3.1 Single Actuation Content through Container Life – 4 kPa Fixed Pressure Drop (100/50 mcg strength)

5.2.3.1.1 Results Summary

Applicant’s results

Pressure Drop	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
4 kPa	FP	BoL	100.25	94.36	1.06	2.78	2.55	1.09
		EoL	97.94	101.74	0.96	4.20	1.37	3.06
		MoL	99.13	97.99	1.01	5.44	2.35	2.32
	Sal	BoL	50.47	46.33	1.09	1.03	1.44	0.71
		EoL	49.26	50.01	0.98	2.30	0.62	3.68
		MoL	49.76	48.06	1.04	2.70	0.95	2.86

Reviewer's Results

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE													
		Dose Counter #	Mean				Variability (% CV)					Mean Ratio (T/R)	
			Drug Mass		% label claim		Within Lot (n=3)			Between Lot (n=3)	Total (n=9)	Arithm (n=9)	Geo (n=9)
			Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3				
FP													
BEG	Test	59	100.28	100.25	107.83	107.79	4.17	2.09	1.89	1.29	2.77	1.06	1.06
	Ref	59	94.39	94.36	101.50	101.47	3.60	1.28	2.57	1.66	2.70		
MID	Test	30	99.26	99.13	106.73	106.59	5.14	2.77	3.90	4.87	5.48	1.01	1.01
	Ref	30	98.02	97.99	105.39	105.37	0.85	1.57	1.83	2.33	2.39		
END	Test	1	98.02	97.94	105.40	105.31	3.87	2.02	2.20	4.08	4.29	0.96	0.96
	Ref	1	101.75	101.74	109.41	109.40	1.60	0.48	1.31	0.95	1.35		
SA													
BEG	Test	59	50.48	50.47	112.17	112.15	2.89	1.76	1.02	1.15	2.04	1.09	1.09
	Ref	59	46.35	46.33	103.00	102.95	2.79	1.39	2.30	2.82	3.11		
MID	Test	30	49.82	49.76	110.72	110.57	5.61	1.76	4.42	4.59	5.43	1.04	1.04
	Ref	30	48.07	48.06	106.82	106.80	0.85	1.48	1.63	1.81	1.97		
END	Test	1	49.31	49.26	109.57	109.47	3.80	2.05	2.64	4.51	4.66	0.99	0.98
	Ref	1	50.02	50.01	111.15	111.14	1.64	0.64	0.90	0.88	1.25		

Reviewer's Comments:

- As mentioned in the original BE review, according to CC13-0422⁸¹, the CC reviewer provided the following reasoning of recommending the 4 kPa fixed pressure drop study to the applicant: “[i]n literature, it has been reported that patients produce around 4 kPa pressure drop across the inhaler when inhale against resistances typical for the marketed DPIs. Comparable emitted dose and fine particle mass measured at 4kPa pressure drop for both the devices can provide additional confirmation that resistance difference between the RLD and MGR001 is acceptable.”

Based on the above information, the reviewer's emitted dose results are summarized above, which is in a good agreement with the applicant's results.

In addition, the reviewer also plotted the emitted dose at each life stage of each batch as shown below.

The emitted dose between the test and reference product for the 100/50 mcg strength at 4 kPa fixed pressure drop is considered comparable.

⁸¹ [\\cdsnas\OGDS6\CONTROLS\2013-docs\13-0422.pdf](#) p. 21 of 28.



- It is noted that the geo-mean of the test product (% of label claim) is not within 95-105% for both FP and SA at each of the 3 lifestages. However, since the emitted dose between the test and reference product is comparable, the mean emitted dose for the test product is within specification (no less than 85% and no more than 115 of the target emitted dose), and Drug Product review did not raise concern on the use of these batches for in vitro studies, the reviewer will not pursue this issue further.

- As detailed in Section 4.31, no PBE analysis will be conducted.

5.2.3.1.2 Conclusions

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE		
REVIEW OF TESTING METHODS:		
Is the testing method validated?	Yes	
Is the Quantitative Analytical Method Validated? (e.g., HPLC)	Yes	
Is testing performed as per RLD labeling?	Yes	
Is testing a single actuation per determination?	Yes	
If yes, what is the actuation number tested?	Dose counter #s 59 (beginning), 30 (middle) and 1 (end)	
Are the testing methods acceptable?	ACCEPTABLE	
If not, why?	N/A	
STUDY RESULTS:		
Are data expressed as actual amount and % of label claim?	Yes	
Is the geo-mean of the test product (% of label claim) within 95-105%?	Beginning	No
	Middle	No
	End	No
Are the PBE results acceptable?	N/A	
If not, why?	N/A	

Comments:

- The emitted dose for test and reference product of the 100/50 mcg strength at 4 kPa fixed pressure drop are comparable.
- It is noted that the geo-mean of the test product (% of label claim) is not within 95-105% for both FP and SA at each of the 3 lifestages. However, as mentioned in Section 5.2.3.1.1, since the emitted dose between the test and reference product is comparable, the mean emitted dose for the test product is within specification (no less than 85% and no more than 115 of the target emitted dose), and Drug Product review did not raise concern on the use of these batches for in vitro studies, the reviewer will not pursue this issue further.

The applicant's SAC study at 4 kPa fixed pressure drop for the 100/50 mcg strength is **acceptable**.

5.2.3.1.3 Deficiencies / Recommendations

N/A

APPEARS THIS WAY ON
ORIGINAL

5.2.3.2 Aerodynamic Particle Size Distribution (APSD) – 4 kPa Fixed Pressure Drop (100/50 mcg strength)

5.2.3.2.1 Results Summary – Aerodynamic Particle Size Distribution

Applicant's results - ISM

Pressure Drop	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
4 kPa	FP	BoL	(b) (4)					
		EoL						
	Sal	BoL						
		EoL						

Reviewer's Results

Aerodynamic Particle Size Distribution										
		Mean Drug Deposition (µg)		Variability (% CV)					Mean Ratio (T/R)	
				Within Lot (n=3)			Between Lot (n=3)	Total (n=9)	Arithm (n=9)	Geo (n=9)
		Arithm	Geo	Lot 1	Lot 2	Lot 3				
FP										
Delivered Dose (µg)	Test	(b) (4)								
	Ref									
Fine Particle Mass (µg)	Test									
	Ref									
Impactor-Sized Mass (µg)	Test									
	Ref									
SA										
Delivered Dose (µg)	Test	(b) (4)								
	Ref									
Fine Particle Mass (µg)	Test									
	Ref									
Impactor-Sized Mass (µg)	Test									
	Ref									

Reviewer's Comments:

- As mentioned in the original BE review, according to CC13-0422⁸², the CC reviewer provided the following reasoning of recommending the 4 kPa fixed pressure drop study to the applicant: “[i]n literature, it has been reported that patients produce around 4 kPa pressure drop across the inhaler when inhale against resistances typical for the marketed DPIs. Comparable emitted dose and fine particle mass measured at 4kPa pressure drop for both the devices can provide additional confirmation that resistance difference between the RLD and MGR001 is acceptable.”

The reviewer's FPM, mass balance, and ISM results are summarized in the table above.

In addition, the reviewer also plotted the FPM at each life stage of each batch as shown below.

The FPM between the test and reference product for the 100/50 mcg strength at 4 kPa fixed pressure drop is considered comparable.

⁸² <\\cdsnas\OGDS6\CONTROLS\2013-docs\13-0422.pdf> p. 21 of 28.



5.2.3.2.2 Conclusions

AERODYNAMIC PARTICLE SIZE DISTRIBUTION	
REVIEW OF TESTING METHODS:	
Is the testing method for CI test validated?	Yes

AERODYNAMIC PARTICLE SIZE DISTRIBUTION		
Is the analytical method (e.g. HPLC) validated?	Yes	
Is testing conducted as per RLD labeling?	Yes	
Are the testing methods acceptable?	ACCEPTABLE	
If not, why?	N/A	
STUDY RESULTS:		
Is drug deposition reported in mass units?	Yes	
Is the mass balance data reported?	Yes	
Results	Does Impactor Size Mass data pass PBE?	N/A
	Does ISM data pass modified chi-square ratio test?	N/A
	Do mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle dose (FPD) pass PBE?	N/A
Mass Balance	Is the mean range for Total B between 85-115% of the label claim? (on a per actuation basis)	Yes
	Is PBE acceptable?	N/A
If not, why?	N/A	

Comments:

- The FPM for test and reference product of the 100/50 mcg strength at 4 kPa fixed pressure drop are comparable.

The applicant's APSD study at 4 kPa fixed pressure drop for the 100/50 mcg strength is **acceptable**.

5.2.3.2.3 Deficiencies / Recommendations

N/A

5.2.3.3 Single Actuation Content through Container Life – 4 kPa Fixed Pressure Drop (250/50 mcg strength)

5.2.3.3.1 Results Summary

Applicant's results

Pressure Drop	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
4 kPa	FP	BoL	235.08	236.16	1.00	6.02	6.12	0.98
		EoL	241.86	241.06	1.00	9.41	10.63	0.89
		MoL	243.82	239.04	1.02	7.72	7.44	1.04
	Sal	BoL	47.57	46.59	1.02	0.80	1.19	0.67
		EoL	48.19	47.99	1.00	1.44	1.60	0.90
		MoL	48.45	47.65	1.02	1.81	1.59	1.14

Reviewer's Results

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE													
		Dose Counter #	Mean				Variability (% CV)					Mean Ratio (T/R)	
			Drug Mass		% label claim		Within Lot (n=3)			Between Lot (n=3)	Total (n=9)	Arithm (n=9)	Geo (n=9)
			Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3				
FP													
BEG	Test	59	235.15	235.08	100.92	100.89	1.38	2.35	1.07	2.43	2.56	1.00	1.00
	Ref	59	236.23	236.16	101.38	101.36	0.72	4.03	2.15	1.30	2.59		
MID	Test	30	243.93	243.82	104.69	104.64	0.90	1.21	5.82	1.20	3.16	1.02	1.02
	Ref	30	239.14	239.04	102.64	102.59	2.62	0.18	5.53	0.74	3.11		
END	Test	1	242.02	241.86	103.87	103.80	2.70	1.78	5.97	2.31	3.89	1.00	1.00
	Ref	1	241.27	241.06	103.55	103.46	1.26	5.60	5.63	2.08	4.41		
SA													
BEG	Test	59	47.58	47.57	105.73	105.71	1.75	0.97	0.98	1.44	1.67	1.02	1.02
	Ref	59	46.60	46.59	103.56	103.54	0.95	3.73	2.16	1.45	2.56		
MID	Test	30	48.48	48.45	107.73	107.66	2.43	1.52	6.44	1.52	3.74	1.02	1.02
	Ref	30	47.68	47.65	105.95	105.89	2.00	1.19	5.72	1.58	3.34		
END	Test	1	48.21	48.19	107.14	107.10	1.13	1.70	5.39	1.02	2.99	1.00	1.00
	Ref	1	48.02	47.99	106.71	106.65	1.14	4.15	4.39	1.45	3.32		

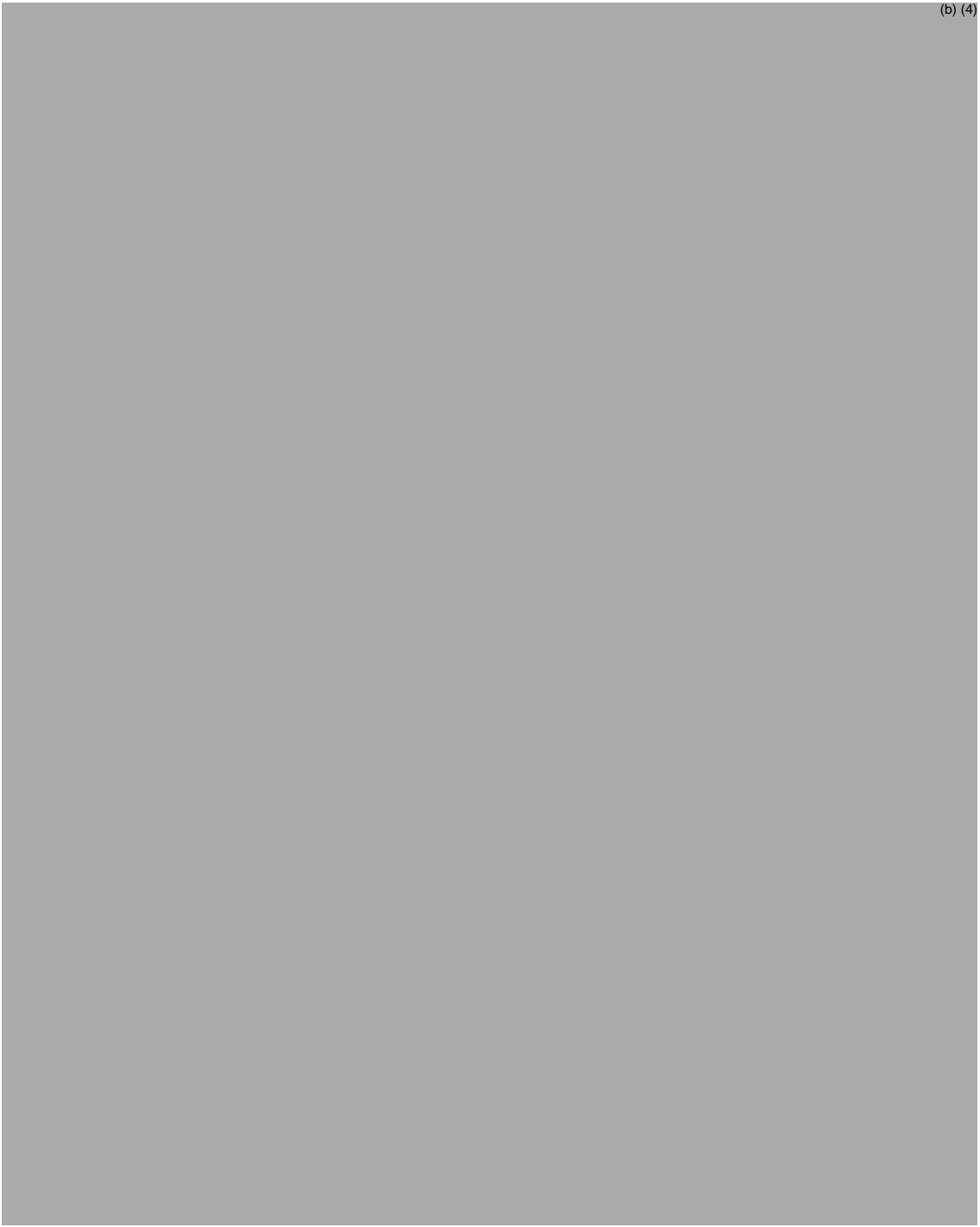
Reviewer's Comments:

- The reviewer's results are in good agreement with the applicant's results.

The reviewer also plotted the emitted dose at each life stage of each batch as shown below.

The emitted dose between the test and reference product for the 250/50 mcg strength at 4 kPa fixed pressure drop is considered comparable.

(b) (4)



- It is noted that the geo-mean of the test product (% of label claim) is not within 95-105% for SA at each of the 3 lifestages. However, since the emitted dose between the test and reference product is comparable, the mean emitted dose for the test product is within specification (no less than 85% and no more than 115 of

the target emitted dose), and Drug Product review did not raise concern on the use of these batches for in vitro studies, the reviewer will not pursue this issue further.

- As detailed in Section 4.31, no PBE analysis will be conducted.

5.2.3.3.2 Conclusions

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE		
REVIEW OF TESTING METHODS:		
Is the testing method validated?	Yes	
Is the Quantitative Analytical Method Validated? (e.g., HPLC)	Yes	
Is testing performed as per RLD labeling?	Yes	
If yes, what is the actuation number tested?	Dose counter #s 59 (beginning), 30 (middle) and 1 (end)	
Are the testing methods acceptable?	Acceptable	
If not, why?	N/A	
STUDY RESULTS:		
Are data expressed as actual amount and % of label claim?	Yes	
Is the geo-mean of the test product (% of label claim) within 95-105%?	Beginning	Yes for FP, no for SA
	Middle	Yes for FP, no for SA
	End	Yes for FP, no for SA
Are the PBE results acceptable?	N/A	
If not, why?	N/A	

Comments:

- The emitted dose for test and reference product of the 250/50 mcg strength at 4 kPa fixed pressure drop are comparable.
- It is noted that the geo-mean of the test product (% of label claim) is not within 95-105% for SA at each of the 3 lifestages. However, as mentioned in Section 5.2.3.3.1, since the emitted dose between the test and reference product is comparable, the mean emitted dose for the test product is within specification (no less than 85% and no more than 115 of the target emitted dose), and Drug Product review did not raise concern on the use of these batches for in vitro studies, the reviewer will not pursue this issue further.

The applicant's SAC study at 4 kPa fixed pressure drop for the 250/50 mcg strength is **acceptable**.

5.2.3.3.3 Deficiencies / Recommendations

N/A

APPEARS THIS WAY ON
ORIGINAL

5.2.3.4 Aerodynamic Particle Size Distribution (APSD) – 4 kPa Fixed Pressure Drop (250/50 mcg strength)

5.2.3.4.1 Results Summary – Aerodynamic Particle Size Distribution

Applicant's results - ISM

Pressure Drop	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
4 kPa	FP	BoL	(b) (4)					
		EoL						
	Sal	BoL						
		EoL						

Reviewer's Results

Aerodynamic Particle Size Distribution										
		Mean Drug Deposition (μg)		Variability (% CV)					Mean Ratio (T/R)	
				Within Lot (n=3)			Between Lot (n=3)	Total (n=9)	Arithm (n=9)	Geo (n=9)
		Arithm	Geo	Lot 1	Lot 2	Lot 3				
FP										
Delivered Dose (μg)	Test	(b) (4)								
	Ref									
Fine Particle Mass (μg)	Test									
	Ref									
Impactor-Sized Mass (μg)	Test									
	Ref									
SA										
Delivered Dose (μg)	Test	(b) (4)								
	Ref									
Fine Particle Mass (μg)	Test									
	Ref									
Impactor-Sized Mass (μg)	Test									
	Ref									

Reviewer's Comments:

- The reviewer's FPM, mass balance, and ISM results are summarized in the table above.

In addition, the reviewer also plotted the FPM at each life stage of each batch as shown below.

The FPM between the test and reference product for the 250/50 mcg strength at 4 kPa fixed pressure drop is considered comparable.

5.2.3.4.2 Conclusions

AERODYNAMIC PARTICLE SIZE DISTRIBUTION		
REVIEW OF TESTING METHODS:		
Is the testing method for CI test validated?	Yes	
Is the analytical method (e.g. HPLC) validated?	Yes	
Is testing conducted as per RLD labeling?	Yes	
Are the testing methods acceptable?	Acceptable	
If not, why?	N/A	
STUDY RESULTS:		
Is drug deposition reported in mass units?	Yes	
Is the mass balance data reported?	Yes	
Results	Does Impactor Size Mass data pass PBE?	N/A
	Does ISM data pass modified chi-square ratio test?	N/A

AERODYNAMIC PARTICLE SIZE DISTRIBUTION		
	Do mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle dose (FPD) pass PBE?	N/A
Mass Balance	Is the mean range for Total B between 85-115% of the label claim? (on a per actuation basis)	Yes
	Is PBE acceptable?	N/A
If not, why?		N/A

Comments:

- The FPM for test and reference product of the 100/50 mcg strength at 4 kPa fixed pressure drop are comparable.

The applicant's APSD study at 4 kPa fixed pressure drop for the 250/50 mcg strength is **acceptable**.

5.2.3.4.3 Deficiencies / Recommendations

N/A

5.2.3.5 Single Actuation Content through Container Life – 4 kPa Fixed Pressure Drop (500/50 mcg strength)

5.2.3.5.1 Results Summary

Applicant's results

Pressure Drop	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
4 kPa	FP	BoL	469.81	460.87	1.02	21.45	8.07	2.66
		EoL	484.52	496.93	0.98	20.94	21.12	0.99
		MoL	469.69	485.83	0.97	23.92	12.49	1.92
	Sal	BoL	47.07	45.61	1.03	1.21	0.94	1.29
		EoL	48.48	48.95	0.99	1.66	2.11	0.78
		MoL	47.35	47.86	0.99	2.16	1.16	1.86

Reviewer's Results

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE													
		Dose Counter #	Mean				Variability (% CV)					Mean Ratio (T/R)	
			Drug Mass		% label claim		Within Lot (n=3)			Between Lot (n=3)	Total (n=9)	Arithm (n=9)	Geo (n=9)
			Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3				
FP													
BEG	Test	59	470.24	469.81	101.13	101.04	2.92	6.29	2.04	3.12	4.56	1.02	1.02
	Ref	59	460.93	460.87	99.12	99.11	1.87	0.85	2.53	0.76	1.75		
MID	Test	30	470.24	469.69	101.13	101.01	5.33	4.65	5.23	2.98	5.09	0.97	0.97
	Ref	30	485.98	485.83	104.51	104.48	1.56	2.27	3.13	1.71	2.57		
END	Test	1	484.92	484.52	104.28	104.20	3.46	5.13	2.06	3.29	4.32	0.98	0.98
	Ref	1	497.34	496.93	106.96	106.87	2.28	5.03	0.55	3.79	4.25		
SA													
BEG	Test	59	47.08	47.07	104.63	104.60	2.33	3.43	0.96	1.64	2.57	1.03	1.03
	Ref	59	45.62	45.61	101.37	101.35	1.73	0.71	3.59	0.43	2.06		
MID	Test	30	47.40	47.35	105.32	105.22	5.05	5.00	4.07	2.29	4.55	0.99	0.99
	Ref	30	47.88	47.86	106.39	106.36	1.55	2.00	2.77	1.77	2.43		
END	Test	1	48.50	48.48	107.79	107.73	3.08	4.90	0.50	2.10	3.41	0.99	0.99
	Ref	1	48.99	48.95	108.88	108.78	2.09	5.15	0.55	3.89	4.32		

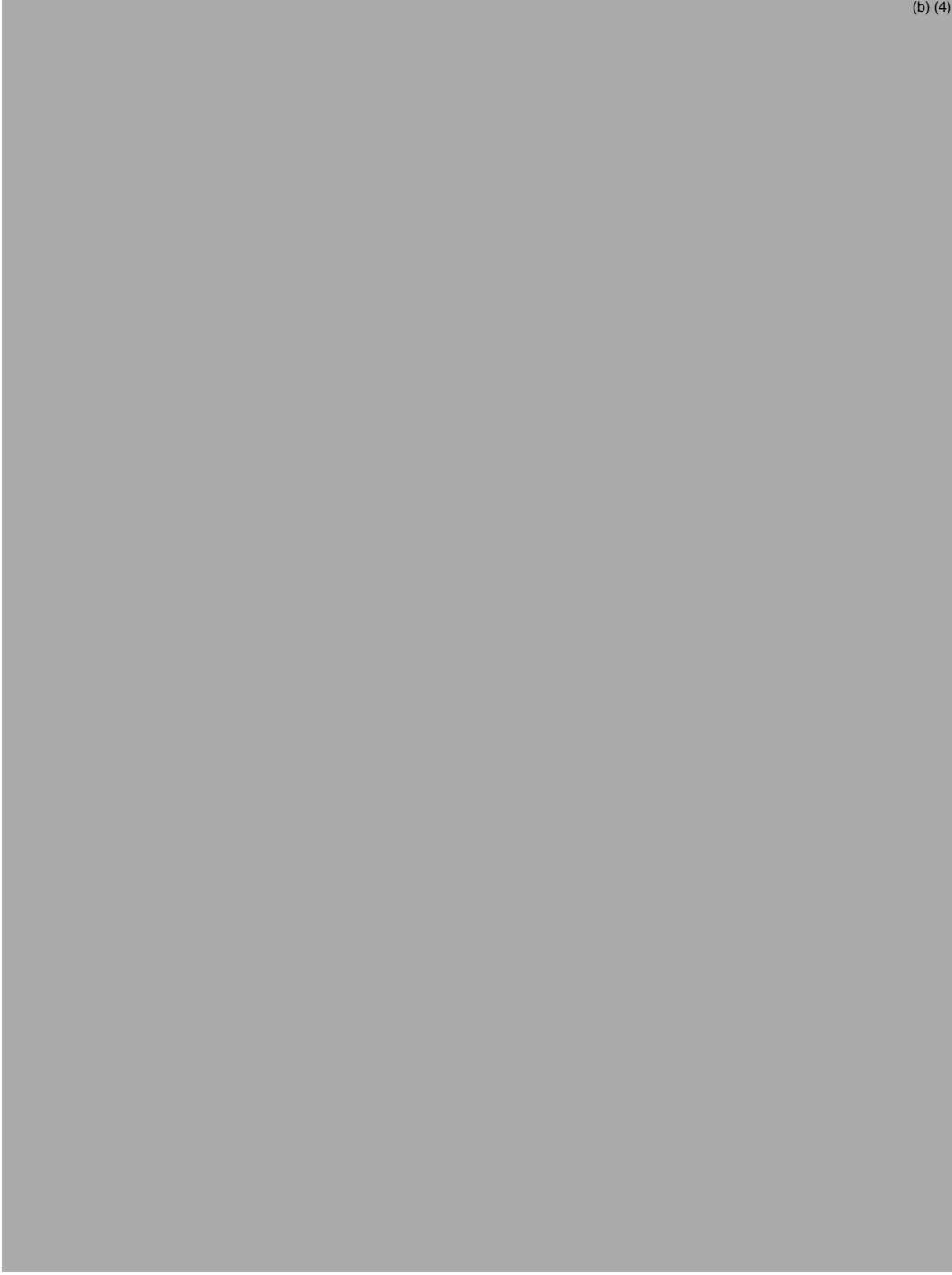
Reviewer's Comments:

- The reviewer's results are in good agreement with the applicant's results.

The reviewer also plotted the emitted dose at each life stage of each batch as shown below.

The emitted dose between the test and reference product for the 500/50 mcg strength at 4 kPa fixed pressure drop is considered comparable.

(b) (4)



- It is noted that the geo-mean of the test product (% of label claim) is not within 95-105% for SA at MOL and EOL. However, since the emitted dose between the test and reference product is comparable, the mean emitted dose for the test product is within specification (no less than 85% and no more than 115% of the

target emitted dose), and Drug Product review did not raise concern on the use of these batches for in vitro studies, the reviewer will not pursue this issue further.

- As detailed in Section 4.31, no PBE analysis will be conducted.

5.2.3.5.2 Conclusions

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE		
REVIEW OF TESTING METHODS:		
Is the testing method validated?	Yes	
Is the Quantitative Analytical Method Validated? (e.g., HPLC)	Yes	
Is testing performed as per RLD labeling?	Yes	
Is testing a single actuation per determination?	Yes	
If yes, what is the actuation number tested?	Dose counter#s 59 (beginning), 30 (middle) and 1 (end)	
Are the testing methods acceptable?	ACCEPTABLE	
If not, why?	N/A	
STUDY RESULTS:		
Are data expressed as actual amount and % of label claim?	Yes	
Is the geo-mean of the test product (% of label claim) within 95-105%?	Beginning	Yes, except for SA at MOL and EOL
	Middle	Yes, except for SA at MOL and EOL
	End	Yes, except for SA at MOL and EOL
Are the PBE results acceptable?	N/A	
If not, why?	N/A	

Comments:

- The emitted dose for test and reference product of the 500/50 mcg strength at 4 kPa fixed pressure drop are comparable.
- It is noted that the geo-mean of the test product (% of label claim) is not within 95-105% for SA at MOL and EOL. However, as mentioned in Section 5.2.3.5.1, since the emitted dose between the test and reference product is comparable, the mean emitted dose for the test product is within specification (no less than 85% and no more than 115 of the target emitted dose), and Drug Product review did not raise concern on the use of these batches for in vitro studies, the reviewer will not pursue this issue further.

The applicant's SAC study at 4 kPa fixed pressure drop for the 500/50 mcg strength is acceptable.

5.2.3.5.3 Deficiencies / Recommendations

N/A

APPEARS THIS WAY ON
ORIGINAL

5.2.3.6 Aerodynamic Particle Size Distribution (APSD) – 4 kPa Fixed Pressure Drop (500/50 mcg strength)

5.2.3.6.1 Results Summary – Aerodynamic Particle Size Distribution

Applicant's results - ISM

Pressure Drop	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
4 kPa	FP	BoL	(b) (4)					
		EoL						
	Sal	BoL						
		EoL						

Reviewer's Results

Aerodynamic Particle Size Distribution										
		Mean Drug Deposition (µg)		Variability (% CV)					Mean Ratio (T/R)	
				Within Lot (n=3)			Between Lot (n=3)	Total (n=9)	Arithm (n=9)	Geo (n=9)
		Arithm	Geo	Lot 1	Lot 2	Lot 3				
FP										
Delivered Dose (µg)	Test	(b) (4)								
	Ref									
Fine Particle Mass (µg)	Test									
	Ref									
Impactor-Sized Mass (µg)	Test									
	Ref									
SA										
Delivered Dose (µg)	Test	(b) (4)								
	Ref									
Fine Particle Mass (µg)	Test									
	Ref									
Impactor-Sized Mass (µg)	Test									
	Ref									

Reviewer's Comments:

- The reviewer's FPM, mass balance, and ISM results are summarized in the table above.

In addition, the reviewer also plotted the FPM at each life stage of each batch as shown below.

The FPM between the test and reference product for the 500/50 mcg strength at 4 kPa fixed pressure drop is considered comparable.

5.2.3.6.2 Conclusions

AERODYNAMIC PARTICLE SIZE DISTRIBUTION		
REVIEW OF TESTING METHODS:		
Is the testing method for CI test validated?	Yes	
Is the analytical method (e.g. HPLC) validated?	Yes	
Is testing conducted as per RLD labeling?	Yes	
Are the testing methods acceptable?	ACCEPTABLE	
If not, why?	N/A	
STUDY RESULTS:		
Is drug deposition reported in mass units?	Yes	
Is the mass balance data reported?	Yes	
Results	Does Impactor Size Mass data pass PBE?	N/A
	Does ISM data pass modified chi-square ratio test?	N/A

AERODYNAMIC PARTICLE SIZE DISTRIBUTION		
	Do mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle dose (FPD) pass PBE?	N/A
Mass Balance	Is the mean range for Total B between 85-115% of the label claim? (on a per actuation basis)	Yes
	Is PBE acceptable?	N/A
If not, why?		N/A

Comments:

- The FPM for test and reference product of the 500/50 mcg strength at 4 kPa fixed pressure drop are comparable.

The applicant's APSD study at 4 kPa fixed pressure drop for the 500/50 mcg strength is **acceptable**.

5.2.3.6.3 Deficiencies / Recommendations

N/A

5.2.4 Individual In Vitro-Test Reviews – Bridging Studies (60 L/min)

Reviewer’s note: Instead of recording actuation numbers, the applicant recorded “dose counter number” for each of their in vitro BE studies. Please note that dose counter number starts with 60, and counts down by 1 following each adequate actuation. Test performed on dose counter # 60 corresponds to actuation #1, and test performed on dose counter #59 corresponds to actuation #2, and so on. To be consistent with the applicant, the reviewer will refer to dose counter number instead of actuation number in this Section 5.2.4.

5.2.4.1 Single Actuation Content through Container Life (100/50 mcg strength)

5.2.4.1.1 Study Information

Study No.	MGR-PRO-2016-106
Study Site	Mylan Global Respiratory Group, IPC008, Discovery Park House, Floor 3, Sandwich, Kent. CT13 9ND. UK
Principal Investigator	Karen Weaver
Study Dates	1/4/2017-2/9/2017
SOP No.	MGR-METH-546070 (v. 9.0)*
SOP Effective Date	6/9/2016
SOP Title	Determination of Emitted Dose of MGR001 (PF-04764793) from Multidose Powder Inhalation Devices using (b) (4) (b) (4)
Test Method Description	(b) (4) for Dry Powder Inhalers (DPIs) is used to determine the single actuation content (emitted dose (ED)) of MGR001 in 100/50, 250/50 and 500/50 mcg multidose dry powder inhalers containing 100, 250 or 500 mcg Fluticasone propionate and 50 mcg Salmeterol as Xinafoate salt respectively and for Advair® Diskus® and Seretide® Accuhaler® Reference Listed Drug (RLD).
Testing Equipment Used (e.g., name, model, etc)	USP <601> Apparatus B with modified end caps
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	60 L/min flow rate; 2 L volume. Testing carried out at ambient laboratory conditions.
Analytical Method Description	(b) (4)
Analytical Equipment Used (e.g., name, model, etc.)	(b) (4) UPLC

* Applicant’s note: Method MGR-METH-546070 is used in conjunction with methods MGR-METH-753121⁸³ and MGR-METH-753122⁸⁴. These additional methods are focused on the operation of the relevant device, and therefore do not require validation.

⁸³ Although the applicant did not specify it in the table footnote, MGR-METH-753121 is “Method for the Use of the Diskus® and Accuhaler™ Device Holder”, version 1.0, effective 8/12/2016.

⁸⁴ Although the applicant did not specify it in the table footnote, MGR-METH-753122 is “Method for the Use of the CRC749 Device Holder”, version 1.0, effective 8/15/2016.

Comments:

Reviewer’s note: The applicant conducted SAC and APSD tests on the same device. Therefore, some of the comments below are common to both SAC and APSD study design (please see “General Comments” below). For reviewer’s comments specific for SAC study, please see “Comments for SAC” below.

General Comments

- The test was conducted on 3 lots of test and 3 lots of reference product. For each lot, 20 test and 20 reference devices were tested, with 3 replicates of SAC (beginning, middle, and end), and 2 replicates of APSD (beginning and end) collected from each device. Each SAC and APSD study was conducted at 60 L/min. This is in accordance with the pre-ANDA meeting request 844398⁸⁵.
- According to the study protocol, the following are the dose counter #s used for SAC and APSD testing. Please note that the applicant conducted SAC (ED) and APSD (NGI) test on the same device.

Test Sequence Dose counter number	Procedure	Testing to be Performed	Test Day
60	ED Beginning	Emitted Dose at target flow	1
59	(b) (4) Beginning	(b) (4) at target flow	
58-33	Waste	Wasting at target flow	
Leave device to rest at least overnight			
32-31	Waste	Wasting at target flow	2
30	ED Middle	Emitted Dose at target flow	
29-5	Waste	Wasting at target flow	
Leave device to rest at least overnight			
4-3	Waste	Wasting at target flow	3
2	(b) (4) End	(b) (4) at target flow	
1	ED End	Emitted Dose at target flow	

NA = Not Applicable

- According to the study protocol, to clear the test device of any potentially extraneous powder, an extra solenoid activation was recommended after a final waste shot, just prior to an ED or (b) (4) collection.
- The applicant also referenced MGR-METH-753121 (v. 1.0, effective 8/12/2016) “Method for the Use of the Diskus® and Accuhaler™ Device Holder”, and MGR-METH-753122 (v. 1.0, effective 8/15/2016) “Method for the Use of the CRC749 Device Holder” in the study protocol. According to these 2 methods, as detailed in Section 4.12, the test and reference devices were set up in the correct orientation.

Comments for SAC

⁸⁵ GDRP: Meeting Request 844398, Primary Review, 844398_Review.doc, 10/19/2015.

- The method referenced in this study (MGR-METH-546070, Version 9.0) is a newer version of the method referenced in the pivotal in vitro BE studies in Section 5.3.2 (MGR-METH-546070, Version 7.0). Based on the method revision history⁸⁶ provide by the applicant, minor changes (e.g. typo correction and clarifications) were made from Version 7.0 to Version 9.0, and are not expected to affect study outcome.
- According to the study protocol, flow rates and actuation times for testing are as follow:

Flow Rate (L/min)	ED Actuation Time (seconds)	Wasting Actuation Time (seconds)
60	2.0	2.0

This is in line with product-specific guidance’s recommendation that the volume of air drawn through the delivery system should be 2L for SAC study.

5.2.4.1.2 Analytical Method Validation for UPLC

Same as the pivotal SAC study for the 100/50 mcg strength.

5.2.4.1.3 Calibration of Manual and/or Automated Spray Pump Actuator (For the Single Actuation Content Study)

Same as the pivotal SAC study for the 100/50 mcg strength.

5.2.4.1.4 Results Summary

Applicant’s results

Active	Lifestage	GM (I)	GM (R)	GMR (I/R)	SD (I)	SD (R)	SD ratio (I/R)
FP	BoL	96.57	91.94	1.05	3.98	5.26	0.76
	MoL	96.36	96.30	1.00	3.29	3.07	1.07
	EoL	98.22	100.89	0.97	3.86	5.14	0.75
Sal	BoL	48.65	45.31	1.07	1.62	2.46	0.66
	MoL	48.82	47.38	1.03	1.45	1.56	0.93
	EoL	49.27	49.20	1.00	1.48	2.43	0.61

⁸⁶ GS Review: ANDA 208891, Quality/Quality Information, 3/2/2017 (Module 3.2.P.2\MGR-METH-546070 Version 9.0 – Determination of Emittted Dose of MGR001, and \MGR-METH-546070 Version 9.0 – Determination of Emittted Dose of MGR001 – (b) (4), p. 19 of 41).

Reviewer's Results

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE													
		Dose Counter #	Mean				Variability (% CV)					Mean Ratio (I/R)	
			Drug Mass		% label claim		Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)	Geo (n=60)
			Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3				
FP													
BEG	Test	60	97.16	97.04	104.47	104.34	6.33	3.12	4.54	1.76	5.03	1.05	1.06
	Ref	60	92.11	91.95	99.04	98.87	4.24	3.50	4.08	5.26	5.94		
MID	Test	30	96.54	96.48	103.81	103.74	3.66	3.95	2.17	1.68	3.50	1.00	1.00
	Ref	30	96.11	96.07	103.35	103.30	2.78	2.89	2.29	2.02	3.09		
END	Test	1	97.61	97.55	104.96	104.90	3.96	3.15	2.96	1.15	3.45	0.97	0.97
	Ref	1	100.75	100.62	108.33	108.20	4.48	1.59	3.90	4.29	4.93		
SA													
BEG	Test	60	48.69	48.66	108.19	108.13	3.45	1.91	3.94	1.55	3.45	1.07	1.07
	Ref	60	45.38	45.31	100.85	100.69	3.87	3.12	3.85	5.09	5.63		
MID	Test	30	48.80	48.78	108.45	108.40	2.95	2.87	2.68	1.48	3.01	1.03	1.03
	Ref	30	47.24	47.21	104.97	104.92	2.81	3.05	2.27	2.17	3.21		
END	Test	1	49.14	49.12	109.20	109.16	2.59	2.36	2.71	0.92	2.62	1.00	1.00
	Ref	1	49.21	49.16	109.36	109.24	3.85	1.67	3.49	4.58	4.82		

Reviewer's Comments:

- It is noted that the applicant's study protocol has the following statement for lost sample collections:

"If during sample preparation, a sample is lost due to an assignable cause (e.g., (b) (4) tube leakage, dropped (b) (4) plate, etc.) during Beginning or Middle-of-Life, the lost sample will be documented and supervisory approval will be obtained to cease further collection/recovery of the sample. A new sample will be prepared from the next dose(s) of the same device per the test method. The tests ...may be performed within ±3 doses..."

For sample lost at the End-of-Life due to an assignable cause, the lost sample will be documented and supervisory approval will be obtained to cease further collection/recovery of the sample.

Beginning and Middle-of-Life collections/results, as well as any successfully collected End-of-Life results from this device will be used as-is.

Where possible, a new device will be used to repeat any lost End-of-Life collections and/or continue testing any End-of-Life collections not originally performed.”

According to study protocol, the SAC study should be performed at dose counter #60 for BOL, #30 for MOL and #1 for EOL. The reviewer checked the applicant’s SAS dataset, and noticed that the following samples had dose counter number other than #s 60, 30 and 1, thus the original samples were likely lost. In the 3/22/2018 DRL response, the applicant provided reason for using alternate dose counter number (please see the table below).

Product	Batch	Unit	Stage	Dose Counter Number	Applicant’s Reason
REF	6ZP7030	84R*	BOL	59	(b) (4) tube leaked after adding the diluent, therefore DCN 59 used.
REF	6ZP7784	111	BOL	59	(b) (4) tube leaked when placed on the rotational shaker, therefore DCN 59 used.

* As mentioned in the bullet point below, this is a replacement device. No original data generated for Unit 84 due to incorrect preparation of mobile phase and diluent.

In the 3/22/2018 DRL response, the applicant stated that for the above samples, no original data was generated, in accordance with the protocol, upon identifying the issue, the analyst sought approval to halt the sample preparation and fire the next available dose counter number (DCN). Based on the reason provided by the applicant, the reviewer considers the applicant rejection of the aforementioned original samples acceptable. However, for both units above, as detailed in the bullet point below, since neither of them had all lifestages tested on the same device (for Unit 84R of reference batch 6ZP7030, only BOL was tested on the replacement device; for unit 111 of reference batch 6ZP7784, only EOL was repeated on the replacement device Unit 111R), these samples will be excluded from reviewer’s statistical evaluation.

- It is also noted that the applicant repeated the following 18 samples using new devices, and each of these 18 samples were repeated for both FP and SA. The applicant stated that the original samples were not analyzed. The reviewer considers the reason for original sample rejection acceptable. However, it should be noted that the applicant only repeated the sample at the end lifestage in the above replacement devices. Therefore, these 18 samples containing lifestage data from different devices were excluded from the reviewer’s statistical evaluation.

Number	Product	Batch number	Original device number	Replacement device number	Life stage	Reason for replacement
1-3	MGR001	60000338	4,7,17	4R, 7R, 17R	BoL	Incorrect preparation of mobile phase and diluent occurred. This was used to prepare original test samples. The samples were not analysed.
4-6	MGR001	60000343	27, 29,30	27R, 29 R, 30R	BoL	
7-8	MGR001	60000344	42,57	42R, 57R	BoL	
9-10	Advair® Diskus®	6ZP4764	65,69	65R, 69R	BoL	
11-16	Advair® Diskus®	6ZP7030	82, 83, 84,87, 90,94	82R, 83R, 84R, 87R, 90R, 94R	BoL	
17	Advair® Diskus®	6ZP7784	107	107R	BoL	
18	Advair® Diskus®	6ZP7784	111	111R	EoL	Leak occurred in dose collection tube during sample recovery. No analysis of resulting solution was undertaken.

- In addition, the following 3 samples were rejected but no replacement devices were used (due to insufficient number of inhalers available for replacement, according to the applicant's 3/22/2018 DRL response). The applicant stated that their original samples were not analyzed. Thus the reviewer considers that the original sample rejection is acceptable.

Product	Batch number	Original device number	Life stage	Reason for replacement
MGR001	60000343	31, 33, 36	BoL	Incorrect preparation of mobile phase and diluent occurred. This was used to prepare original test samples. The samples were not analysed.

- In the study report, the applicant also stated that one laboratory investigation was instigated for device #8, batch 60000338 at BOL. The applicant stated that FP SAC value was aberrantly high (115.124 mcg), and the SA result was expected (48.690 mcg). The applicant's conclusion of the investigation was that the original HPLC vial had been contaminated and thus the original result was invalidated. The applicant stated that the retained solution stored in a volumetric flask gave normal results and these results for both FP and SA were reported.

According to the study protocol, aberrant results should be investigated in accordance with MGR-SOP-ACD-GEN-0025. According to this SOP, which was provided in the 3/22/2018 DRL response, the definition of "aberrant results" is "any result that is not consistent with previous or concurrently generated data for a batch, anticipated results, product history, regulatory specification or internal control limits." The aforementioned SOP further stated that aberrant results may be classified as out of specification (OOS) result and out of trend (OOT) result with the following definition:

- OOS: OOS “is a result that does not meet approved specification acceptance criteria. Any individual quantitative result outside specification limits should be investigated even if the mean is within specification, unless the acceptance criteria for individual results are defined by the specification (e.g. uniformity tests).”
- OOT: OOT “is a result which is atypical, unexpected or questionable but not OOS, e.g. results which are not consistent with previous or concurrently generated data for a batch, previous batches or stability data; results outside internal control limits (if established for tests carried out on clinical batch characterization samples).”

Based on the definition of aberrant result above, when “aberrant results” are OOS result, then the definition of aberrant result is objective. Otherwise, the definition is not objective. It should be noted that for in vitro bridging SAC studies, the applicant does not have specification for the test results. It is noted that in the test product certificate of analysis, the applicant has specification for the test product uniformity of delivered dose, which states that for “[s]tage 1 (10 doses):

1. Mean emitted dose is NLT 85% and NMT 115% of the target emitted dose.
2. NMT 1 emitted dose is outside 80% to 120% of the target emitted dose.
3. No dose is outside 75% to 125% of the target emitted dose.”

“If either requirement 1 or requirement 2 above is not met, then test an additional 20 units” (stage 2).

For this specific case, the FP SAC value is (b) (4)
 (b) (4)

(b) (4). Therefore, even if the test product specification in the certificate of analysis is used, this is still not an OOS result, thus this “aberrant sample” was not identified per objective criteria. Hence, the reviewer will use its original value for statistical analysis for both FP (115.124 mcg) and SA (48.690 mcg, please note that as mentioned above, although the original SA value was not “aberrant” for SA, the applicant still used results from the retained solution) as a conservative approach. Please note that using the reassayed values of this sample does not change the study outcome.

- The applicant’s and the reviewer’s results are not the same due to the reviewer’s exclusion/use of original values of the above samples.

5.2.4.1.5 In Vitro PBE Analysis

5.2.4.1.5.1 FP

In Vitro PBE Analysis - Approximate Confidence Interval

Using Moment-Based Simplified Parameter Estimates
for
ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0097
	CI:	-0.0078
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0229
	CI:	-0.0221
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0 , PASS. For linearized theta P, if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	97.02	Mean: 96.15	Ratio: 100.91
		90% CI for ratio: (99.8,102.0)	
(log scale) Mean:	4.57	Mean: 4.57	Diff: 0.01
(log scale) CV:	0.88	CV: 1.33	
(log scale) SigmaBT:	0.019	SigmaBR: 0.013	Ratio: 1.426
(log scale) SigmaWT:	0.035	SigmaWR: 0.059	Ratio: 0.597
(log scale) SigmaT:	0.040	SigmaR: 0.061	Ratio: 0.662

5.2.4.15.2 SA

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0081
	CI:	-0.0063
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0221
	CI:	-0.0211
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0 , PASS. For linearized theta P, if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	48.85	Mean: 47.20	Ratio: 103.50
		90% CI for ratio:	(102.5, 104.5)
(log scale) Mean:	3.89	Mean: 3.85	Diff: 0.03
(log scale) CV:	0.79	CV: 1.49	
(log scale) σ_{BT} :	0.019	σ_{BR} : 0.016	Ratio: 1.144
(log scale) σ_{WT} :	0.024	σ_{WR} : 0.055	Ratio: 0.443
(log scale) σ_{T} :	0.031	σ_{R} : 0.057	Ratio: 0.536

5.2.4.1.6 Conclusions

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE	
REVIEW OF TESTING METHODS:	
Is the testing method validated?	Yes
Is the Quantitative Analytical Method Validated? (e.g., HPLC)	Yes
Is the method sufficiently sensitive?	Yes
Is testing performed as per RLD labeling?	Yes
Are data measured at both beginning, middle & end lifestages?	Yes
Is testing a single actuation per determination?	Yes

If yes, what is the actuation number tested?		Study protocol states that dose counter #s 60 (beginning), 30 (middle) and 1 (end) were to be used. The actual dose counter# are dose counter#s 60 or 59 (beginning), 30 (middle) and 1 (end)	
Are the testing methods acceptable?		ACCEPTABLE	
If not, why?		N/A	
STUDY RESULTS:			
Are data expressed as actual amount and % of label claim?		Yes	
Is the geo-mean of the test product (% of label claim) within 95-105% ?		FP	SA
	Beginning	Yes (104.34%)	No (108.13%)
	Middle	Yes (103.74%)	No (108.40%)
	End	Yes (104.90%)	No (109.16%)
Are the PBE results acceptable?		ACCEPTABLE	
If not, why?		N/A	

Comments:

- The geo-mean of the test product is within 95-105% of label claim for FP for each of the 3 lifestages, but is not for SA for each of the 3 lifestages. However, since the PBE analysis of both FP and SA passed BE criteria, the reviewer will not pursue this issue further.

The applicant's bridging SAC study for the 100/50 mcg strength is **acceptable**.

5.2.4.1.7 Deficiencies / Recommendations

N/A

5.2.4.2 Aerodynamic Particle Size Distribution (APSD) (100/50 mcg strength)

5.2.4.2.1 Study Information

Study No.	MGR-PRO-2016-106
Study site	Mylan Global Respiratory Group, IPC008, Discovery Park House, Floor 3, Sandwich, Kent. CT13 9ND. UK
Principal Investigator	Karen Weaver
Study dates	1/4/2017-2/9/2017
SOP No.	MGR-METH-546069*
SOP Effective Date	6/15/2016
SOP Title	Determination of Aerodynamic Particle Size Distribution of Fluticasone propionate and Salmeterol Xinafoate Dry Powder Inhaler Products at 60 L per minute using a (b) (4) (b) (4) Impactor (b) (4) by UPLC.
Testing Method Description	(b) (4) Impactor (b) (4) is used to determine the aerodynamic particle size distribution (APSD) of MGR001 in 100/50, 250/50 and 500/50 mcg multidose dry powder inhalers containing 100, 250 or 500 mcg Fluticasone propionate and 50 mcg Salmeterol as Xinafoate salt respectively and for Advair® Diskus® and Seretide® Accuhaler® Reference Listed Drug (RLD).
Testing Equipment Used (e.g., name, model, etc)	USP <601> Apparatus 5
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	60 L/min flow rate; 4 L volume. Testing carried out at ambient laboratory conditions.
Analytical Method Description	(b) (4)
Analytical Equipment Used (e.g., name, model, etc)	(b) (4) UPLC

* Method MGR-METH-546069 is used in conjunction with methods MGR-METH-753121⁸³ and MGR-METH-753122⁸⁴. These additional methods are focused on the operation of the relevant device, and therefore do not require validation.

Comments:

Reviewer's note: The applicant conducted SAC and APSD tests on the same device. Therefore, some of the comments are common to both SAC and APSD study design (please refer to reviewer's general comments in Section 5.3.4.1.1). For reviewer's comments specific for APSD study, please see below.

Comments for APSD

- The method referenced in this study (MGR-METH-546069, Version 8.0) is a newer version of the method referenced in the pivotal in vitro BE studies in Section 5.3.2 (MGR-METH-546069, Version 6.0). Based on the method revision

history⁸⁷ provide by the applicant, minor changes (e.g. comments added to including testing for EU products) were made from Version 6.0 to Version 8.0, and are not expected to affect study outcome.

- According to the study protocol, flow rates and actuation times for testing are as follow:

Flow Rate (L/min)	(b) (4) Actuation Time (seconds)	Wasting Actuation Time (seconds)
60	4.0	2.0

This is in line with product-specific guidance’s recommendation that the volume of air drawn through the delivery system should be 4L for APSD study.

- According to the study report, the applicant evaluated each individual (b) (4) component, total recovery, and impactor sized mass (ISM), FPM (b) (4) (b) (4) MMAD, GSD and mass balance for each determination.
- The applicant considered that the target delivered dose are 45 mcg for SA and 93 mcg for FP, which is the delivered dose labeling under standardized in vitro test conditions when tested at a flow rate of 60 L/min for 2 seconds as listed in the RLD. This is also the target emitted dose in USP monograph for Fluticasone Propionate and Salmeterol Inhalation Powder.

According to the guidance-generating review⁸⁸, the total mass of drug collected on all stages⁸⁹ and accessories should be between 85 and 115%⁹⁰ of label claim on a per actuation basis⁹¹.

5.2.4.2.2 Validation Summary Table for Particle Size Distribution by Cascade Impactor

5.2.4.2.2.1 Analytical Method Validation for UPLC

Same as the pivotal APSD study for the 100/50 mcg strength.

⁸⁷ GS Review: ANDA 208891, Quality/Quality Information, 3/2/2017 (Module 3.2.P.2\MGR-METH-546069 Version 8.0 – Determination of APSD of MGR001, and \MGR-METH-546069 Version 8.0 – Determination of APSD of MGR001 – (b) (4), p. 22-23 of 40).

⁸⁸ V:\Science Group\Master Files BE Posting\Fluticasone Propionate_Salmeterol Xinafoate_021077\Fluticasone Propionate_Salmeterol Xinafoate_21077_RC09-13.doc, p. 14 of 62.

⁸⁹ Footnote as in the guidance-generating review: “Total mass of drug includes drug deposition on each individual site, to include the mouthpiece adapter, throat, preseparator, and each stage of the impactor including the filter, is requested.”

⁹⁰ Footnote as in the guidance-generating review:

“<http://www.fda.gov/downloads/Drugs/Guidances/ucm070573.pdf>”

⁹¹ Footnote as in the guidance-generating review: “As determined by USP <601> apparatus B.”

5.2.4.2.2 Validation Table for Cascade Impaction

Same as the pivotal APSD study for the 100/50 mcg strength.

5.2.4.2.3 Results Summary – Drug in Small Particles / Cascade Impactor (CI)

Applicant’s Results - ISM

Active	Lifestage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
FP	BoL	(b) (4)					
	EoL						
Sal	BoL						
	EoL						

Reviewer’s Results

Aerodynamic Particle Size Distribution										
		Mean Drug Deposition (µg)		Variability (% CV)					Mean Ratio (T/R)	
				Within Lot (n=20)			Between Lot (n=3)	Total (n=60)		
		Arithm	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=60)	Geo (n=60)
FP										
Delivered Dose (µg)	Test	(b) (4)								
	Ref									
Fine Particle Mass (µg)	Test									
	Ref									
Impactor-Sized Mass (µg)	Test									
	Ref									
SA										
Delivered Dose (µg)	Test	(b) (4)								
	Ref									
Fine Particle Mass (µg)	Test									
	Ref									
Impactor-Sized Mass (µg)	Test									
	Ref									

Reviewer's Comments:

- According to study protocol, the APSD study should be performed at dose counter #59 for beginning lifestage and #2 for end lifestage. As detailed in the SAC study, if a sample is lost due to an assignable cause (e.g., (b) (4) tube leakage, dropped (b) (4) plate, etc.) during sample preparation in beginning or middle lifestage, further collection/recovery of the lost sample will be ceased, and a new sample will be prepared from the next dose(s) (may be performed within ± 3 doses of those stated) of the same device per the test method.

The reviewer checked the applicant's SAS dataset, and noticed that the following samples had dose counter number other than #59 and #2, thus the original samples were likely lost. For sample #s 2 and 3 below, since the #59 of the corresponding device were used as alternative dose counter number for the SAC study (please see details in Section 5.3.4.1.4), the reviewer considers the use of the next available dose (#58) acceptable for these 2 samples. For #1 below, in the 3/22/2018 DRL response, the applicant provided reason for using alternate dose counter number (please see the table below). The applicant also stated that for the above samples, no original data was generated, in accordance with the protocol, upon identifying the issue, the analyst sought approval to halt the sample preparation and fire the next available dose counter number. Based on the reason provided by the applicant, the reviewer considers the applicant rejection of the original sample of #1 below acceptable.

Number	Product	Batch	Unit	Stage	Dose Counter Number	Applicant's Reason
1	TEST	60000343	38	BOL	58	15mL of diluent was not added to the preseparator before actuating the device, therefore DCN 58 was used
2	REF	6ZP7030	84R*	BOL	58	Not provided. Please see reviewer's comments above.
3	REF	6ZP7784	111	BOL	58	Not provided. Please see reviewer's comments above.

* As mentioned in the bullet point below, this is a replacement device. No original data generated for Unit 84 due to incorrect preparation of mobile phase and diluent.

- For #s 1 and 3 above, the data generated from the acceptable alternative dose counter numbers was used for reviewer's statistical analysis.
- For #2 above, as detailed in the bullet point below, since this unit did not have all lifestages tested on the same device (only BOL was tested on the replacement device), this sample was excluded from reviewer's statistical evaluation.
- It is also noted that the applicant repeated the following 18 samples using new devices, and each of these 18 samples were repeated for both FP and SA. The applicant stated that the original samples were either not analyzed (sample #s 1-17), or no results were obtained from the analysis (sample #18). The reviewer considers the reason for original sample rejection acceptable. However, it should be noted that the applicant only repeated the sample at the beginning lifestage in the replacement devices. Therefore, these 18 samples containing lifestage data from different devices were excluded from the reviewer's statistical evaluation.

Number	Product	Batch number	Original device number	Replacement device number	Life stage	Reason for replacement
1-3	MGR001	60000338	4,7,17	4R, 7R, 17R	BoL	Incorrect preparation of mobile phase and diluent occurred. This was used to prepare original test samples. The samples were not analysed.
4-6	MGR001	60000343	27, 29,30	27R, 29 R, 30R	BoL	
7-8	MGR001	60000344	42,57	42R, 57R	BoL	
9-10	Advair® Diskus®	6ZP4764	65,69	65R, 69R	BoL	
11-16	Advair® Diskus®	6ZP7030	82, 83, 84,87, 90,94	82R, 83R, 84R, 87R, 90R, 94R	BoL	
17	Advair® Diskus®	6ZP7784	107	107R	BoL	
18	MGR001	60000344	49	49R	BoL	

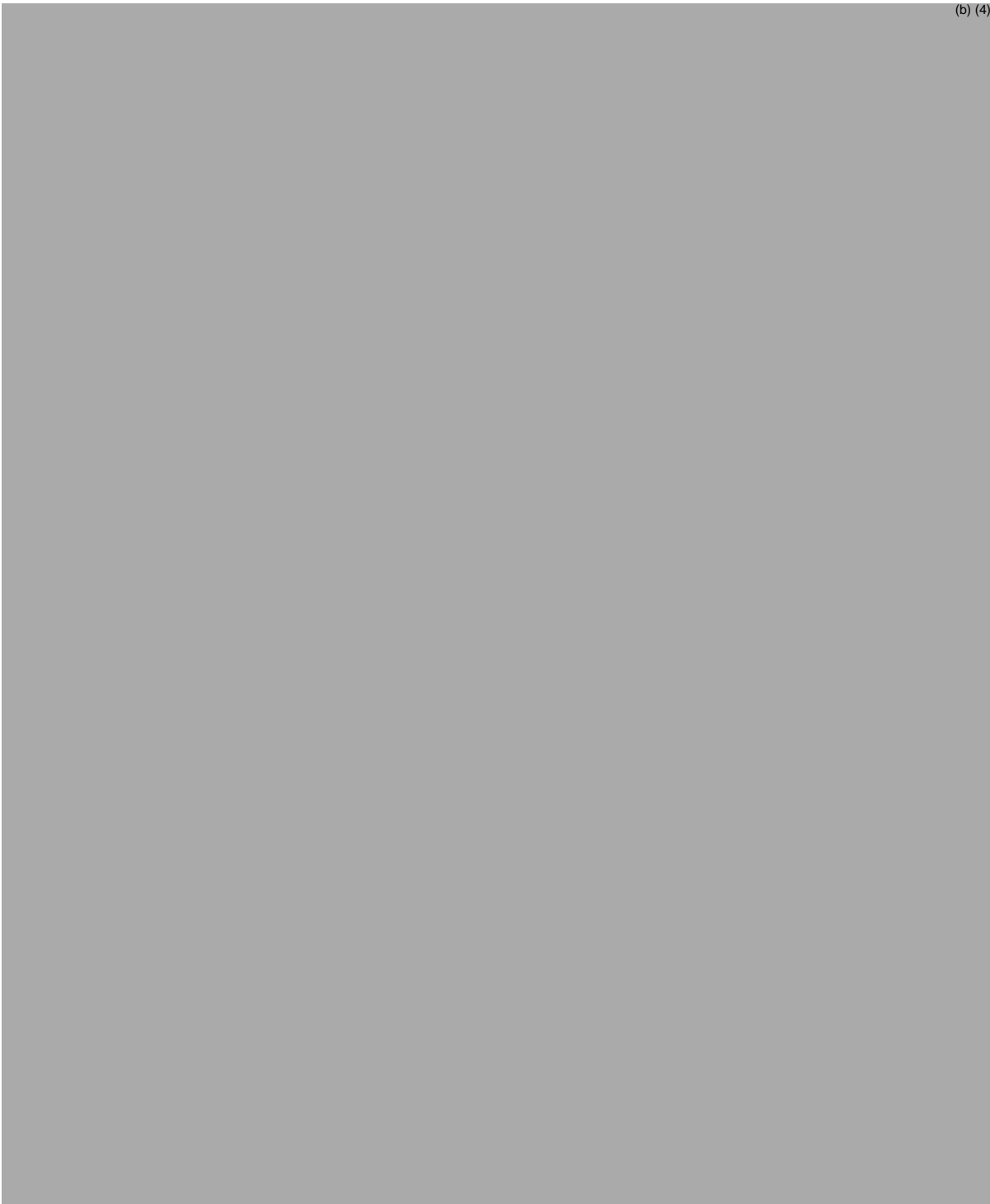
- In addition, similar to the SAC study in Section 5.3.4.1.4, the following 3 samples were rejected but no replacement devices were used (due to insufficient number of inhalers available for replacement, according to the applicant's 3/22/2018 DRL response). The applicant stated that their original samples were not analyzed. And the reviewer considers that the original sample rejection is acceptable. Since the applicant only repeated the sample at the end lifestage in the above replacement devices, these 3 samples that contained lifestage data from different devices were excluded from the reviewer's statistical evaluation.

Product	Batch number	Original device number	Life stage	Reason for replacement
MGR001	60000343	31, 33, 36	BoL	Incorrect preparation of mobile phase and diluent occurred. This was used to prepare original test samples. The samples were not analysed.

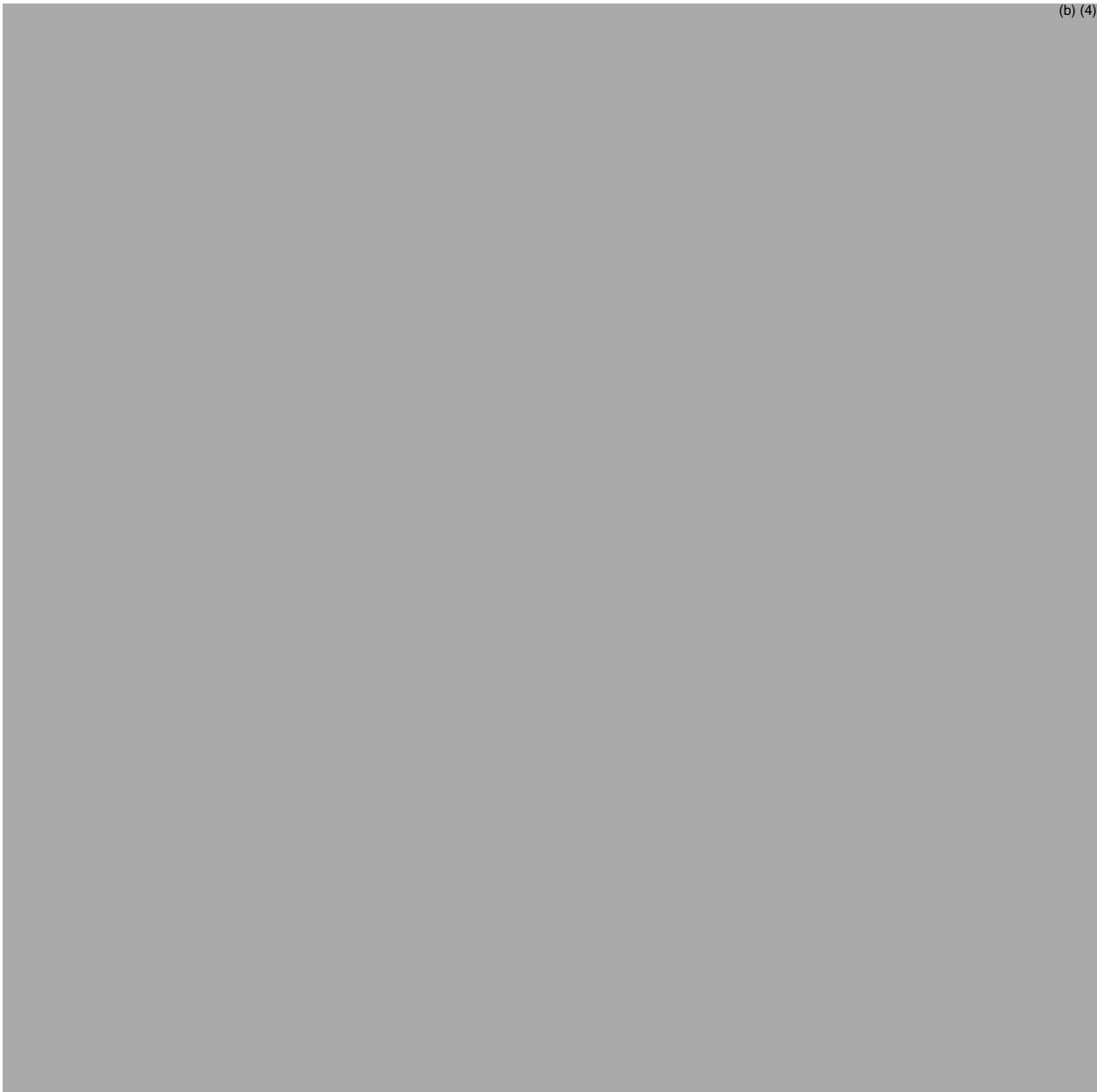


⁹² GS Review: ANDA 208891, Quality/Quality Information, 3/2/2017 (Module 3.2.P.2\MGR-PRO-2016-106 – IVBE- APSD -100/50 mcg – Chromatograms, p. 391 of 1517).

⁹³ GS Review: ANDA 208891, Quality/Quality Information, 3/2/2017 (Module 3.2.P.2\MGR-PRO-2016-106 – IVBE- APSD -100/50 mcg – Chromatograms, p. 833 of 1517).



- The applicant provided FPM in the study report, but did not provide it in their SAS .xpt dataset. It is noted that the reviewer-calculated FPM for each individual unit is slightly different than the one reported by the applicant in the study report. This is likely because the reviewer's FPM is calculated based (b) (4)
(b) (4)



⁹⁴ Input cutoff diameters as provided by Applicant based on Apparatus used in the study.

5.2.4.2.5 Conclusions

DRUG IN SMALL PARTICLES / DROPLETS PER ACTUATION	
REVIEW OF TESTING METHODS:	
Is the testing method for CI test validated?	Yes
Is the analytical method (e.g. HPLC) validated?	Yes
Is the analytical method sufficiently sensitive?	Yes
Is testing conducted as per RLD labeling?	Yes
What is the size of the induction port (or expansion chamber) used for testing?	N/A
Are ≤ 10 actuations used for cascade impactor study?	Yes (1 actuation)
If >1 actuation, what is the # of actuations used?	N/A
Are the testing methods acceptable?	ACCEPTABLE
If not, why?	N/A
STUDY RESULTS:	

DRUG IN SMALL PARTICLES / DROPLETS PER ACTUATION		
Is drug deposition reported in mass units?		Yes
Is the mass balance data reported?		Yes
Results	Does Impactor -Sized Mass data pass PBE?	Yes
	Does APSD analysis pass modified chi-square ratio test?	Yes
	Are the mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle mass (FPM) supportive?*	Yes
Mass Balance	Is the mean range for Total B between 85-115% of the label claim? (on a per actuation basis)	FP: Yes SA: No [REDACTED] (b) (4)
	Is PBE acceptable?	Acceptable
If not, why?		N/A

Reviewer's Comments:

- The test product passes PBE analysis. In addition, it passes the modified chi-square test using acceptance criteria of 25% difference.



The applicant's bridging APSD study for the 100/50 mcg strength is **acceptable**.

5.2.4.2.6 Deficiencies / Recommendations

N/A

5.2.4.3 Single Actuation Content through Container Life (250/50 mcg strength)

5.2.4.3.1 Study Information

Study No.	MGR-PRO-2016-107
Study Site	Mylan Global Respiratory Group, IPC008, Discovery Park House, Floor 3, Sandwich, Kent. CT13 9ND. UK
Principal Investigator	Karen Weaver
Study Dates	1/4/2017-2/6/2017
SOP No.	MGR-METH-546070*
SOP Effective Date	6/9/2016
SOP Title	Determination of Emitted Dose of MGR001 (PF-04764793) from Multidose Powder Inhalation Devices using USP Dosage Unit Sampling Apparatus
Test Method Description	(b) (4) Sampling Apparatus (b) (4) for Dry Powder Inhalers (DPIs) is used to determine the single actuation content (emitted dose (ED)) of MGR001 in 100/50, 250/50 and 500/50 mcg multidose dry powder inhalers containing 100, 250 or 500 mcg Fluticasone propionate and 50 mcg Salmeterol as Xinafoate salt respectively and for Advair® Diskus® and Seretide® Accuhaler® Reference Listed Drug (RLD).
Testing Equipment Used (e.g., name, model, etc.)	USP <601> Apparatus B with modified end caps
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc.)	60 L/min flow rate; 2 L volume. Testing carried out at ambient laboratory conditions.
Analytical Method Description	(b) (4)
Analytical Equipment Used (e.g., name, model, etc.)	(b) (4) UPLC

* Method MGR-METH-546070 is used in conjunction with methods MGR-METH-753121⁸³ and MGR-METH-753122⁸⁴. These additional methods are focused on the operation of the relevant device, and therefore do not require validation.

Comments:

Reviewer's note: The applicant's study protocol (MGR-PRO-2016-107, version 1.0) for the current study is similar to the study protocol (MGR-PRO-2016-106, version 1.0) for the 100/50 mcg strength SAC study. The reviewer has the same comments regarding the study information as compared to the 100/50 mcg strength SAC study (please see reviewer's comments in Section 5.2.4.1.1).

5.2.4.3.2 Analytical Method Validation for UPLC

Same as the pivotal SAC study for the 100/50 mcg strength.

5.2.4.3.3 Calibration of Manual and/or Automated Spray Pump Actuator (For Single Actuation Content Study)

Same as the pivotal SAC study for the 100/50 mcg strength.

5.2.4.3.4 Results Summary

Applicant's Results

Active	Lifestage	GM (I)	GM (R)	GMR (I/R)	SD (I)	SD (R)	SD ratio (T/R)
FP	BoL	241.92	226.71	1.07	7.00	10.98	0.64
	MoL	238.42	238.87	1.00	8.95	5.29	1.69
	EoL	243.77	250.50	0.97	8.61	9.07	0.95
Sal	BoL	49.37	44.97	1.10	1.42	2.19	0.65
	MoL	48.76	47.25	1.03	1.60	1.10	1.45
	EoL	49.44	49.49	1.00	1.59	1.84	0.86

Reviewer's Results

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE													
		Dose Counter #	Mean				Variability (% CV)					Mean Ratio (T/R)	
			Drug Mass		% label claim		Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)	Geo (n=60)
			Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3				
FP													
BEG	Test	60	242.48	242.40	104.07	104.03	3.29	2.22	2.51	0.47	2.68	1.07	1.07
	Ref	60	227.00	226.71	97.42	97.30	3.58	3.59	6.76	0.99	4.84		
MID	Test	30	238.42	238.26	102.33	102.26	4.86	3.83	2.47	0.72	3.80	1.00	1.00
	Ref	30	238.92	238.87	102.54	102.52	1.53	2.07	2.85	0.47	2.21		
END	Test	1	243.77	243.62	104.62	104.56	3.47	3.18	4.08	0.41	3.56	0.97	0.97
	Ref	1	250.66	250.50	107.58	107.51	1.56	1.43	2.19	3.85	3.62		
SA													
BEG	Test	60	49.49	49.47	109.98	109.94	2.27	2.05	3.10	1.34	2.71	1.10	1.10
	Ref	60	45.03	44.97	100.06	99.94	3.59	3.49	6.89	0.76	4.85		
MID	Test	30	48.75	48.72	108.34	108.28	4.04	2.61	2.89	1.02	3.30	1.03	1.03
	Ref	30	47.26	47.25	105.03	105.00	1.90	2.30	2.78	0.37	2.34		
END	Test	1	49.44	49.42	109.88	109.82	3.10	3.12	3.44	0.83	3.24	1.00	1.00
	Ref	1	49.53	49.49	110.06	109.98	1.60	1.71	2.13	3.95	3.72		

Reviewer's Comments:

- The SAC study was performed using dose counter #60 for BOL, #30 for MOL and #1 for EOL, as per protocol.

- It is noted that the applicant repeated the following 2 samples using new devices, and each of these 2 samples were repeated for both FP and SA. The reviewer considers the reason for original sample rejection acceptable. However, it should be noted that the applicant only repeated the sample at the end lifestage in the replacement devices. Therefore, these 2 samples containing lifestage data from different devices were excluded from the reviewer's statistical evaluation.

Number	Product	Batch number	Original device number	Replacement device number	Life stage	Reason for replacement
1	MGR001	60000259	133	133R	EoL	Device jammed during waste shot firing. Defect investigation concluded the root cause to be operator error. The mouthpiece cover was not fully closed upon the previous indexing stroke.
2	MGR001	60000260	149	149R	EoL	Leak occurred in dose collection tube during sample recovery. No analysis of resulting solution was undertaken.

- The applicant's and the reviewer's results are not the same due to the reviewer's exclusion of the above samples.

5.2.4.3.5 In Vitro PBE Analysis

5.2.4.3.5.1 FP

In Vitro PBE Analysis - Approximate Confidence Interval
 Using Moment-Based Simplified Parameter Estimates
 for
 ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
 MIXED SCALING APPROACH
 Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0083
	CI:	-0.0069
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0227
	CI:	-0.0221
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and

Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	241.41	Mean: 238.49	Ratio: 101.22
		90% CI for	ratio: (100.4,102.1)
(log scale) Mean:	5.49	Mean: 5.47	Diff: 0.01
(log scale) CV:	0.64	CV: 1.02	
(log scale) SigmaBT:	0.012	SigmaBR: 0.000	Ratio: -
(log scale) SigmaWT:	0.033	SigmaWR: 0.056	Ratio: 0.586
(log scale) SigmaT:	0.035	SigmaR: 0.056	Ratio: 0.625

5.2.4.3.5.2 SA

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0067
	CI:	-0.0051
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0212
	CI:	-0.0203
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	49.20	Mean: 47.20 90% CI for ratio: (103.4, 105.1)	Ratio: 104.24
(log scale) Mean:	3.90	Mean: 3.85	Diff: 0.04
(log scale) CV:	0.82	CV: 1.43	
(log scale) SigmaBT:	0.013	SigmaBR: 0.000	Ratio: -
(log scale) SigmaWT:	0.029	SigmaWR: 0.055	Ratio: 0.524
(log scale) SigmaT:	0.032	SigmaR: 0.055	Ratio: 0.575

5.2.4.3.6 Conclusions

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE			
REVIEW OF TESTING METHODS:			
Is the testing method validated?		Yes	
Is the Quantitative Analytical Method Validated? (e.g., HPLC)		Yes	
Is the method sufficiently sensitive?		Yes	
Is testing performed as per RLD labeling?		Yes	
Are data measured at both beginning, middle & end lifestages?		Yes	
Is testing a single actuation per determination?		Yes	
If yes, what is the actuation number tested?		dose counter#s 60 (beginning), 30 (middle) and 1 (end)	
Are the testing methods acceptable?		ACCEPTABLE	
If not, why?		N/A	
STUDY RESULTS:			
Are data expressed as actual amount and % of label claim?		Yes	
Is the geo-mean of the test product (% of label claim) within 95-105%?		FP	SA
	Beginning	Yes (104.07%)	No (109.94%)
	Middle	Yes (102.26%)	No (108.28%)
	End	Yes (104.56%)	No (109.82%)
Are the PBE results acceptable?		ACCEPTABLE	
If not, why?		N/A	

Comments:

- The geo-mean of the test product is within 95-105% of label claim for FP for each of the 3 lifestages, but is not for SA for each of the 3 lifestages. However, since the PBE analysis of both FP and SA passed BE criteria, the reviewer will not pursue this issue further.

The applicant's bridging SAC study for the 250/50 mcg strength is **acceptable**.

5.2.4.3.7 Deficiencies / Recommendations

N/A

5.2.4.4 Aerodynamic Particle Size Distribution (APSD) (250/50 mcg strength)

5.2.4.4.1 Study Information

Study No.	MGR-PRO-2016-107
Study site	Mylan Global Respiratory Group, IPC008, Discovery Park House, Floor 3, Sandwich, Kent. CT13 9ND. UK
Principal Investigator	Karen Weaver
Study dates	1/4/2017-2/6/2017
SOP No.	MGR-METH-546069*
SOP Effective Date	6/15/2016
SOP Title	Determination of Aerodynamic Particle Size Distribution of Fluticasone propionate and Salmeterol Xinafoate Dry Powder Inhaler Products at 60 L per minute using a (b) (4) (b) (4) Impactor (b) (4) by UPLC.
Testing Method Description	(b) (4) Impactor (b) (4) is used to determine the aerodynamic particle size distribution (APSD) of MGR001 in 100/50, 250/50 and 500/50 mcg multidose dry powder inhalers containing 100, 250 or 500 mcg Fluticasone propionate and 50 mcg Salmeterol as Xinafoate salt respectively and for Advair® Diskus® and Seretide® Accuhaler® Reference Listed Drug (RLD).
Testing Equipment Used (e.g., name, model, etc)	USP <601> Apparatus 5
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	60 L/min flow rate; 4 L volume. Testing carried out at ambient laboratory conditions.
Analytical Method Description	(b) (4)
Analytical Equipment Used (e.g., name, model, etc)	(b) (4) UPLC

* Method MGR-METH-546069 is used in conjunction with methods MGR-METH-753121⁸³ and MGR-METH-753122⁸⁴. These additional methods are focused on the operation of the relevant device, and therefore do not require validation.

Comments:

Reviewer's note: The applicant's study protocol (MGR-PRO-2016-107, version 1.0) for the current study is similar to the study protocol (MGR-PRO-2016-106, version 1.0) for the 100/50 mcg strength APSD study. The reviewer has the same comments regarding the study information as compared to the 100/50 mcg strength APSD study (please see reviewer's comments in Section 5.2.4.2.1), except that the applicant has different definition for mass balance as detailed below.

- Mass Balance (MB): The applicant considered that the target delivered dose are 45 mcg for SA and 233 mcg for FP, which is the delivered dose labeling under standardized in vitro test conditions when tested at a flow rate of 60 L/min for 2

seconds as listed in the RLD. This is also the target emitted dose in USP monograph for Fluticasone Propionate and Salmeterol Inhalation Powder.

According to guidance-generating review⁹⁷, the total mass of drug collected on all stages⁹⁸ and accessories should be between 85 and 115%⁹⁹ of label claim on a per actuation basis¹⁰⁰.

5.2.4.4.2 Validation Summary Table for Particle Size Distribution by Cascade Impactor

5.2.4.4.2.1 Analytical Method Validation for UPLC

Same as the pivotal APSD study for the 100/50 mcg strength.

5.2.4.4.2.2 Validation Table for Cascade Impaction

Same as the pivotal APSD study for the 100/50 mcg strength.

5.2.4.4.3 Results Summary – Drug in Small Particles / Cascade Impactor (CI)

Applicant’s Results – ISM

Active	Lifestage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
FP	BoL	(b) (4)					
	EoL						
Sal	BoL						
	EoL						

Reviewer’s Results

Aerodynamic Particle Size Distribution										
		Mean Drug Deposition (µg)		Variability (% CV)					Mean Ratio (T/R)	
				Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)	Geo (n=60)
		Arithm	Geo	Lot 1	Lot 2	Lot 3				

⁹⁷ V:\Science Group\Master Files BE Posting\Fluticasone Propionate_Salmeterol Xinafoate_021077\Fluticasone Propionate_Salmeterol Xinafoate_21077_RC09-13.doc, p. 14 of 62.

⁹⁸ Footnote as in the guidance-generating review: “Total mass of drug deposition on each individual site, to include the mouthpiece adapter, throat, preseparator, and each stage of the impactor including the filter, is requested.”

⁹⁹ Footnote as in the guidance-generating review: “<http://www.fda.gov/downloads/Drugs/Guidances/ucm070573.pdf>”

¹⁰⁰ Footnote as in the guidance-generating review: “As determined by USP <601> apparatus B.”

FP		
Delivered Dose (μg)	Test	(b) (4)
	Ref	
Fine Particle Mass (μg)	Test	
	Ref	
Impactor-Sized Mass (μg)	Test	
	Ref	
SA		
Delivered Dose (μg)	Test	(b) (4)
	Ref	
Fine Particle Mass (μg)	Test	
	Ref	
Impactor-Sized Mass (μg)	Test	
	Ref	

(b) (4)

Reviewer's Comments:

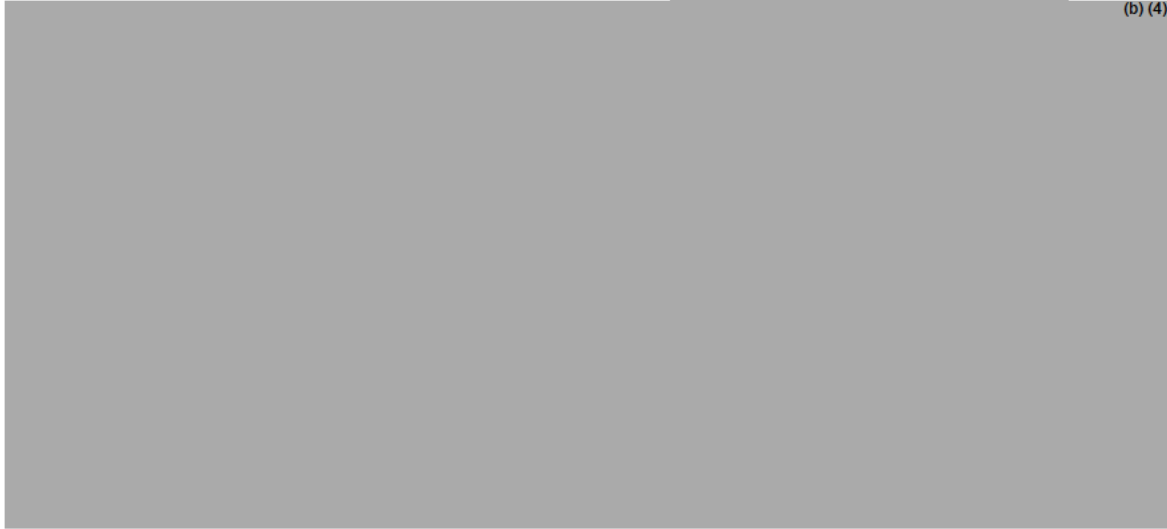
- The APSD study was performed using dose counter #60 for BOL, #30 for MOL and #1 for EOL, as per protocol.
- It is noted that the applicant repeated the following sample using a new device, and it was repeated for both FP and SA. The reviewer considers the reason for original sample rejection acceptable. However, it should be noted that the applicant only repeated the sample at the end lifestage in the above replacement devices. Therefore, this sample containing lifestage data from different devices was excluded from the reviewer's statistical evaluation.

Number	Product	Batch number	Original device number	Replacement device number	Life stage	Reason for replacement
1	MGR001	60000259	133	133R	EoL	Device jammed during waste shot firing. Defect investigation concluded the root cause to be operator error. The mouthpiece cover was not fully closed upon the previous indexing stroke.

- As with the APSD bridging study for the 100/50 mcg strength, the applicant provided FPM in the study report, but did not provide it in their SAS .xpt dataset. It is noted that the reviewer-calculated FPM for each individual unit is slightly different than the one reported by the applicant in the study report. This is likely because the reviewer's FPM is calculated based

(b) (4)

(b) (4)



5.2.4.4.5 Conclusions

DRUG IN SMALL PARTICLES / DROPLETS PER ACTUATION		
REVIEW OF TESTING METHODS:		
Is the testing method for CI test validated?	Yes	
Is the analytical method (e.g. HPLC) validated?	Yes	
Is the analytical method sufficiently sensitive?	Yes	
Is testing conducted as per RLD labeling?	Yes	
What is the size of the induction port (or expansion chamber) used for testing?	N/A	
Are ≤ 10 actuations used for cascade impactor study?	Yes (1 actuation)	
If >1 actuation, what is the # of actuations used?	N/A	
Are the testing methods acceptable?	ACCEPTABLE	
If not, why?	N/A	
STUDY RESULTS:		
Is drug deposition reported in mass units?	Yes	
Is the mass balance data reported?	Yes	
Results	Does Impactor -Sized Mass data pass PBE?	Yes
	Does APSD analysis pass modified chi-square ratio test?	Yes
	Are the mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle mass (FPM) supportive?*	Yes
Mass Balance	Is the mean range for Total B between 85-115% of the label claim? (on a per actuation basis)	FP: Yes for the test product. SA: No [REDACTED] (b) (4) [REDACTED] [REDACTED]
	Is PBE acceptable?	Acceptable
If not, why?	N/A	

Reviewer's Comments:

- The test product passes PBE analysis. In addition, it passes the modified chi-square test using acceptance criteria of 25% difference.



This study is **acceptable**.

5.2.4.4.6 Deficiencies / Recommendations

N/A

5.2.4.5 Single Actuation Content through Container Life (500/50 mcg strength)

5.2.4.5.1 Study Information

Study No.	MGR-PRO-2016-108
Study Site	(b) (4)
Principal Investigator	(b) (4)
Study Dates	1/18/2017-2/10/2017
SOP No.	MGR-METH-546070*
SOP Effective Date	6/9/2016
SOP Title	Determination of Emitted Dose of MGR001 (PF-04764793) from Multidose Powder Inhalation Devices using (b) (4) (b) (4)
Test Method Description	(b) (4) for Dry Powder Inhalers (DPIs) is used to determine the single actuation content (emitted dose (ED)) of MGR001 in 100/50, 250/50 and 500/50 mcg multidose dry powder inhalers containing 100, 250 or 500 mcg Fluticasone propionate and 50 mcg Salmeterol as Xinafoate salt respectively and for Advair® Diskus® and Seretide® Accuhaler® Reference Listed Drug (RLD).
Testing Equipment Used (e.g., name, model, etc.)	USP <601> Apparatus B with modified end caps
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	60 L/min flow rate; 2 L volume. Testing carried out at ambient laboratory conditions.
Analytical Method Description	(b) (4)
Analytical Equipment Used (e.g., name, model, etc.)	(b) (4) LC (b) (4) UPLC

* Method MGR-METH-546070 ((b) (4)) is used in conjunction with methods MGR-METH-753121 ((b) (4))⁸³ and MGR-METH-753122 ((b) (4))⁸⁴. These additional methods are focused on the operation of the relevant device, and therefore do not require validation.

Comments:

Reviewer's note: The applicant's study protocol (MGR-PRO-2016-108, version 1.0) for the current study is similar to the study protocol (MGR-PRO-2016-106, version 1.0) for the 100/50 mcg strength SAC study. The reviewer has the same comments regarding the study information as compared to the 100/50 mcg strength SAC study (please see reviewer's comments in Section 5.2.2.1.1).

5.2.4.5.2 Analytical Method Validation for UPLC

Same as the pivotal SAC study for the 100/50 mcg strength.

5.2.4.5.3 Calibration of Manual and/or Automated Spray Pump Actuator (For Single Actuation Content and Priming/Repriming studies)

Same as the pivotal SAC study for the 100/50 mcg strength.

5.2.4.5.4 Results Summary

Applicant's Results

Active	Lifestage	GM (I)	GM (R)	GMR (T/R)	SD (I)	SD (R)	SD ratio (T/R)
FP	BoL	454.03	435.87	1.04	17.22	29.10	0.59
	MoL	457.81	477.82	0.96	13.94	12.88	1.08
	EoL	467.11	479.91	0.97	14.07	46.95	0.30
Sal	BoL	44.86	42.39	1.06	1.43	2.81	0.51
	MoL	45.12	46.17	0.98	1.13	1.26	0.90
	EoL	46.24	46.47	0.99	1.26	4.54	0.28

Reviewer's Results

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE													
		Dose Counter #	Mean				Variability (% CV)					Mean Ratio (T/R)	
			Drug Mass		% label claim		Within Lot (n=20)			Between Lot (n=3)	Total (n=60)	Arithm (n=60)	Geo (n=60)
			Arith	Geo	Arith	Geo	Lot 1	Lot 2	Lot 3				
FP													
BEG	Test	60	455.35	455.05	97.92	97.86	3.90	3.57	2.97	1.42	3.64	1.04	1.04
	Ref	60	436.99	435.87	93.98	93.73	4.05	8.20	6.70	2.34	6.66		
MID	Test	30	457.88	457.66	98.47	98.42	2.21	2.39	3.87	1.44	3.09	0.96	0.96
	Ref	30	477.99	477.82	102.79	102.76	1.71	2.06	2.62	2.00	2.69		
END	Test	1	467.70	467.48	100.58	100.53	2.47	3.39	2.39	1.61	3.03	0.97	0.97
	Ref	1	483.34	479.91	103.94	103.21	16.37	1.99	3.03	4.09	9.71		
SA													
BEG	Test	60	44.94	44.92	99.87	99.83	3.54	3.16	2.70	0.57	3.13	1.06	1.06
	Ref	60	42.50	42.39	94.45	94.21	3.96	8.09	6.58	2.52	6.60		
MID	Test	30	45.09	45.08	100.20	100.17	2.31	2.32	2.72	0.78	2.50	0.98	0.98
	Ref	30	46.19	46.17	102.64	102.60	2.49	1.76	2.36	1.98	2.74		
END	Test	1	46.29	46.27	102.86	102.83	2.57	3.35	2.30	0.40	2.74	0.99	1.00
	Ref	1	46.80	46.47	104.01	103.28	16.28	1.94	3.09	4.19	9.69		

Reviewer’s Comments:

- According to study protocol, the SAC study should be performed at dose counter #60 for BOL, #30 for MOL and #1 for EOL. As detailed in the SAC study, if a sample is lost due to an assignable cause (e.g., (b) (4) tube leakage, dropped (b) (4) plate, etc.) during sample preparation in beginning or middle lifestage, further collection/recovery of the lost sample will be ceased, and a new sample will be prepared from the next dose(s) (may be performed within ±3 doses of those stated) of the same device per the test method.

The reviewer checked the applicant’s SAS dataset, and noticed that the following samples had dose counter number other than #s 60, 30 and 1. The applicant provided reasons for using alternate dose counter number of these samples in the study report (please see the table below). The reviewer considers these reasons acceptable.

Product	Batch	Unit	Stage	Dose Counter Number	Reason for Alternate Dose Counter Number ¹⁰⁴
TEST	60000262	4	BoL	59	The delivered dose tubes leaked.
TEST	60000262	5	BoL	59	
TEST	60000264	43	MoL	29	During wasting device to MoL, the device was wasted through DCN 32. The following day the device was wasted with DCN31 and DCN30.
TEST	60000263	31	MoL	29	The delivered dose tubes leaked.
REF	6ZP7124	67	MoL	29	

- It is also noted that the applicant repeated the following 2 samples using new devices, and each of these 2 samples were repeated for both FP and SA. The reviewer considers the reason for original sample rejection acceptable. However, it should be noted that the applicant only repeated the sample at the end lifestage in the replacement devices. Therefore, these 2 samples containing lifestage data from different devices were excluded from the reviewer’s statistical evaluation.

¹⁰⁴ GS Review: ANDA 208891, Quality/Quality Information, 3/2/2017 [Module 3.2.P.2\MGR-PRO-REP-2016-108 (P25848.01) – 500/50 IVBE Study Report – (b) (4), p. 12-13 of 69].

Number	Product	Batch number	Original device number	Replacement device number	Life stage	Reason for replacement
1	MGR001	60000263	35	35R	EoL	An error occurred during waste shot firing from MOL to EOL. A replacement device was obtained and waste shot firing was carried out correctly and the test was carried out.
2	MGR001	60000264	54	54R	EoL	(b) (4) tube leaked during EOL sample collection. A replacement device was used to generate EOL sample.

- The applicant's and the reviewer's results are not the same due to the reviewer's exclusion of the above samples.

5.2.4.5.5 In Vitro PBE Analysis

5.2.4.5.5.1 FP

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for

ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled: Point estimate: -0.0300
CI: -0.0255
Pass/Fail: PASS

Constant-scaled: Point estimate: -0.0298
CI: -0.0282
Pass/Fail: PASS

Overall Test Outcome: Pass/Fail: **PASS**

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0 , PASS. For linearized theta P, if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST	REFERENCE	T/R Ratio
(orig scale) Mean:	460.04	Mean: 464.08	Ratio: 99.13
		90% CI for ratio: (97.8,100.5)	
(log scale) Mean:	6.13	Mean: 6.14	Diff: -0.01
(log scale) CV:	0.56	CV: 1.64	
(log scale) SigmaBT:	0.012	SigmaBR: 0.000	Ratio: -
(log scale) SigmaWT:	0.032	SigmaWR: 0.101	Ratio: 0.321
(log scale) SigmaT:	0.034	SigmaR: 0.101	Ratio: 0.342

5.2.4.5.2 SA

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for

ANDA 208891 SAC Test:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH

Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0292
	CI:	-0.0248
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0296
	CI:	-0.0281
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

TEST	REFERENCE	T/R Ratio

(orig scale) Mean:	45.42	Mean:	44.97	Ratio:	100.99
				90% CI for ratio:	(99.7, 102.3)
(log scale) Mean:	3.82	Mean:	3.81	Diff:	0.01
(log scale) CV:	0.81	CV:	2.60		
(log scale) SigmaBT:	0.006	SigmaBR:	0.000	Ratio:	-
(log scale) SigmaWT:	0.030	SigmaWR:	0.099	Ratio:	0.305
(log scale) SigmaT:	0.031	SigmaR:	0.099	Ratio:	0.311

5.2.4.5.6 Conclusions

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE			
REVIEW OF TESTING METHODS:			
Is the testing method validated?		Yes	
Is the Quantitative Analytical Method Validated? (e.g., HPLC)		Yes	
Is the method sufficiently sensitive?		Yes	
Is testing performed as per RLD labeling?		Yes	
Are data measured at both beginning, middle & end lifestages?		Yes	
Is testing a single actuation per determination?		Yes	
If yes, what is the actuation number tested?		Study protocol states that dose counter #s 60 (beginning), 30 (middle) and 1 (end) were to be used. The actual dose counter# used were 60 or 59 (beginning), 30 or 29 (middle) and 1 (end)	
Are the testing methods acceptable?		ACCEPTABLE	
If not, why?		N/A	
STUDY RESULTS:			
Are data expressed as actual amount and % of label claim?		Yes	
Is the geo-mean of the test product (% of label claim) within 95-105%?		FP	SA
	Beginning	Yes (97.86%)	Yes (99.83%)
	Middle	Yes (98.42%)	Yes (100.17%)
	End	Yes (100.53%)	Yes (102.83%)
Are the PBE results acceptable?		ACCEPTABLE	
If not, why?		N/A	

Comments:

The applicant's bridging SAC study for the 500/50 mcg strength is **acceptable**.

5.2.4.5.7 Deficiencies / Recommendations

N/A

5.2.4.6 Aerodynamic Particle Size Distribution (APSD) (500/50 mcg strength)

5.2.4.6.1 Study Information

Study No.	MGR-PRO-2016-108
Study site	(b) (4)
Principal Investigator	(b) (4)
Study dates	1/18/2017-2/10/2017
SOP No.	MGR-METH-546069*
SOP Effective Date	6/15/2016
SOP Title	Determination of Aerodynamic Particle Size Distribution of Fluticasone propionate and Salmeterol Xinafoate Dry Powder Inhaler Products at 60 L per minute using a (b) (4) (b) (4) Impactor (b) (4) by UPLC.
Testing Method Description	(b) (4) Impactor (b) (4) is used to determine the aerodynamic particle size distribution (APSD) of MGR001 in 100/50, 250/50 and 500/50 mcg multidose dry powder inhalers containing 100, 250 or 500 mcg Fluticasone propionate and 50 mcg Salmeterol as Xinafoate salt respectively and for Advair® Diskus® and Seretide® Accuhaler® Reference Listed Drug (RLD).
Testing Equipment Used (e.g., name, model, etc)	USP <601> Apparatus 5
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	60 L/min flow rate; 4 L volume. Testing carried out at ambient laboratory conditions.
Analytical Method Description	(b) (4)
Analytical Equipment Used (e.g., name, model, etc)	(b) (4) LC (b) (4) UPLC

* Method MGR-METH-546069 (b) (4) is used in conjunction with methods MGR-METH-753121 (b) (4)⁸³ and MGR-METH-753122 (b) (4)⁸⁴. These additional methods are focused on the operation of the relevant device, and therefore do not require validation.

Comments:

Reviewer's note: The applicant's study protocol (MGR-PRO-2016-108, version 2.0¹⁰⁵) for the current study is similar to the study protocol (MGR-PRO-2016-106, version 1.0) for the 100/50 mcg strength APSD study. The reviewer has the same comments regarding the study information as compared to the 100/50 mcg strength APSD study (please see reviewer's comments in Section 5.2.4.2.1), except that the applicant has different definition for mass balance as detailed below.

¹⁰⁵ According to the revision history of the protocol (3/2/2017 submission, Module 3.2.P.2\In vitro BE Protocol – 500/50 mcg – MGR-PRO-2016-108, p. 10 of 12), version 2.0 added reference batch numbers.

- **Mass Balance (MB):** The applicant considered that the target delivered dose are 45 mcg for SA and 465 mcg for FP, which is the delivered dose labeling under standardized in vitro test conditions when tested at a flow rate of 60 L/min for 2 seconds as listed in the RLD. This is also the target emitted dose in USP monograph for Fluticasone Propionate and Salmeterol Inhalation Powder.

According to guidance-generating review¹⁰⁶, the total mass of drug collected on all stages¹⁰⁷ and accessories should be between 85 and 115%¹⁰⁸ of label claim on a per actuation basis¹⁰⁹.

5.2.4.6.2 Validation Summary Table for Particle Size Distribution by Cascade Impactor

5.2.4.6.2.1 Analytical Method Validation for UPLC

Same as the pivotal APSD study for the 100/50 mcg strength.

5.2.4.6.2.2 Validation Table for Cascade Impaction

Same as the pivotal APSD study for the 100/50 mcg strength.

5.2.4.6.3 Results Summary – Drug in Small Particles / Cascade Impactor (CI)

Applicant’s Results - ISM

Active	Lifestage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
FP	BoL	(b) (4)					
	EoL						
Sal	BoL						
	EoL						

¹⁰⁶ V:\Science Group\Master Files BE Posting\Fluticasone Propionate_Salmeterol Xinafoate_021077\Fluticasone Propionate_Salmeterol Xinafoate_21077_RC09-13.doc, p. 14 of 62.

¹⁰⁷ Footnote as in the guidance-generating review: “Total mass of drug includes drug deposition on each individual site, to include the mouthpiece adapter, throat, preseparator, and each stage of the impactor including the filter, is requested.”

¹⁰⁸ Footnote as in the guidance-generating review:
[“http://www.fda.gov/downloads/Drugs/Guidances/ucm070573.pdf”](http://www.fda.gov/downloads/Drugs/Guidances/ucm070573.pdf)

¹⁰⁹ Footnote as in the guidance-generating review: “As determined by USP <601> apparatus B.”

Reviewer's Results

Aerodynamic Particle Size Distribution										
		Mean Drug Deposition (μg)		Variability (% CV)				Mean Ratio (T/R)		
				Within Lot (n=20)			Between Lot (n=3)	Total (n=60)		
		Arithm	Geo	Lot 1	Lot 2	Lot 3			Arithm (n=60)	Geo (n=60)
FP										
Delivered Dose (μg)	Test								(b) (4)	
	Ref									
Fine Particle Mass (μg)	Test									
	Ref									
Impactor-Sized Mass (μg)	Test									
	Ref									
SA										
Delivered Dose (μg)	Test								(b) (4)	
	Ref									
Fine Particle Mass (μg)	Test									
	Ref									
Impactor-Sized Mass (μg)	Test									
	Ref									

(b) (4)



middle lifestage, further collection/recovery of the lost sample will be ceased, and a new sample will be prepared from the next dose(s) (may be performed within ± 3 doses of those stated) of the same device per the test method.

The reviewer checked the applicant's SAS dataset, and noticed that the following 2 samples had dose counter number other than #59 and #2. The applicant provided reasons for using alternate dose counter number of these samples in the study report (please see the table below). The reviewer considers the reason provided acceptable.

Product	Batch	Unit	Stage	Dose Counter Number	Reason for Alternate Dose Counter Number ¹¹⁰
TEST	60000262	4	BOL	58	For the SAC BOL sample collection on the same device, the delivered dose tubes leaked.
TEST	60000262	5	BOL	58	

In addition to the 2 samples listed above, the study report also reported another sample (reference batch #6ZP7951, unit #102, BOL, dose counter number #58) using alternate dose counter number, which was not reflected in the SAS .xpt dataset. According to the study report, during the original BOL sample collection, there was an error made with pipetting solution into the cups, thus the next available dose (dose counter number #58) was collected. The reviewer verified that the APSD data reported in the SAS .xpt dataset is consistent with data from dose counter number #58 that was reported in the study report. Therefore, it is likely that the dose counter number in the SAS .xpt file was a typo, hence the reviewer will not pursue this issue further.

- It is also noted that the applicant repeated the following 3 samples using new devices, and each of these 3 samples were repeated for both FP and SA. The reviewer considers the reason for original sample rejection acceptable. However, it should be noted that the applicant only repeated the sample at the end lifestage in the replacement devices. Therefore, these 3 samples containing lifestage data from different devices were excluded from the reviewer's statistical evaluation.

¹¹⁰ GS Review: ANDA 208891, Quality/Quality Information, 3/2/2017 [Module 3.2.P.2\MGR-PRO-REP-2016-108 (P25848.01) – 500/50 IVBE Study Report – (b) (4), p. 12-13 of 69].

Number	Product	Batch number	Original device number	Replacement device number	Life stage	Reason for replacement
1	MGR001	60000263	25	25R	EoL	An incorrect pipetting at the EOL life stage occurred during sample preparation. Collection was ceased and a replacement device was used to generate EOL results.
2	MGR001	60000263	35	35R	EoL	An error occurred during waste shot firing from MOL to EOL. A replacement device was obtained and waste shot firing was carried out correctly and the test was carried out.
3	Advair® Diskus®	6ZP7898	99	99R	EoL	(b) (4) induction port (pre separator) solution was spilled prior to diluting to volume. A replacement device was obtained to perform recollection.

- 

(b) (4)

5.2.4.6.5 Conclusions

DRUG IN SMALL PARTICLES / DROPLETS PER ACTUATION		
REVIEW OF TESTING METHODS:		
Is the testing method for CI test validated?	Yes	
Is the analytical method (e.g. HPLC) validated?	Yes	
Is the analytical method sufficiently sensitive?	Yes	
Is testing conducted as per RLD labeling?	Yes	
What is the size of the induction port (or expansion chamber) used for testing?	N/A	
Are ≤ 10 actuations used for cascade impactor study?	Yes (1 actuation)	
If >1 actuation, what is the # of actuations used?	N/A	
Are the testing methods acceptable?	Acceptable	
If not, why?	N/A	
STUDY RESULTS:		
Is drug deposition reported in mass units?	Yes	
Is the mass balance data reported?	Yes	
Results	Does Impactor -Sized Mass data pass PBE?	Yes
	Does APSD analysis pass modified chi-square ratio test?	Yes for FP No for SA
	Are the mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle mass (FPM) supportive?*	Yes for GSD and FPM, but no for MMAD for SA
Mass Balance	Is the mean range for Total B between 85-115% of the label claim? (on a per actuation basis)	FP: No [REDACTED] (b) (4) SA: Yes for the test product.
	Is PBE acceptable?	Acceptable
If not, why?	N/A	

Reviewer's Comments:

- The test product passes PBE analysis for ISM and mass balance. In addition, it passes the modified chi-square test using acceptance criteria of 25% difference for FP. For SA, the test product does not pass the modified chi-square test using acceptance criteria of 25% difference, but pass it using acceptance criteria of 30% difference. DBI consulted ORS (which is the office who recommends conducting modified chi-square test for APSD study) on the acceptability of the APSD study based on this observation. ORS consult reviewer evaluated 1) the role of modified chi-square test under the current weight-of-evidence approach recommended in the product-specific guidance, 2) availability of in vivo BE information, and 3) impact of low deposition sites on modified chi-square test outcome, and considers that the current APSD study is acceptable.¹¹⁴ Therefore, the reviewer will not pursue this issue further.

It is noted that in BE review of ANDA 209959 (Albuterol Inhalation Aerosol), the modified chi-square analysis also passed at the 30% difference but failed at the 25% difference for the APSD study. The BE reviewer of ANDA 209959 considers it acceptable since “this data is considered supportive only at this time

(b) (5)

(b) (5).¹¹⁵

- The test product passes PBE analysis for GSD and FPM, but did not pass MMAD. However, since MMAD is not one of the BE criteria in the product-specific guidance, the reviewer will not pursue this issue further.

-  (b) (4)

The applicant's bridging APSD study for the 500/50 mcg strength is **acceptable**.

5.2.4.6.6 Deficiencies / Recommendations

N/A

¹¹⁴ GDRP: ANDA-208891-ORIG-1-AMEND-22, Respond to Consult Request, 23136539_Consult response_ORIS.doc, 5/25/2018.

¹¹⁵ GDRP: ANDA-209959-ORIG-1, Bioequivalence Review, A209959N000DB-Review01-11032016, 12/26/2017.

5.3 Attachments

5.3.1 DRL Issued to the Applicant on 2/23/2018

On 2/23/2018, a Discipline Review Letter (DRL) with following comments was communicated to the applicant. The current review includes evaluation of the applicant's response dated 3/22/2018.

IN VITRO STUDIES

Deficiency Related to Method Transfer for In Vitro Studies

Method Transfer – Common to Single Actuation Content (SAC) and Aerodynamic Particle Size Distribution (APSD) Studies

1. For SAC method transfer from (b) (4) to (b) (4), you stated in the method transfer report [8/28/2017 submission, Module 3.2.P.2\Method Transfer Report – (b) (4) (b) (4) p. 11 of 26] that “[a]n equivalence testing approach will be used to compare the mean emitted dose generated across the two sites. This involves calculating a 90% confidence interval (CI) for the ratio of geometric means between the two sites. Successful method transfer is demonstrated if 90% CI for the ratio of means falls within 0.95-1.05... Mylan Global Respiratory Group will determine the success of the method transfer”. You had a similar statement for the APSD method transfer from (b) (4) to (b) (4), (b) (4) [8/28/2017 submission, Module 3.2.P.2\Method Transfer Report – (b) (4) (b) (4) p. 17 of 52] regarding Fine Particle Mass (FPM) generated across the two sites. However, although you provided testing results in the method transfer reports, the reviewer could not locate the 90% CI for the ratio of geometric means of emitted dose and of FPM between the two sites ((b) (4)). Therefore, please provide this information.

Deficiency Related to Information Common to All In Vitro Studies (057755-02-04, MGR-PRO-2015-080, 057755-02-07, MGR-REP-2015-092, MGR-PRO-REP-2015-103, MGR-REP-2015-093, MGR-PRO-2016-106, MGR-PRO-2016-107, and MGR-PRO-2016-108)

Both SAC and APSD Studies

2. The Agency acknowledges your statement that you did not use blinding approach in any of the SAC and APSD studies [8/28/2017 submission, Module 1.2\Cover Letter – 0021 – Addendum 5a – Bioequivalence (General and In-Vivo), p. 22 of 65]. You stated that it is necessary to use a device holder and mouthpiece adaptor during SAC and APSD testing and thus blinding during laboratory testing is not possible. According to the *Guidance for Industry - Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal sprays for Local Actions* (posted April 2003), “it is important that the analyst performing the postactuation evaluations of the collected data be blinded to the identity of the samples.” Please clarify if analysts performing the post actuation evaluations were blinded to the identity of the samples in any of the aforementioned in vitro studies.

Deficiencies Related to In Vitro Equivalence Study 057755-02-04 Only

APSD Study

3. The Agency acknowledges that you have provided a list of APSD study samples that were collected on dose counter numbers (DCNs) other than 59 and 2, and reason for alternate DCN use. However, it is noted that the reason for alternate DCN use was not provided for the following sample. Therefore, please provide the detailed reason(s) for using different dose counter number. If applicable, please also provide its supporting documents (e.g. investigational report), original actuation data, as well as corrective action taken.

Flow Rate	Product	Batch	Unit	Stage	Dose Counter Number
60	REF	4ZP3863	40	BOL	57

4. It is noted that for the 30 L/min flow rate, the chromatogram for Stage 1 of the Test Order 58 is abnormal (8/28/2017 submission, Module 3.2.P.2\Study 057755-02-04 (P20987) – APSD – 100/50mcg – 30 L/min – Chromatograms, p. 916 of 2029) (please see figure below). Please explain how you derived the fluticasone propionate (FP) and salmeterol (SA) concentration from this chromatogram.



Deficiency Related to In Vitro Equivalence Study 057755-02-07 Only

APSD Study

5. According to your study report MGR-REP-2015-097 (version 1.0, p. 13 of 178), you stated that “for units 180 and 221 EOL 60 L/min, no acceptable data will be reported for FP and SA”. The Agency acknowledges that in your 8/28/2017 submission, you have provided data obtained as well as supporting documentations for these samples. However, for Unit #221 EOL 60 L/min, it is noted that in (b) (4) (8/28/2017 submission,

Module 3.2.P.2\ (b) (4), p. 6 of 6), you stated “there is no reportable result for cup 3 for this sample. As a sufficient number of data points were generated for the purposes of this IVBE study, the original results for TO 104 EoL (b) (4) will be reported however, a statement will be added to the (b) (4) Results Summary Section of the report that due to this investigation and apparent sample contamination, the results are considered to be atypical.” However, it is noted that in addition to Stage 3 results, results from all other stages/mouthpiece/pre-separator of this unit was also not reported. Therefore, please provide original results of all stages/mouthpiece/pre-separator of this unit.

Deficiencies Related to In Vitro Studies MGR-PRO-2016-106 Only

Both SAC and APSD Studies

6. According your study protocol, the SAC study should be performed at dose counter #s 60, 30 and 1, and the APSD study should be performed at dose counter #s 59 and 2. It is noted that the following samples used alternate DCNs. Therefore, for each of these samples, please provide the detailed reason(s) for using different dose counter number. If applicable, please also provide its supporting documents (e.g. investigational report), original actuation data, as well as corrective action taken.

Product	Batch	Unit	Stage	Dose Counter Number
SAC study				
REF	6ZP7030	84	BOL	59
REF	6ZP7784	111	BOL	59
APSD study				
TEST	60000343	38	BOL	58

7. According to your study report, the following 3 samples were rejected, but no replacement devices were used. Please explain why no replacement devices were used for these 3 rejected samples.

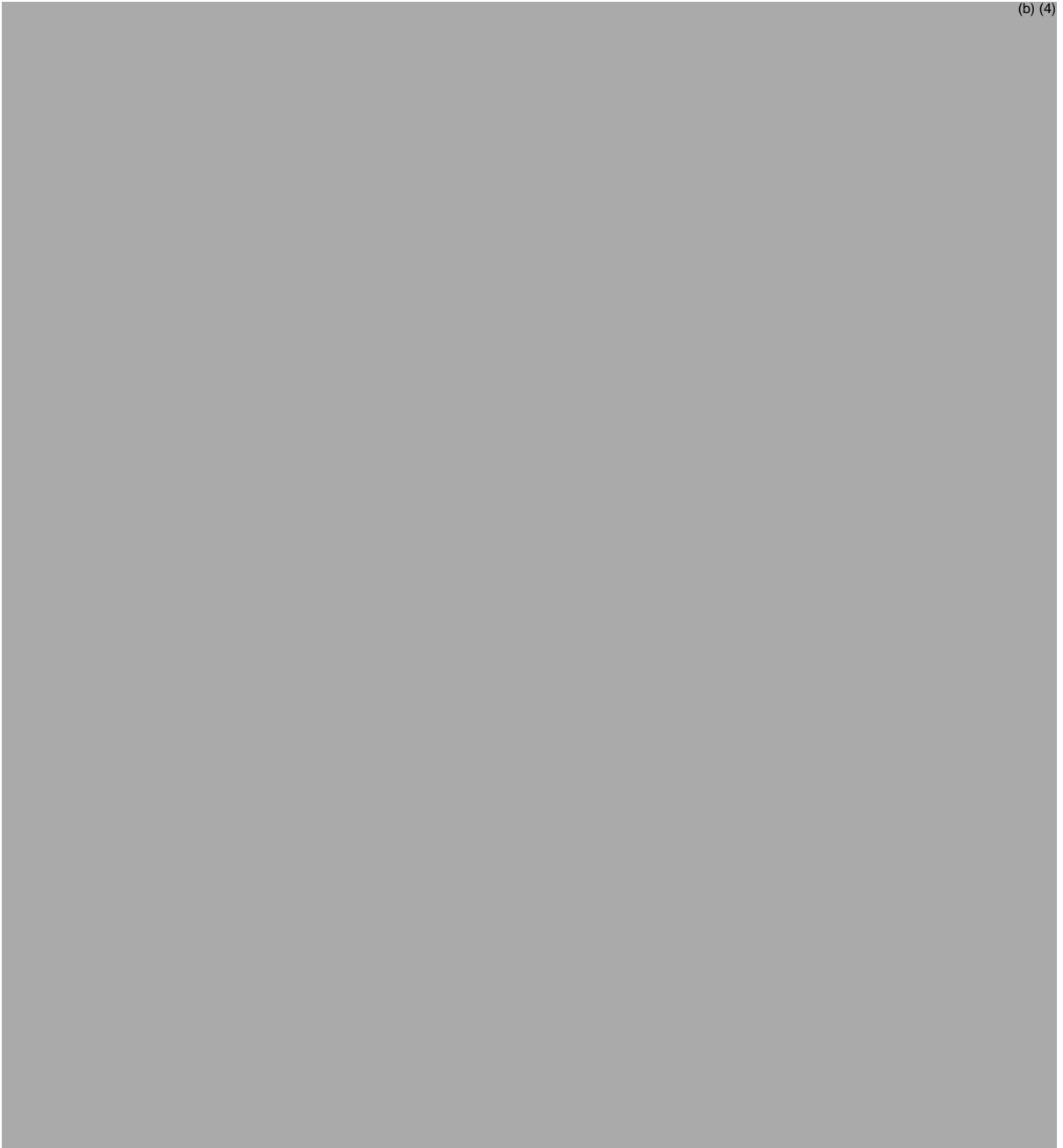
Product	Batch number	Original device number	Life stage	Reason for replacement
MGR001	60000343	31, 33, 36	BoL	Incorrect preparation of mobile phase and diluent occurred. This was used to prepare original test samples. The samples were not analysed.

SAC Study

8. Please provide MGR-SOP-ACD-GEN-0025 that was effective at the time of the in vitro bridging studies.

APSD Study

9. It is noted that chromatograms for the following samples are abnormal (please see chromatograms below). Please specify which unit # these chromatograms correspond to, and justify your peak integration.



PK BE STUDIES

Deficiency Related to Fasting Study MGR001-1016

10. According to your bioanalytical report, 16 samples were reassayed for SA due to sample outside limits of curve range (ALQ). It is noted that the original concentrations of all these

samples were listed as “ALQ”. Please provide the original concentration numbers (e.g. 12.34 pg/mL instead of “ALQ”) for each of these samples.

5.3.2 SAS Output

PK Study

Study	SAS Data	SAS Code	SAS Stat	SAS Output/Table
Fasting (FP)	 208891_Fasting_Data sets_Fluticasone Propi	 TWOWAYCALCKE fasting grp effect 2.SA	 208891_Fasting_stat_ Fluticasone Propionate	 208891_Fasting_table _Fluticasone Propiona
Fasting (SA)	 208891_Fasting_Data sets_Salmeterol.doc	 TWOWAYCALCKE fasting no potential Cr	 208891_Fasting_stat_ SalmeterolACTUAL.do	 208891_Fasting_table _SalmeterolACTUAL.d

Pivotal In Vitro Study

Study			SAC		APSD	
			SAS Code	SAS Output/Table	SAS Code	SAS Output/Table
100/50 mcg strength	30 L/min	FP	 208891SAC FP 30.SAS	 SAC_.doc	 CI for APSD 208891 FP 30-1.SAS	 CI_ISM.doc
		SA	 208891SAC SA 30.SAS	 SAC_.doc	 CI for APSD 208891 SA 30-1.SAS	 CI_ISM.doc
	60 L/min	FP	 208891SAC FP 60.SAS	 SAC_.doc	 CI for APSD 208891 FP 60-1.SAS	 CI_ISM.doc
		SA	 208891SAC SA 60.SAS	 SAC_.doc	 CI for APSD 208891 SA 60-1.SAS	 CI_ISM.doc
	90 L/min	FP	 208891SAC FP 90.SAS	 SAC_.doc	 CI for APSD 208891 FP 90-1.SAS	 CI_ISM.doc
		SA	 208891SAC SA 90.SAS	 SAC_.doc	 CI for APSD 208891 SA 90-1.SAS	 CI_ISM.doc
250/50 mcg strength	30 L/min	FP	 208891SAC FP 30.SAS	 SAC_.doc	 CI for APSD 208891 FP 30-1.SAS	 CI_ISM.doc

	60 L/min	SA	 208891SAC SA 30.SAS	 SAC_.doc	 CI for APSD 208891 SA 30-1.SAS	 CI_ISM.doc	
		FP	 208891SAC FP 60.SAS	 SAC_.doc	 CI for APSD 208891 FP 60-1.SAS	 CI_ISM.doc	
	90 L/min	SA	 208891SAC SA 60.SAS	 SAC_.doc	 CI for APSD 208891 SA 60-1.SAS	 CI_ISM.doc	
		FP	 208891SAC FP 90.SAS	 SAC_.doc	 CI for APSD 208891 FP 90-1.SAS	 CI_ISM.doc	
	500/50 mcg strength	30 L/min	FP	 208891SAC FP 30.SAS	 SAC_.doc	 CI for APSD 208891 FP 30-1.SAS	 CI_ISM.doc
			SA	 208891SAC SA 30.SAS	 SAC_.doc	 CI for APSD 208891 SA 30-1.SAS	 CI_ISM.doc
60 L/min		FP	 208891SAC FP 60.SAS	 SAC_.doc	 CI for APSD 208891 FP 60-1.SAS	 CI_ISM.doc	
		SA	 208891SAC SA 60.SAS	 SAC_.doc	 CI for APSD 208891 SA 60-1.SAS	 CI_ISM.doc	
90 L/min		FP	 208891SAC FP 90.SAS	 SAC_.doc	 CI for APSD 208891 FP 90-1.SAS	 CI_ISM.doc	
		SA	 208891SAC SA 90.SAS	 SAC_.doc	 CI for APSD 208891 SA 90-1.SAS	 CI_ISM.doc	

In vitro Bridging Study

Study		SAC		APSD	
		SAS Code	SAS Output/Table	SAS Code	SAS Output/Table
100/50 mcg strength	FP	 208891SAC 100 FP.SAS	 SAC_.doc	 CI for APSD 208891 100 FP.SAS	 CI_ISM.doc
	SA	 208891SAC 100 SA.SAS	 SAC_.doc	 CI for APSD 208891 100 SA.SAS	 CI_ISM.doc
250/50 mcg strength	FP	 208891SAC 250 FP.SAS	 SAC_.doc	 CI for APSD 208891 250 FP.SAS	 CI_ISM.doc
	SA	 208891SAC 100 SA.SAS	 SAC_.doc	 CI for APSD 208891 250 SA.SAS	 CI_ISM.doc
500/50 mcg strength	FP	 208891SAC 500 FP.SAS	 SAC_.doc	 CI for APSD 208891 500 FP.SAS	 CI_ISM.doc
	SA	 208891SAC 500 SA.SAS	 SAC_.doc	 CI for APSD 208891 500 SA.SAS	 CI_ISM.doc

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 208891
APPLICANT: Mylan Pharmaceuticals Inc.
DRUG PRODUCT: Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate)
Inhalation Powder, 0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ
0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation

The Division of Bioequivalence I (DBI) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Bing V. Li, Ph.D.
Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5.4 Outcome Page

Completed Assignment for 208891 ID: 35301

Reviewer: Ma, Tian

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder, 0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ 0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>		
35301	8/28/2017	BIO	ANDA Amendment [1]	1	1	Edit	Delete
35301	8/28/2017	BIO	Consult Review (For Consults to Other Office) [1]	1	1	Edit	Delete
35301	8/28/2017	Parallel	Study Amendment [1]	1	1	Edit	Delete
35301	8/28/2017	Parallel	Fasting Study (Full template) [1]	1	1	Edit	Delete
35301	8/28/2017	Parallel	Fasting Study (Full Template - Additional Analyte) [0.25]	0.25	0.25	Edit	Delete
35301	8/28/2017	Parallel	In-Vitro Study (Nasal/Inhaled Dosage Forms) Per Study [0.5]	3	3	Edit	Delete
35301	8/28/2017	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1	Edit	Delete
				Total:	8.25		

DIVISION OF BIOEQUIVALENCE REVIEW FOR DRY POWDER INHALER PRODUCTS

ANDA No.	208891			
Drug Product Name	Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder			
Strength(s)	0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ 0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation			
Applicant Name	Mylan Pharmaceuticals Inc.			
Applicant Address	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310			
US Agent Name and the Mailing Address	Joseph J. Sobekli, Head of Regulatory Affairs - North America joseph.sobekli@mylan.com OR Wayne Talton, Head of Global Regulatory Science & Operations wayne.talton@mylan.com			
US agent's Telephone Number	(304) 599-6429 (JS) 304) 554-6551 (WT)			
US Agent's Fax Number	(304) 285-6407			
Original Submission Date(s)	December 29, 2015 February 15, 2016 (concentration data, graphs and SAS output for pharmacokinetic studies; tabular listing of all clinical studies; information on unblinding, randomization and datasets for the pharmacodynamic study) August 11, 2016 (Response to ECD/Bioequivalence) [@] September 22, 2016 (Response to ECD/Bioequivalence) September 28, 2016 (Response to ECD/Bioequivalence) [@] January 12, 2017 (Response to ECD/Bioequivalence)			
Submission Date(s) of Amendment(s) Under Review	April 4, 2017 (Meeting/Meeting Request)			
Primary Reviewer	Tian Ma, Ph.D.			
Secondary Reviewer	Vipra Kundoor, Ph.D.			
Tertiary Reviewer	Bing V. Li, Ph.D.			
Study Number (s)	MGR001-1006	MGR001-1007	MGR001-1005	MGR001-1014
Study Type (s)	Fasting	Fasting	Fasting (failed, but was used in pooled analysis by the firm with MGR001-1014)	Fasting(failed, but was used in pooled analysis by the firm with MGR001-1005)
Strength (s)	100/50 mcg ¹	500/50 mcg	250/50 mcg	250/50 mcg
Clinical Site	Worldwide Clinical Trials Early Phase Services, LLC			
Clinical Site Address	2455 NE Loop 410, Suite 150			

¹ From now on in this review, product strength of “x/y mcg” will be used to indicate the strength of fluticasone propionate and salmeterol xinafoate (EQ y mcg base) per inhalation, respectively.

	San Antonio, Texas 78217		
Analytical Site	Mylan Pharmaceuticals Inc.		
Analytical Site Address	Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505		
Study Number (s)	057755-02-04	MGF-PRO-2015-080	057755-02-07
Study Type (s)	In Vitro BE [single actuation content (SAC) and aerodynamic particle size distribution (APSD)]	In Vitro BE (SAC and APSD)	In Vitro BE (SAC and APSD)
Strength (s)	100/50 mcg	250/50 mcg	500/50 mcg
Analytical Site	(b) (4)	Mylan Global Respiratory Group	(b) (4)
Analytical Site Address	(b) (4)	IPC008, Discovery Park House, Floor 3 Sandwich, Kent. CT13 9ND. UK	(b) (4)
Study Number (s)	MGR-REP-2015-092	MGR-PRO-REP-2015-103	MGR-REP-2015-093
Study Type (s)	Pressure Differential (4 kPa) (SAC and APSD)	Pressure Differential (4 kPa) (SAC and APSD)	Pressure Differential (4 kPa) (SAC and APSD)
Strength (s)	100/50 mcg	250/50 mcg	500/50 mcg
Analytical Site	(b) (4)	Mylan Global Respiratory Group	(b) (4)
Analytical Site Address	(b) (4)	IPC008, Discovery Park House, Floor 3 Sandwich, Kent. CT13 9ND. UK	(b) (4)
Study Number (s)	MGR001-3001		
Study Type (s)	Clinical Endpoint		
Strength (s)	100/50 mcg		
Clinical Site	Site Number	Principal Investigator and Location	Address
	3001001	Idalia A. Acosta, Miami, FL 33015	5941 NW 173 Dr, Ste 1 Miami, FL 33015
	3001002	Niran J. Amar, Waco, TX 76712	333 Londonderry Dr, Ste 110 Waco, TX 76712
	3001003	James W. Baker, Portland, OR 97223	9495 SW Locust St Portland, OR 97223
	3001004	G Daniel Brooks, Bellevue, NE 68123-4303	3503 Samson Way, Ste 108 Bellevue, NE 68123-4303
	3001006	Warner W. Carr, Mission Viejo, CA 92691	27800 Medical Center Rd, #240/#244 Mission Viejo, CA 92691
	3001007	Jonathan Corren, Los Angeles, CA 90025	10780 Santa Monica Blvd Ste 280 Los Angeles, CA 90025

3001008	David Cypcar, Asheville, NC 28801	14 McDowell St Asheville, NC 28801
3001009	Joseph D. Diaz, San Antonio, TX 78229	2414 Babcock Rd, Ste 108- 109 San Antonio, TX 78229
3001010	Manuel A. Franco, Miami, FL 33133	2720 SW 37 Ave Miami, FL 33133
3001011	Sherwin A. Gillman, Orange, CA 92868	725 West La Veta Ave, Ste 100 Orange, CA 92868
3001012	John T. Given, Canton, OH 44718	Allergy, Respiratory & Sleep Center 4048 Dressier Rd NW, Ste 100 Canton, OH 44718
3001013	Stanley Goldstein, Rockville Centre, NY 11570	242 Merrick Rd, Ste 401 Rockville Centre, NY 11570
3001014	Richard G. Gower, Spokane, WA 99202	324 S Sherman St Spokane, WA 99202
3001015	Leon S. Greos, Centennial, CO 80112	14000 E. Arapahoe Rd, Ste 260 Centennial, CO 80112
3001016	Amina Z. Haggag, Anaheim, CA 92801	Anaheim Clinical Trials, LLC 1085 N. Harbor Blvd Anaheim, CA 92801
3001017	Frank C. Hampel Jr., New Braunfels, TX 78130	705-A Landa St New Braunfels, TX 78130
3001018	Edward Francis Kent Jr., South Burlington, VT 05403	Timber Lane Allergy & Asthma Research, LLC 54 Timber Lane South Burlington, VT 05403
3001019	Phillip E. Korenblat, St. Louis, MO 63141	1040 N Mason Rd, Ste 112 St. Louis, MO 63141
3001020	Craig Fred LaForce, Raleigh, NC 27607	North Carolina Clinical Research 2615 Lake Dr, Ste 301 Raleigh, NC 27607
3001022	Edward E. Lisberg, River Forest, IL 60305	7420 Central Ave, Ste 2020 River Forest, IL 60305
3001023	Stephen Maddock, Lenexa, KS 66219	Analab Clinical Research Inc 15335 W 95th St Lenexa, KS 66219
3001024	Lyndon E. Mansfield, El Paso, TX 79903	2121 Wyoming Ave El Paso, TX 79903
3001025	Jonathan Matz, Baltimore, MD 21236	Chesapeake Clinical Research, Inc 7939 Honeygo Blvd, Ste 219 Baltimore, MD 21236
3001026	Curtis J. Mello, North Dartmouth, MA 02747	370 Faunce Corner Rd 2nd Fl North Dartmouth, MA 02747

3001027	S. David Miller, North Dartmouth, MA 02747	Northeast Medical Research Associates, Inc. 49 State Rd Watuppa Bldg, Ste 202 North Dartmouth, MA 02747
3001028	Anthony Montanaro, Portland, OR 97202	6327 SE Milwaukie Ave, 2nd Floor Portland, OR 97202
3001029	Nancy K. Ostrom, San Diego, CA 92123	5776 Ruffin Rd San Diego, CA 92123
3001031	Amit I. Patel, Riverside, CA 92506	Integrated Research Group, Inc. 4646 Brockton Ave, Ste 202-3 Riverside, CA 92506
3001032	David S. Pearlman, Denver, CO 80230	125 Rampart Way, Ste 150 Denver, CO 80230
3001033	Andrew J. Pedinoff, Skillman, NJ 08558	Montgomery Professional Center 24 Vreeland Dr Skillman, NJ 08558
3001034	Warren William Pleskow, Encinitas, CA 92024	317 N El Camino Real, Ste 506 Encinitas, CA 92024
3001035	Larry S. Posner, Napa, CA 94558	1100 Pear Tree Lane Napa, CA 94558
3001036	Gordon D. Raphael, Bethesda, MD 20814	4915 Auburn Ave, Ste 202 Bethesda, MD 20814
3001037	Paul H. Ratner, San Antonio, TX 78229	7711 Louis Pasteur Dr, Ste 406 San Antonio, TX 78229
3001038	Syed M. Rehman, Toledo, OH 43617	7247 W. Central Ave, Ste A Toledo, OH 43617
3001039	Michael E. Ruff, Dallas, TX 75231	5499 Glen Lakes Dr, Ste 200 Dallas, TX 75231
3001040	Russell A. Settipane, East Providence, RI 02914	450 Veterans Memorial Pkwy #15 East Providence, RI 02914
3001041	Ellen R. Sher, Ocean, NJ 07712	802 West Park Ave, Ste 213 Ocean, NJ 07712
3001042	Lawrence D. Sher, Rolling Hills Estates, CA 90274	550 Deep Valley Dr, Ste 317 Rolling Hills Estates, CA 90274
3001045	Stephen A. Tilles, Seattle, WA 98115	9725 Third Ave NE, Ste 500 Seattle, WA 98115
3001046	Mark L. Vandewalker, Columbia, MO 65203	601 W Nifong Bldg 2-A Columbia, MO 65203
3001047	David P. Chen, Bozeman, MT 59718	950 Stoneridge Dr, Ste 1 Bozeman, MT 59718
*3001048	Patrick H. Win, Shiloh, IL 62269	325 Tamarack Lane Shiloh, IL 62269

3001049	John A. Winder, Sylvania, OH 43560	5800 Monroe St, Ste A-9 Sylvania, OH 43560
3001050	James D. Wolfe, San Jose, CA 95117	4050 Moorpark Ave, Ste 6 San Jose, CA 95117
3001051	Robert N. Wolfe, Los Angeles, CA 90048	Southern California Institute For Respiratory Diseases, Inc. 8635 West 3rd St, Ste 965-W Los Angeles, CA 90048
3001053	Thomas R. Murphy, N. Charleston, SC 29420	7555 Northside Dr N. Charleston, SC 29420
3001054	David I. Bernstein, Cincinnati, OH 45231	Bernstein Clinical Research Center, LLC 8444 Winton Rd Cincinnati, OH 45231
3001055	Charles M. Fogarty, Spartanburg, SC 29303	485 Simuel Rd Spartanburg, SC 29303
3001056	Philip C. Halverson, Minneapolis, MN 55402	825 Nicollet Mall, Ste 1135 Minneapolis, MN 55402
3001057	Sanchayita "Ita" Tripathy, Rolla, MO 65401	509 East 10th St Rolla, MO 65401
3001058	John F. Zwetchkenbaum, Warwick, RI 02886	470 Toll Gate Rd, Ste 203 Warwick, RI 02886
3001059	Dario D. Altamirano, Hialeah, FL 33012	900 W 49th St, Ste 430 Hialeah, FL 33012
3001060	Philip A. Emrie, Wheat Ridge, CO 80033	8550 W 38th Ave, Ste 202 Wheat Ridge, CO 80033
3001061	Timothy Harrison Elder, Gainesville, FL 32607	4343 W Newberry Rd, Ste 17 Gainesville, FL 32607
3001062	Gregory J. Feldman, Spartanburg, SC 29303	141 Harold Fleming Court Spartanburg, SC 29303
3001063	Jason H. Friesen, Eugene, OR 97401	Allergy and Asthma Research Group 1488 Oak St Eugene, OR 97401
3001064	Gregory M. Gottschlich, Cincinnati, OH 45242	9395 Kenwood Rd, Ste 101 Cincinnati, OH 45242
3001065	James Lawrence Pearle, Fullerton, CA 92835	301 W Bastanchury Rd, Ste 220 Fullerton, CA 92835
*3001066	Ronald H. Saff, Tallahassee, FL 32308	Allergy & Asthma Diagnostic Treatment Center 2300 Centerville Rd Tallahassee, FL 32308
3001067	Teresa S. Sligh, North Hollywood, CA 91606	6400 Laurel Canyon Blvd, Ste 300A North Hollywood, CA 91606
3001068	Kurt W. Jensen, Tacoma, WA 98405	Pulmonary Consultants, PLLC 1708 S. Yakima Ave, Ste 300 Tacoma, WA 98405
3001069	Edward M. Kerwin, Medford, OR 97504	Clinical Research Institute of Southern Oregon, PC 3860 Crater Lake Ave, Ste B Medford, OR 97504

3001071	Daniel F. Soteres, Colorado Springs, CO 80907	2709 North Tejon St Colorado Springs, CO 80907
3001074	William R. Lumry, Dallas, TX 75231	10100 N Central Expressway, Ste 125 Dallas, TX 75231
3001075	Mikhail Palatnik, Gold River, CA 95670	2485 Sunrise Blvd Gold River, CA 95670
3001076	Paul Y. Qaqudah, Huntington Beach, CA 92647	17822 Beach Blvd, Ste 278 Huntington Beach, CA 92647
3001077	Weily Soong, Birmingham, AL 35209	504 Brookwood Blvd, Ste 250 Birmingham, AL 35209
3001078	Selwyn Spangenthal, Charlotte, NC 28207	1918 Randolph Rd, Ste 440 Charlotte, NC 28207
*3001079	William W. Storms, Colorado Springs, CO 80907	1625 Medical Center Point, Ste 190 Colorado Springs, CO 80907
3001080	Martha V. White, Wheaton, MD 20902	11002 Veirs Mill Rd, Ste 414 Wheaton, MD 20902
3001081	Isaac R. Melamed, Centennial, CO 80112	6801 S. Yosemite St Centennial, CO 80112
3001082	Vosudesh K. Pai, Lawrenceville, GA 30046	555 Old Norcross Rd, Ste 250 Lawrenceville, GA 30046
3001083	Paul A. Shapero, Bangor, ME 04401	700 Mt. Hope Ave, Ste 430 Bangor, ME 04401
3001084	Daniel Sousa, Fall River, MA 02720	373 New Boston Rd Fall River, MA 02720
3001085	Sheldon Spector, Los Angeles, CA 90025	11645 Wilshire Blvd, Ste 1155 Los Angeles, CA 90025
3001086	Gary C. Steven, Greenfield, WI 53228	8585 W Forest Home Ave, Ste 200 Greenfield, WI 53228
3001087	Manuel A. Fernandez- Gonzalez, Miami, FL 33135	590 SW 27th Ave Miami, FL 33135
3001088	Agustin J. Latorre, Miami, FL 33155	6850 Coral Way, Ste 409 Miami, FL 33155
3001089	Robert S. Call, Henrico, VA 23233	9920 Independence Park Dr, Ste 101 Henrico, VA 23233
3001090	Marcy Jo Goisse, Smithfield, PA 15478	100 Ridge View Dr, Ste 3 Smithfield, PA 15478
3001091	Anoshie Ratnayake, Costa Mesa, CA 92626	3545 Howard Way Costa Mesa, CA 92626
3001092	Marvin Kalafer, Jenkintown, PA 19046	815 Greenwood Ave, Ste 12 Jenkintown, PA 19046
3001093	Santiago Reyes, Oklahoma City, OK 73112	3366 NW Expressway, Bldg D, Ste 330 Oklahoma City, OK 73112

	3001095	Karl V. Sitz, Little Rock, AR 72205	18 Corporate Hill, Ste 110 Little Rock, AR 72205
	3001096	Stephen G. Basheda, Pittsburgh, PA 15243	1050 Bower Hill Rd, Ste 307 Pittsburgh, PA 15243
	3001097	Iftikhar Hussain, Tulsa, OK 74136	7307 S. Yale Ave, Ste 200 Tulsa, OK 74136
	3001100	Manav Singla, White Marsh, MD 21162	Asthma Allergy & Sinus Center 5430 Campbell Blvd, Ste 103 White Marsh, MD 21162
	3001102	Daniel Rodriguez, New Port Richey, FL 34653	Advanced Research Institute, Inc. 7114 Congress St New Port Richey, FL 34653
	3001104	Edward Joseph Campbell, Provo, UT 84604	2230 North at University Pkwy Cottontree Square, Bldg 6A Provo, UT 84604
	3001107	Stephen Ryan, Tacoma, WA 98405	316 Martin Luther King Jr. Way, Ste 401 Tacoma, WA 98405
	3001108	Tonny Tanus, Bakersfield, CA 93301	2116 17th St Bakersfield, CA 93301
	3001109	Carl Thornblade, Missoula, MT 59808	2683 Palmer St, Ste B Missoula, MT 59808
	3001111	Miguel E. Trevino, Clearwater, FL 33756	1573 South Fort Harrison Ave Clearwater, FL 33756
	3001112	Steven F. Weinstein, Huntington Beach, CA 92647	Allergy and Asthma Specialists Medical Group 17742 Beach Blvd, Ste 310 Huntington Beach, CA 92647
	3001114	David Fuentes, Boerne, TX 78006	1420 River Rd, Ste 100 Boerne, TX 78006
	3001115	Susan L. Andrew, Dickinson, TX 77539	914 FM 517 Road West Dickinson, TX 77539
	*3001116	William L. Ebbeling, Fresno, CA 93720	1646 E. Herndon Ave, Ste 106 Fresno, CA 93720
	3001119	Bruce A. DeCotiis, Brick, NJ 08724	1673 Hwy 88 West Brick, NJ 08724
3001120	Ernesto Diaz, Coral Gables, FL 33134	5200 SW 8th St, Ste 119-120 Coral Gables, FL 33134	
3001122	Lawrence P. Landwehr, Warrensburg, MO 64093	407A East Russell Ave, Ste 3 Warrensburg, MO 64093	
Clinical Site Address	Please see table above		
Study Number (s)	MGR000-1003		
Study Type (s)	Flow Profiling		
Strength (s)	N/A (empty inhaler which did not contain drug or placebo)		
Clinical Site	Site	Principal Investigator	Address
	1	Dominik Kappeler	Inamed Clinical Unit,

			82131 Gauting, Germany
	2	Isabelle Schenkenberger	Clinical Research Berlin GbR; 10787 Berlin, Germany
	3	Prof. Dr. med. Walter Dorsch	Practice for Child and Adolescent Medicine, Allergy, Pediatric Pulmonology, Naturopathic, 81379 Munich, Germany
	4	Dr. med. Manfred Praun	Practice for Child and Adolescent Medicine Dr. Praun & Dr. Stiebing, 82205 Gilching, Germany
	5 (not activated)	Prof. Dr. med. Stefan Zielen	University Hospital Johann Wolfgang Goethe-Universität Frankfurt/Main, Centre for children and adolescents, Departement of paediatric pneumology, allergology and cystic fibrosis, 60590 Frankfurt/Main, Germany
Clinical Site Address	Please see table above		
Study Number (s)	MGR000-1004		
Study Type (s)	Device Orientation		
Strength (s)	N/A (empty inhaler which did not contain drug or placebo)		
Market Research Facilities^s	(b) (4)		
Market Research Facilities^s Address	Please see table above		
OSI Status	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete ☐ N/A (Waiver) ²		<u>Post October 1, 2014 ANDAs</u> ☐ To Be Determined by OSIS ☐ Pending ☒ Complete

² Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☐ Not granted ☒ N/A		
QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ N/A		
Formulation	☒ Adequate ☐ Inadequate		
Will Response to CR Result in a Reformulation?	☐ Possibly ☒ No ☐ N/A		
BE Guidance Version Used for Evaluation of Current ANDA	Draft Guidance on Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder (Recommended Sep 2013)		
Deficiency Classification	☒ Major (Deficiencies to be communicated by CR) ☐ Minor ☐ N/A (Review is Adequate)		
Overall Review Result	☐ Adequate ☒ Inadequate		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1,2,10,14	Fasting	100/50 mcg	INCOMPLETE
1,2,10,14	Fasting	500/50 mcg	INCOMPLETE
1,2,10,14	Fasting (Failed, but was used in pooled analysis by the firm with MGR001-1014)	250/50 mcg	UNACCEPTABLE
1,2,10,14	Fasting (Failed, but was used in pooled analysis by the firm with MGR001-1005)	250/50 mcg	UNACCEPTABLE
1,10,14	In Vitro BE (SAC and APSD)	100/50 mcg	INCOMPLETE
1,10,14	In Vitro BE (SAC and APSD)	250/50 mcg	INCOMPLETE
1,10,14	In Vitro BE (SAC and APSD)	500/50 mcg	INCOMPLETE
1,10,14	Pressure Differential (4 kPa) (SAC and APSD)	100/50 mcg	UNACCEPTABLE
1,10,14	Pressure Differential (4 kPa) (SAC and APSD)	250/50 mcg	UNACCEPTABLE
1,10,14	Pressure Differential (4 kPa) (SAC and APSD)	500/50 mcg	UNACCEPTABLE
1,2	Clinical Endpoint	100/50 mcg	INCOMPLETE
1,2,10	Flow Profiling	N/A (empty inhaler which did not contain drug or placebo)	UNACCEPTABLE
1,8@,11@,14	Device Orientation	N/A (empty inhaler which did	UNACCEPTABLE

		not contain drug or placebo)	

@ Submission in response to Office of Surveillance and Epidemiology (OSE)/ Division of Medication Error Prevention and Analysis (DMEPA)'s ECD [issued through Division of Bioequivalence I (DBI)], which is reviewed by DMEPA for their response to DBI's consult request for evaluation of the firm's device orientation study.

* The firm stated that these sites screened subjects but did not enroll any subjects.

§ The firm stated that these sites provided the facility in which user handling sessions were conducted; these facilities provided no other function or resource in the user handling assessment

1 EXECUTIVE SUMMARY

This is a review of a request submitted by the firm for clarification following Agency's issuance of a Complete Response (CR) letter.

On 3/28/2017, the Agency issued a CR letter to the firm³. On 4/3/2017, the firm submitted a meeting request for a face-to-face meeting to discuss with the Agency about certain issues raised in the CR letter. On 4/4/2017, the firm submitted a clarification request to seek written response from the Agency for certain additional clarifications.

In the original submission dated 12/29/2015, the firm Mylan Pharmaceuticals Inc. submitted the current application for Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder, 0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ 0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation. The test product, also refers to as MGR001 by the firm, contains fluticasone propionate (FP) and salmeterol xinafoate (SX) inhalation powder in CRC749 inhaler device. The reference-listed drug (RLD) is Advair Diskus® 100/50 (fluticasone propionate and salmeterol xinafoate), 0.1 mg/EQ 0.05 mg base per inhalation; Advair Diskus® 250/50 (fluticasone propionate and salmeterol xinafoate), 0.25 mg/EQ 0.05 mg base per inhalation; and Advair Diskus® 500/50 (fluticasone propionate and salmeterol xinafoate), 0.5 mg/EQ 0.05 mg base per inhalation manufactured by GLAXO GRP LTD (approved on August 24, 2000 under NDA 021077). The firm submitted the following studies:

- Four fasting pharmacokinetic (PK) BE studies (#MGR001-1006 for the 100/50 mcg strength, #s MGR001-1005 and MGR001-1014 for the 250/50 mcg strength, and #MGR001-1007 for the 500/50 mcg strength)
- One clinical endpoint study (#MGR001-3001 at the 100/50 mcg strength)
- Two types [single actuation content (SAC) and aerodynamic particle size distribution (APSD)] of in vitro BE studies for each of the three strengths of the drug product (#057755-02-04 for the 100/50 mcg strength, #MGR-PRO-2015-080 for the 250/50 mcg strength, and #057755-02-07 for the 500/50 mcg strength)
- Two types (SAC and APSD) of in vitro studies at 4 kPa fixed pressure drop for each of the three strengths of the drug product (#MGR-REP-2015-092 for the 100/50 mcg strength, # MGR-PRO-REP-2015-103 for the 250/50 mcg strength, and #057755-02-08 for the 500/50 mcg strength) comparing the test and RLD products
- One flow profiling study (#MGR000-1003) comparing the empty test and RLD devices
- One device orientation study (#MGR000-1004) using empty test device

³ GDRP: ANDA-208891-ORIG-1, Upload Final Decision, A208891N000CR, 3/28/2017.

None of the aforementioned studies were acceptable due to deficiencies. A CR letter was sent to the firm on 3/28/2017³.

In the current request dated 4/4/2017, the firm is requesting a written response to seek clarification from the Agency about 18 questions that are related to pharmaceutical quality and bioequivalence (BE). Among these questions, 1 question is related to BE deficiencies (BE deficiency #49). Division of Bioequivalence I (DBI)'s written response to this BE-related question is given in the attached letter.

NOTE TO REGULATORY PROJECT MANAGER (RPM): Only the letter at the end of the current document should be incorporated into the written communication to the firm. The remainder of the current document should not be communicated to the firm.

2 SUBMISSION SUMMARY

Below is the review of the firm's BE-related question, with the following listed:

- The BE-related deficiency in the CR letter that the firm raised question about in their request for clarification submitted on 4/4/2017
- The firm's clarification request *in italic* and their questions *in bold italic*
- DBI's written response
- Reviewer's comments are included in the box at the end of the response, intended for "Internal Use Only".

CLINICAL ENDPOINT STUDY

Deficiencies Related to the Office of Study Integrity and Surveillance (OSIS) Inspectional Finding for the Clinical Site

2.1 Deficiency Comment # 49

The FDA investigators inspected several clinical sites for study MGR001-3001. Form FDA 483 was issued at the close of inspection at Prestige Clinical Research Center, Inc. (PCRC), Miami, FL from 6/7/2016 to 6/10/2016 and 6/13/2016 to 6/15/2016. One of the observations was as follows:

“Failure to retain sealed randomization schedule prior to commencement of subject enrollment. Specifically, a sealed randomization scheme, including blinding codes, was not maintained in the possession of the clinical site prior to the dosing of the initial subject (Run-in placebo on [REDACTED] (b) (6) and Randomized dosing on [REDACTED] (b) (6)). The site completed the study and was closed by the IRB on September 2015; however, the randomization scheme, which was not sealed, was sent to your site from PPD on November 6, 2015.”

It is FDA's understanding that before the start of study MGR001-3001, the packager [REDACTED] (b) (4) [REDACTED] (b) (4) did not send the records with subject dosing materials, at the time of the study or before the study started. We believe that this finding applies to all 97 sites. Therefore, to enable tracing the history of actions from the time when blinding codes were assigned to dosing materials until today, please provide a copy of [REDACTED] (b) (4) original blinding-packaging records and any log/event history, for all shipments to all 97 clinical sites.

2.1.1 Firm's Clarification Request on Deficiency Comment #49

The provision of a coding system for the emergency unblinding was implemented for Study MGR001-3001 at all Investigational Sites and throughout the duration of study recruitment in accordance with Guidance for Industry ICH E6 Good Clinical Practice: Consolidated Guidance (<http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073122.pdf>). The process was described in the clinical study protocol and was fully reviewed with all Investigational Site staff prior to study initiation. It utilised a web and telephone based Interactive Response Technology

(IRT) system, which is routinely used in multi-site, double-blind clinical studies where the randomisation code is stored and randomisation is conducted centrally, rather than on a site-by-site basis. The randomisation schedule for the whole study was generated prior to the study by PPD, and held centrally throughout the study within the secure IRT system.

During conduct of the study, Mylan supplied sealed unblinding envelopes to each Investigation Site only for the supplies selected by Investigational Site staff for the purposes of IP retention, in order to provide a mechanism by which retention samples may be identified at the site during any subsequent FDA inspections, without the need to contact PPD for access to the central IRT records.

Mylan also provided a copy of the entire unsealed randomisation schedule for the study to all sites after completion of the study (i.e. finalisation of the CSR), in response to a specific request from an FDA inspector at one of the sites for a copy of the full schedule.

Please would the Agency clarify where the requirement for a “sealed randomization schedule” to be held at each Investigational site during the study is detailed?

Furthermore, considering that IRT was used to store the randomisation schedule securely and centrally during the study, and there were therefore no unblinding codes provided to the sites (except for retained IP samples), Mylan cannot provide “actions from the time the blinding codes were assigned” and therefore cannot fulfil the Agencies request. Therefore, please can the Agency clarify the purpose of the information requested? For example, does the Agency want details of how patients were assigned to treatment codes, or clarification regarding how supplies were labelled with the correct patient number, or further explanation of the IRT system used for assignment of treatment and emergency unblinding in the MGR001-3001 study?

2.1.2 Agency’s Response:

Reviewer’s note: In the firm’s request for clarification, the firm asked 2 questions regarding the clinical endpoint study, which are addressed individually below.

Firm’s Question 1: *Please would the Agency clarify where the requirement for a “sealed randomization schedule” to be held at each Investigational site during the study is detailed?*

Agency’s Response:

As specified in the preamble to the final rule *Retention of Bioavailability and Bioequivalence Testing Samples*, 58 FR 25918, 25920 (April 28, 1993), as well as in *Guidance for Industry – Handling and Retention of BA and BE Testing Samples* (May 2004) (<https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf> Section III, page 3 of 12), we recommend providing sealed unblinding codes to the clinical sites prior to the start of the study, typically with shipments of bioequivalence drug products. The unblinding information stays at the clinical site until broken by the FDA investigator during an inspection. This ensures data integrity, and confirms that subjects at the site received the treatments reported

by the sponsor. We would like to clarify that “sealed randomization schedule” mentioned in the original Agency response refers to unblinding codes.

Please note that since the above deficiency #49 in the CR letter is from Office of Study Integrity and Surveillance (OSIS), the DBI communicated with OSIS via email for the firm’s question above and the above response is from OSIS’ email response⁴. In addition, DBI also communicated with OGD Policy regarding the way to reference to the Final Rule document OSIS cited⁵, and updated reference in the above response accordingly. This final response is concurred by OSIS.⁴

Firms’ Question 2: Furthermore, considering that IRT was used to store the randomisation schedule securely and centrally during the study, and there were therefore no unblinding codes provided to the sites (except for retained IP samples), Mylan cannot provide “actions from the time the blinding codes were assigned” and therefore cannot fulfil the Agencies request. Therefore, please can the Agency clarify the purpose of the information requested? For example, does the Agency want details of how patients were assigned to treatment codes, or clarification regarding how supplies were labelled with the correct patient number, or further explanation of the IRT system used for assignment of treatment and emergency unblinding in the MGR001-3001 study?

Agency’s Response:

FDA uses the combination of reserve samples, written assurance, and possibly additional written or electronic records maintained at each clinical site, to verify the identity of drug products used in the bioequivalence study. Once we became aware that the clinical sites had not been given the unblinding codes (except for retention samples), we requested alternative records (such as the audit trail). However, the audit trail was not available to the clinical sites to reconstruct the unblinding codes.

In summary, we request records or event log history (e.g., audit trail of the IRT system) to more completely reconstruct events during the study.

Similar to Agency’s response to Firm’s Question 1 above, the above response is from OSIS’ email response⁴.

⁴ V:\DIVISION\BIO\BIO1\Email Reference\208891 Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder\RE Sponsors clarification request regarding blinding code-related deficiency for the clinical endpoint study of ANDA 208891.msg

⁵ V:\DIVISION\BIO\BIO1\Email Reference\208891 Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder\ RE question about how to refer to a regulatory document in response to Mylan's clarification question A208891 fluticasonesalmeterol.msg

NOTE TO REGULATORY PROJECT MANAGER (RPM): Only the letter at the end of the current document should be incorporated into the written communication to the firm. The remainder of the current document should not be communicated to the firm.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 208891
APPLICANT: Mylan Pharmaceuticals Inc.
DRUG PRODUCT: Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate)
Inhalation Powder, 0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ
0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation

The Division of Bioequivalence I (DBI) has completed its review of your request for clarification dated 4/4/2017. Please see the response below:

In your 4/4/2017 Request for Clarification, Appendix 3 - Clinical Clarification – Bioequivalence, you stated:

“Please would the Agency clarify where the requirement for a ‘sealed randomization schedule’ to be held at each Investigational site during the study is detailed?”

Agency’s Response:

As specified in the preamble to the final rule *Retention of Bioavailability and Bioequivalence Testing Samples*, 58 FR 25918, 25920 (April 28, 1993), as well as in *Guidance for Industry – Handling and Retention of BA and BE Testing Samples* (May 2004) (<https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf> Section III, page 3 of 12), we recommend providing sealed unblinding codes to the clinical sites prior to the start of the study, typically with shipments of bioequivalence drug products. The unblinding information stays at the clinical site until broken by the FDA investigator during an inspection. This ensures data integrity, and confirms that subjects at the site received the treatments reported by the sponsor. We would like to clarify that “sealed randomization schedule” mentioned in the original Agency response refers to unblinding codes.

In the same Appendix 3 of the aforementioned document, you also stated:

“Furthermore, considering that IRT was used to store the randomisation schedule securely and centrally during the study, and there were therefore no unblinding codes provided to the sites (except for retained IP samples), Mylan cannot provide “actions from the time the blinding codes were assigned” and therefore cannot fulfil the Agencies request. Therefore, please can the Agency clarify the purpose of the information requested? For example, does the Agency want details of how patients were assigned to treatment codes, or clarification regarding how supplies were labelled with the correct patient number, or further explanation of the IRT system used for assignment of treatment and emergency unblinding in the MGR001-3001 study?”

Agency's Response:

FDA uses the combination of reserve samples, written assurance, and possibly additional written or electronic records maintained at each clinical site, to verify the identity of drug products used in the bioequivalence study. Once we became aware that the clinical sites had not been given the unblinding codes (except for retention samples), we requested alternative records (such as the audit trail). However, the audit trail was not available to the clinical sites to reconstruct the unblinding codes.

In summary, we request records or event log history (e.g., audit trail of the IRT system) to more completely reconstruct events during the study.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Bing V. Li, Ph.D.
Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

2.2 Outcome Page

Completed Assignment for 208891 ID: 31638

Reviewer: Ma, Tian

Date Completed:
Date Verified:

Verifier: ,

Division: Division of Bioequivalence

Description: Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder, 0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ 0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>		
31638	4/4/2017	BIO	Post CR Meeting Request Review [1]	1	1	Edit	Delete
31638	4/4/2017	Parallel	Post CR Meeting Request [1]	1	1	Edit	Delete
				Total:	2		

**DIVISION OF BIOEQUIVALENCE REVIEW FOR DRY POWDER INHALER
PRODUCTS**

ANDA No.	208891			
Drug Product Name	Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder			
Strength(s)	0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ 0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation			
Applicant Name	Mylan Pharmaceuticals Inc.			
Applicant Address	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310			
US Agent Name and the Mailing Address	Joseph J. Sobekli, Head of Regulatory Affairs - North America joseph.sobekli@mylan.com OR Wayne Talton, Head of Global Regulatory Science & Operations wayne.talton@mylan.com			
US agent's Telephone Number	(304) 599-6429 (JS) 304) 554-6551 (WT)			
US Agent's Fax Number	(304) 285-6407			
Original Submission Date(s)	December 29, 2015 February 15, 2016 (concentration data, graphs and SAS output for pharmacokinetic studies; tabular listing of all clinical studies; information on unblinding, randomization and datasets for the pharmacodynamic study) August 11, 2016 (Response to ECD/Bioequivalence) [@] September 22, 2016 (Response to ECD/Bioequivalence) September 28, 2016 (Response to ECD/Bioequivalence) [@] January 12, 2017 (Response to ECD/Bioequivalence)			
Submission Date(s) of Amendment(s) Under Review	April 3, 2017 (Meeting/Meeting Request) May 19, 2017 (Meeting/Other, Amendment Correspondence/Amendment Verification Statement)			
Primary Reviewer	Tian Ma, Ph.D.			
Secondary Reviewer	Vipra Kundoor, Ph.D.			
Tertiary Reviewer	Bing V. Li, Ph.D.			
Study Number (s)	MGR001-1006	MGR001-1007	MGR001-1005	MGR001-1014
Study Type (s)	Fasting	Fasting	Fasting (failed, but was used in pooled analysis by the firm with MGR001-1014)	Fasting(failed, but was used in pooled analysis by the firm with MGR001-1005)
Strength (s)	100/50 mcg ¹	500/50 mcg	250/50 mcg	250/50 mcg
Clinical Site	Worldwide Clinical Trials Early Phase Services, LLC			

¹ From now on in this review, product strength of “x/y mcg” will be used to indicate the strength of fluticasone propionate and salmeterol xinafoate (EQ y mcg base) per inhalation, respectively.

Clinical Site Address	2455 NE Loop 410, Suite 150 San Antonio, Texas 78217		
Analytical Site	Mylan Pharmaceuticals Inc.		
Analytical Site Address	Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505		
Study Number (s)	057755-02-04	MGF-PRO-2015-080	057755-02-07
Study Type (s)	In Vitro BE [single actuation content (SAC) and aerodynamic particle size distribution (APSD)]	In Vitro BE (SAC and APSD)	In Vitro BE (SAC and APSD)
Strength (s)	100/50 mcg	250/50 mcg	500/50 mcg
Analytical Site	(b) (4)	Mylan Global Respiratory Group	(b) (4)
Analytical Site Address	(b) (4)	IPC008, Discovery Park House, Floor 3 Sandwich, Kent. CT13 9ND. UK	(b) (4)
Study Number (s)	MGR-REP-2015-092	MGR-PRO-REP-2015-103	MGR-REP-2015-093
Study Type (s)	Pressure Differential (4 kPa) (SAC and APSD)	Pressure Differential (4 kPa) (SAC and APSD)	Pressure Differential (4 kPa) (SAC and APSD)
Strength (s)	100/50 mcg	250/50 mcg	500/50 mcg
Analytical Site	(b) (4)	Mylan Global Respiratory Group	(b) (4)
Analytical Site Address	(b) (4)	IPC008, Discovery Park House, Floor 3 Sandwich, Kent. CT13 9ND. UK	(b) (4)
Study Number (s)	MGR001-3001		
Study Type (s)	Clinical Endpoint		
Strength (s)	100/50 mcg		
Clinical Site	Site Number	Principal Investigator and Location	Address
	3001001	Idalia A. Acosta, Miami, FL 33015	5941 NW 173 Dr, Ste 1 Miami, FL 33015
	3001002	Niran J. Amar, Waco, TX 76712	333 Londonderry Dr, Ste 110 Waco, TX 76712
	3001003	James W. Baker, Portland, OR 97223	9495 SW Locust St Portland, OR 97223
	3001004	G Daniel Brooks, Bellevue, NE 68123-4303	3503 Samson Way, Ste 108 Bellevue, NE 68123-4303
	3001006	Warner W. Carr, Mission Viejo, CA 92691	27800 Medical Center Rd, #240/#244 Mission Viejo, CA 92691

3001007	Jonathan Corren, Los Angeles, CA 90025	10780 Santa Monica Blvd Ste 280 Los Angeles, CA 90025
3001008	David Cypcar, Asheville, NC 28801	14 McDowell St Asheville, NC 28801
3001009	Joseph D. Diaz, San Antonio, TX 78229	2414 Babcock Rd, Ste 108- 109 San Antonio, TX 78229
3001010	Manuel A. Franco, Miami, FL 33133	2720 SW 37 Ave Miami, FL 33133
3001011	Sherwin A. Gillman, Orange, CA 92868	725 West La Veta Ave, Ste 100 Orange, CA 92868
3001012	John T. Given, Canton, OH 44718	Allergy, Respiratory & Sleep Center 4048 Dressier Rd NW, Ste 100 Canton, OH 44718
3001013	Stanley Goldstein, Rockville Centre, NY 11570	242 Merrick Rd, Ste 401 Rockville Centre, NY 11570
3001014	Richard G. Gower, Spokane, WA 99202	324 S Sherman St Spokane, WA 99202
3001015	Leon S. Greos, Centennial, CO 80112	14000 E. Arapahoe Rd, Ste 260 Centennial, CO 80112
3001016	Amina Z. Haggag, Anaheim, CA 92801	Anaheim Clinical Trials, LLC 1085 N. Harbor Blvd Anaheim, CA 92801
3001017	Frank C. Hampel Jr., New Braunfels, TX 78130	705-A Landa St New Braunfels, TX 78130
3001018	Edward Francis Kent Jr., South Burlington, VT 05403	Timber Lane Allergy & Asthma Research, LLC 54 Timber Lane South Burlington, VT 05403
3001019	Phillip E. Korenblat, St. Louis, MO 63141	1040 N Mason Rd, Ste 112 St. Louis, MO 63141
3001020	Craig Fred LaForce, Raleigh, NC 27607	North Carolina Clinical Research 2615 Lake Dr, Ste 301 Raleigh, NC 27607
3001022	Edward E. Lisberg, River Forest, IL 60305	7420 Central Ave, Ste 2020 River Forest, IL 60305
3001023	Stephen Maddock, Lenexa, KS 66219	Analab Clinical Research Inc 15335 W 95th St Lenexa, KS 66219
3001024	Lyndon E. Mansfield, El Paso, TX 79903	2121 Wyoming Ave El Paso, TX 79903
3001025	Jonathan Matz, Baltimore, MD 21236	Chesapeake Clinical Research, Inc 7939 Honeygo Blvd, Ste 219 Baltimore, MD 21236

3001026	Curtis J. Mello, North Dartmouth, MA 02747	370 Faunce Corner Rd 2nd Fl North Dartmouth, MA 02747
3001027	S. David Miller, North Dartmouth, MA 02747	Northeast Medical Research Associates, Inc. 49 State Rd Watuppa Bldg, Ste 202 North Dartmouth, MA 02747
3001028	Anthony Montanaro, Portland, OR 97202	6327 SE Milwaukie Ave, 2nd Floor Portland, OR 97202
3001029	Nancy K. Ostrom, San Diego, CA 92123	5776 Ruffin Rd San Diego, CA 92123
3001031	Amit I. Patel, Riverside, CA 92506	Integrated Research Group, Inc. 4646 Brockton Ave, Ste 202-3 Riverside, CA 92506
3001032	David S. Pearlman, Denver, CO 80230	125 Rampart Way, Ste 150 Denver, CO 80230
3001033	Andrew J. Pedinoff, Skillman, NJ 08558	Montgomery Professional Center 24 Vreeland Dr Skillman, NJ 08558
3001034	Warren William Pleskow, Encinitas, CA 92024	317 N El Camino Real, Ste 506 Encinitas, CA 92024
3001035	Larry S. Posner, Napa, CA 94558	1100 Pear Tree Lane Napa, CA 94558
3001036	Gordon D. Raphael, Bethesda, MD 20814	4915 Auburn Ave, Ste 202 Bethesda, MD 20814
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3001038	Syed M. Rehman, Toledo, OH 43617	7247 W. Central Ave, Ste A Toledo, OH 43617
3001039	Michael E. Ruff, Dallas, TX 75231	5499 Glen Lakes Dr, Ste 200 Dallas, TX 75231
3001040	Russell A. Settipane, East Providence, RI 02914	450 Veterans Memorial Pkwy #15 East Providence, RI 02914
3001041	Ellen R. Sher, Ocean, NJ 07712	802 West Park Ave, Ste 213 Ocean, NJ 07712
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3001045	Stephen A. Tilles, Seattle, WA 98115	9725 Third Ave NE, Ste 500 Seattle, WA 98115
3001046	Mark L. Vandewalker, Columbia, MO 65203	601 W Nifong Bldg 2-A Columbia, MO 65203

3001047	David P. Chen, Bozeman, MT 59718	950 Stoneridge Dr, Ste 1 Bozeman, MT 59718
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3001049	John A. Winder, Sylvania, OH 43560	5800 Monroe St, Ste A-9 Sylvania, OH 43560
3001050	James D. Wolfe, San Jose, CA 95117	4050 Moorpark Ave, Ste 6 San Jose, CA 95117
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3001053	Thomas R. Murphy, N. Charleston, SC 29420	7555 Northside Dr N. Charleston, SC 29420
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3001055	Charles M. Fogarty, Spartanburg, SC 29303	485 Simuel Rd Spartanburg, SC 29303
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3001057	Sanchayita "Ita" Tripathy, Rolla, MO 65401	509 East 10th St Rolla, MO 65401
3001058	John F. Zwetchkenbaum, Warwick, RI 02886	470 Toll Gate Rd, Ste 203 Warwick, RI 02886
3001059	Dario D. Altamirano, Hialeah, FL 33012	900 W 49th St, Ste 430 Hialeah, FL 33012
3001060	Philip A. Emrie, Wheat Ridge, CO 80033	8550 W 38th Ave, Ste 202 Wheat Ridge, CO 80033
3001061	Timothy Harrison Elder, Gainesville, FL 32607	4343 W Newberry Rd, Ste 17 Gainesville, FL 32607
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3001063	Jason H. Friesen, Eugene, OR 97401	Allergy and Asthma Research Group 1488 Oak St Eugene, OR 97401
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3001069	Edward M. Kerwin, Medford, OR 97504	Clinical Research Institute of Southern Oregon, PC 3860 Crater Lake Ave, Ste B Medford, OR 97504
3001071	Daniel F. Soteres, Colorado Springs, CO 80907	2709 North Tejon St Colorado Springs, CO 80907
3001074	William R. Lumry, Dallas, TX 75231	10100 N Central Expressway, Ste 125 Dallas, TX 75231
3001075	Mikhail Palatnik, Gold River, CA 95670	2485 Sunrise Blvd Gold River, CA 95670
3001076	Paul Y. Qaqundah, Huntington Beach, CA 92647	17822 Beach Blvd, Ste 278 Huntington Beach, CA 92647
3001077	Weily Soong, Birmingham, AL 35209	504 Brookwood Blvd, Ste 250 Birmingham, AL 35209
3001078	Selwyn Spangenthal, Charlotte, NC 28207	1918 Randolph Rd, Ste 440 Charlotte, NC 28207
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3001080	Martha V. White, Wheaton, MD 20902	11002 Veirs Mill Rd, Ste 414 Wheaton, MD 20902
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3001082	Vosudesh K. Pai, Lawrenceville, GA 30046	555 Old Norcross Rd, Ste 250 Lawrenceville, GA 30046
3001083	Paul A. Shapero, Bangor, ME 04401	700 Mt. Hope Ave, Ste 430 Bangor, ME 04401
3001084	Daniel Sousa, Fall River, MA 02720	373 New Boston Rd Fall River, MA 02720
3001085	Sheldon Spector, Los Angeles, CA 90025	11645 Wilshire Blvd, Ste 1155 Los Angeles, CA 90025
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3001087	Manuel A. Fernandez- Gonzalez, Miami, FL 33135	590 SW 27th Ave Miami, FL 33135
3001088	Agustin J. Latorre, Miami, FL 33155	6850 Coral Way, Ste 409 Miami, FL 33155
3001089	Robert S. Call, Henrico, VA 23233	9920 Independence Park Dr, Ste 101 Henrico, VA 23233
3001090	Marcy Jo Gousse, Smithfield, PA 15478	100 Ridge View Dr, Ste 3 Smithfield, PA 15478
3001091	Anoshie Ratnayake, Costa Mesa, CA 92626	3545 Howard Way Costa Mesa, CA 92626
3001092	Marvin Kalafer, Jenkintown, PA 19046	815 Greenwood Ave, Ste 12 Jenkintown, PA 19046

	3001093	Santiago Reyes, Oklahoma City, OK 73112	3366 NW Expressway, Bldg D, Ste 330 Oklahoma City, OK 73112
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	3001096	Stephen G. Basheda, Pittsburgh, PA 15243	1050 Bower Hill Rd, Ste 307 Pittsburgh, PA 15243
	3001097	Iftikhar Hussain, Tulsa, OK 74136	7307 S. Yale Ave, Ste 200 Tulsa, OK 74136
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	3001115	Susan L. Andrew, Dickinson, TX 77539	914 FM 517 Road West Dickinson, TX 77539
	*3001116	William L. Ebbeling, Fresno, CA 93720	1646 E. Herndon Ave, Ste 106 Fresno, CA 93720
	3001119	Bruce A. DeCotiis, Brick, NJ 08724	1673 Hwy 88 West Brick, NJ 08724
	3001120	Ernesto Diaz, Coral Gables, FL 33134	5200 SW 8th St, Ste 119-120 Coral Gables, FL 33134
	3001122	Lawrence P. Landwehr, Warrensburg, MO 64093	407A East Russell Ave, Ste 3 Warrensburg, MO 64093
Clinical Site Address	Please see table above		
Study Number (s)	MGR000-1003		
Study Type (s)	Flow Profiling		

Strength (s)	N/A (empty inhaler which did not contain drug or placebo)		
Clinical Site	Site	Principal Investigator	Address
	1	Dominik Kappeler	Inamed Clinical Unit, 82131 Gauting, Germany
	2	Isabelle Schenkenberger	Clinical Research Berlin GbR; 10787 Berlin, Germany
	3	Prof. Dr. med. Walter Dorsch	Practice for Child and Adolescent Medicine, Allergy, Pediatric Pulmonology, Naturopathic, 81379 Munich, Germany
	4	Dr. med. Manfred Praun	Practice for Child and Adolescent Medicine Dr. Praun & Dr. Stiebing, 82205 Gilching, Germany
	5 (not activated)	Prof. Dr. med. Stefan Zielen	University Hospital Johann Wolfgang Goethe-Universität Frankfurt/Main, Centre for children and adolescents, Departement of paediatric pneumology, allergology and cystic fibrosis, 60590 Frankfurt/Main, Germany
Clinical Site Address	Please see table above		
Study Number (s)	MGR000-1004		
Study Type (s)	Device Orientation		
Strength (s)	N/A (empty inhaler which did not contain drug or placebo)		
Market Research Facilities^s	(b) (4)		
Market Research Facilities^s Address	Please see table above		
OSI Status	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete	<u>Post October 1, 2014 ANDAs</u> ☐ To Be Determined by OSIS ☐ Pending	

	☐ N/A (Waiver) ²	☒ Complete	
Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☐ Not granted ☒ N/A		
QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ N/A		
Formulation	☒ Adequate ☐ Inadequate		
Will Response to CR Result in a Reformulation?	☐ Possibly ☒ No ☐ N/A		
BE Guidance Version Used for Evaluation of Current ANDA	Draft Guidance on Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder (Recommended Sep 2013)		
Deficiency Classification	☒ Major (Deficiencies to be communicated by CR) ☐ Minor ☐ N/A (Review is Adequate)		
Overall Review Result	☐ Adequate ☒ Inadequate		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1,2,10,14	Fasting	100/50 mcg	INCOMPLETE
1,2,10,14	Fasting	500/50 mcg	INCOMPLETE
1,2,10,14	Fasting (Failed, but was used in pooled analysis by the firm with MGR001-1014)	250/50 mcg	UNACCEPTABLE
1,2,10,14	Fasting (Failed, but was used in pooled analysis by the firm with MGR001-1005)	250/50 mcg	UNACCEPTABLE
1,10,14	In Vitro BE (SAC and APSD)	100/50 mcg	INCOMPLETE
1,10,14	In Vitro BE (SAC and APSD)	250/50 mcg	INCOMPLETE
1,10,14	In Vitro BE (SAC and APSD)	500/50 mcg	INCOMPLETE
1,10,14	Pressure Differential (4 kPa) (SAC and APSD)	100/50 mcg	UNACCEPTABLE
1,10,14	Pressure Differential (4 kPa) (SAC and APSD)	250/50 mcg	UNACCEPTABLE
1,10,14	Pressure Differential (4 kPa) (SAC and APSD)	500/50 mcg	UNACCEPTABLE
1,2	Clinical Endpoint	100/50 mcg	INCOMPLETE
1,2,10	Flow Profiling	N/A (empty inhaler which did	UNACCEPTABLE

² Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

		not contain drug or placebo)	
1,8@,11@,14	Device Orientation	N/A (empty inhaler which did not contain drug or placebo)	UNACCEPTABLE

@ Submission in response to Office of Surveillance and Epidemiology (OSE)/ Division of Medication Error Prevention and Analysis (DMEPA)'s ECD [issued through Division of Bioequivalence I (DBI)], which is reviewed by DMEPA for their response to DBI's consult request for evaluation of the firm's device orientation study.

* The firm stated that these sites screened subjects but did not enroll any subjects.

§ The firm stated that these sites provided the facility in which user handling sessions were conducted; these facilities provided no other function or resource in the user handling assessment

1 EXECUTIVE SUMMARY

This is a review of a meeting request.

On 3/28/2017, the Agency issued a Complete Response (CR) letter to the firm³. On 4/3/2017, the firm submitted a meeting request for a face-to-face meeting to discuss with the Agency.

In the original submission dated 12/29/2015, the firm Mylan Pharmaceuticals Inc. submitted the current application for Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder, 0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ 0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation. The test product, also refers to as MGR001 by the firm, contains fluticasone propionate (FP) and salmeterol xinafoate (SX) inhalation powder in CRC749 inhaler device. The reference-listed drug (RLD) is Advair Diskus® 100/50 (fluticasone propionate and salmeterol xinafoate), 0.1 mg/EQ 0.05 mg base per inhalation; Advair Diskus® 250/50 (fluticasone propionate and salmeterol xinafoate), 0.25 mg/EQ 0.05 mg base per inhalation; and Advair Diskus® 500/50 (fluticasone propionate and salmeterol xinafoate), 0.5 mg/EQ 0.05 mg base per inhalation manufactured by GLAXO GRP LTD (approved on August 24, 2000 under NDA 021077). The firm submitted the following studies:

- Four fasting pharmacokinetic (PK) BE studies (#MGR001-1006 for the 100/50 mcg strength, #s MGR001-1005 and MGR001-1014 for the 250/50 mcg strength, and #MGR001-1007 for the 500/50 mcg strength)
- One clinical endpoint study (#MGR001-3001 at the 100/50 mcg strength)
- Two types [single actuation content (SAC) and aerodynamic particle size distribution (APSD)] of in vitro BE studies for each of the three strengths of the drug product (#057755-02-04 for the 100/50 mcg strength, #MGR-PRO-2015-080 for the 250/50 mcg strength, and #057755-02-07 for the 500/50 mcg strength)
- Two types (SAC and APSD) of in vitro studies at 4 kPa fixed pressure drop for each of the three strengths of the drug product (#MGR-REP-2015-092 for the 100/50 mcg strength, # MGR-PRO-REP-2015-103 for the 250/50 mcg strength, and #057755-02-08 for the 500/50 mcg strength) comparing the test and RLD products
- One flow profiling study (#MGR000-1003) comparing the empty test and RLD devices

³ GDRP: ANDA-208891-ORIG-1, Upload Final Decision, A208891N000CR, 3/28/2017.

- One device orientation study (#MGR000-1004) using empty test device

None of the aforementioned studies were acceptable due to deficiencies. A CR letter was sent to the firm on 3/28/2017³.

In the current meeting request dated 4/3/2017, the firm is requesting a face-to-face meeting to discuss and seek agreement with the Agency about 10 questions that are related to pharmaceutical quality, bioequivalence (BE) or labeling. Among these questions, 5 questions were related to BE deficiencies (BE deficiency #s 1, 31, 37, and 40, and 47) Division of Bioequivalence I (DBI)'s preliminary response that are intended to facilitate discussion during the meeting regarding the 5 BE-related questions is given in the attached letter.

NOTE TO REGULATORY PROJECT MANAGER (RPM): Only the letter at the end of the current document should be incorporated into the written communication to the firm. The remainder of the current document should not be communicated to the firm.

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3 BACKGROUND

On 3/28/2017, the Agency issued a CR letter to the firm.

On 4/3/2017, the firm sent a meeting request to the Agency. The meeting request contains 10 questions, 5 for pharmaceutical quality, and 5 for bioequivalence. For 1 of the bioequivalence questions, there is also a sub-question for labeling.

On 5/1/2017, DBI met with multiple divisions/offices to discuss the firm's meeting request. Multiple divisions/offices included the Office of Surveillance and Epidemiology (OSE)/ Division of Medication Error Prevention and Analysis (DMEPA), Office of Generic Drugs Policy (OGDP), Office of Pharmaceutical Quality (OPQ), Office of Research and Standards (ORS), Office of Translational Science (OTS)/ Office of Biostatistics (OB)/ Division of Biostatistics VIII (DBVIII), Division of Labeling Review (DLR), Division of Clinical Review (DCR) and Office of Study Integrity and Surveillance (OSIS). Based on discussion with DMEPA, ORS and DBVIII at the meeting, it was decided to ask the firm to provide additional information regarding device orientation and PK studies in order to address the firm's related questions.

On 5/10/2017, following concurrence of language by multiple divisions/offices (language for device orientation was concurred by DMEPA, OGDP and DBI; and language for PK studies was concurred by ORS, DBVIII and DBI), the firm was asked to provide additional information regarding device orientation and PK studies. The firm's response was received on 5/19/2017.

On 5/23/2017, DBI sent consult request to DMEPA for evaluation of the firm's device orientation question.⁴ On 7/3/2017, OGDP provided their proposed pre-meeting written response to DBI.⁵ According to this proposed pre-meeting written response, the Agency will be prepared to discuss the device orientation of the firm's product at the 7/13/2017 meeting. The Agency intends to provide a written response to the firm's question regarding device orientation after that meeting.

On 5/25/2017, DBI met with ORS and DBVIII to discuss about the firm's question about the PK studies at the 250/50 mcg strength.

On 5/31/2017, DBI sent consult request to DBVIII for the evaluation of the firm's PK-related questions.⁶ On 6/23/2017, DBVIII provided their consult response to DBI.⁷

⁴ GDRP: ANDA-208891-GI-1-MEETING-17, Send Consult Request, A208891 Scientific Meeting Request_Conult to DMEPA.doc, 5/23/2017.

⁵ V:\DIVISION\BIO\BIO1\Email Reference\208891 Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder\RE pre-meeting written response to Mylan about their device orientation question A208891.msg

⁶ GDRP: ANDA-208891-GI-1-MEETING-17, Send Consult Request, A208891 Scientific Meeting Request_Conult to DBVIII.doc, 5/31/2017.

⁷ GDRP: ANDA-208891-GI-1-MEETING-17, Respond to Consult Request, 208891_stat_postCR consult, 6/23/2017.

On 6/1/2017, DBI sent consult request to ORS for the evaluation of the firm's PK-related questions.⁸ On 6/15/2017, ORS provided their consult response to DBI and DBVIII.⁹

⁸ GDRP: ANDA-208891-GI-1-MEETING-17, Send Consult Request, A208891 Scientific Meeting Request_Conult to ORS.doc, 6/1/2017.

⁹ GDRP: ANDA-208891-GI-1-MEETING-17, Respond to Consult Request, Review, 6/15/2017.

4 SUBMISSION SUMMARY

Below is the review of the firm's 5 BE-related questions. For each of the firm's question, the following are listed:

- The BE-related deficiency in the CR letter that the firm raised questions about in their meeting request submitted on 4/3/2017
- The firm's discussion about these deficiencies *in italic* and their questions *in bold italic*.
- The Agency's request for additional information from the firm (if applicable), and the firm's responses (if applicable).
- DBI's preliminary response intended to facilitate discussion during the face-to-face meeting on 7/13/2017.
- Reviewer's comments/justifications are included in the box at the end of each response, intended for "Internal Use Only".

DEVICE ORIENTATION STUDY

Deficiency Related to the Device Orientation Study (MGR000-1004)

4.1 Deficiency Comment # 47

Your proposed Wixela Inhub device has a different device orientation when compared to the reference listed drug (RLD), Advair Diskus. Specifically, your Wixela Inhub device is intended to be held vertically during administration, while the Advair Diskus device is intended to be held horizontally during administration. The Agency has reviewed the Device Orientation Study submitted to your application. The study you submitted does not provide FDA with sufficient information to conclude that proposed product can be substituted with the full expectation that it will produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling, including whether the proposed product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use.

In addressing this deficiency, we refer you to the general principles in FDA's draft guidance entitled Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA (January 2017) (available at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm536959.pdf>). Although this is draft guidance, it sets forth FDA's current thinking regarding important principles for evaluating proposed generic combination products submitted in ANDAs. As reflected in that draft guidance, FDA recommends that applicants seek to minimize differences in the user interface of a proposed generic combination product and the RLD. You may consider modifying the design of the user interface for the Wixela Inhub device to minimize differences from the RLD product, specifically with regard to the orientation of your proposed product. To the extent that differences remain between the user interface of the proposed generic combination product and the user interface of the RLD, the guidance provides recommendations on the identification and assessment of differences in the design of the user interface for a proposed generic combination product when compared to its RLD, including a discussion of when data from a comparative use human factors study may be

warranted to address certain identified differences. It would be useful to provide the Agency with the results of the three threshold analyses (e.g., comparative labeling analysis, comparative task analyses, comparison in the design of the delivery device constituent) described in this draft guidance, as well as your overall assessment of the identified differences for your proposed product when compared to the RLD. Please note that the Agency may view the design differences for your proposed presentation as not being minor if these analyses suggest that differences in the user interface of your product as compared to that of the RLD may impact the clinical effect or safety profile of your proposed product as compared to the RLD when the proposed product is substituted for the RLD. In such cases, additional information and/or data, such as data from comparative human factors studies, may be warranted.

The Agency will consider these analyses and any comparative use human factors data or information submitted to evaluate the acceptability of the differences in device and labeling resulting from these differences in user interface, and to evaluate whether your proposed product can be substituted for the RLD with the full expectation that your proposed product will produce the same clinical effect and safety under the conditions specified in labeling when the proposed product is substituted for the RLD. Should you have an alternative approach to addressing this deficiency that you believe would be acceptable, please contact the regulatory project manager (RPM).

4.1.1 Firm's Discussion on Deficiency Comment #47

(b) (4)

Given the publication of the DRAFT ‘Comparative Analyses and Related Comparative Use Human Factor Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry’ of January 2017, Mylan understands that the Agency has evolved their thinking in this area and has opened the first draft of such guidance for public comment and feedback. Mylan understands that there is significant discussion to be had between the Agency and Industry on the concepts within this Draft guidance, including a major concern around the use of comparative error rates in the determination of safe and effective use of a substitutable product. Mylan believes that, for public health needs, any new inhaler to be approved must be safe and effective for the intended user population and be demonstrated to be capable of delivering a therapeutically appropriate dose – regardless of whether the RLD would have been subject to the same Human Factors approach at time of its approval. It is also noteworthy that Mylan had proposed to include an RLD comparator arm, but OGD advised that they would focus their review on the Inhub device. Although the comparative Human Factors approach agreed with OGD prior to study conduct has been provided in the ANDA (3.2.P.7.2), Mylan commits to providing additional retrospective information to support the threshold analysis described in the DRAFT guidance to underwrite substitutability. A labelling comparison has previously been provided; a comparative task analysis and physical comparison of the delivery device constituent parts vs the RLD will be developed and provided. Given the design difference between the RLD and Mylan’s CRC749 inhaler has previously been agreed with the Agency to be the orientation of use at inhalation, Mylan strongly considers that the pre-agreed comparative Human Factors study conducted and presented in the ANDA provides the data required to demonstrate that the difference in design has no impact on safe and effective use of the device to deliver a therapeutic dose, demonstrating a low-likelihood of orientation-related use errors and demonstrating that the inhaler can be successfully substituted without the need for training or HCP intervention.

In summary, the device development programme for MGR001 has been discussed and agreed with the Agency in five pre-submission scientific interactions spanning a 7 year period. The Agency have provided clear direction regarding the Human Factors programme of work required to provide evidence that the orientation of the device enables both naïve and current RLD users to achieve a therapeutically effective dose, in a safe and effective manner, when substituted for the RLD without training or the intervention of the health care provider. The culmination of the effort was study MGR000-1004, the design of which was agreed in a Controlled Correspondence (Protocol Assessment Request) with the Agency. The results of this study demonstrate that use of Mylan’s CRC749 inhaler in the horizontal orientation does not introduce a risk that impacts the clinical effect or safety profile of MGR001 when a patient is switched from the RLD without the intervention of a health care provider and/or without additional training prior to use.

Firm’s Question:

Does the Agency agree that the Human Factor Orientation Study (MGR000-1004), designed in collaboration with OGD demonstrates that the horizontal orientation does not introduce a risk that impact the safe and effective use of MGR001 when a patient is switched from the RLD without training or instruction from the healthcare provider.

Reviewer's Notes: Following the firm's meeting request, on 5/10/2017, the Agency requested the following information from the firm in order to address the firm's question. Please note that the following request was concurred by DMEPA and OGD and DBI. On 5/19/2017, the firm responded to the Agency's follow-up question. Please see the Agency's follow up question and the firm's response below.

4.1.2 Agency's Follow-Up Question to the Firm's Question

In order for the Agency to address your question in Section 10.1 ("Device Orientation") of your request for a post complete response scientific meeting (4/3/2017 submission, Module 1.2\Cover Letter -0016 – Meeting Request - 20170403), please provide the following information:

- a. The cover letter to your meeting request notes that you plan to provide additional information related to the threshold analyses described in FDA's draft guidance entitled Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA (January 2017) (available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf>). To assist us in evaluating your question in Section 10.1, please submit this information (e.g., comparative labeling analysis, comparative task analyses, comparison in the design of the delivery device constituent).
- b. Please provide your overall assessment of the identified differences for your proposed product when compared to the reference listed product (RLD), including your assessment as to whether any differences in the user interface of your product as compared to that of the RLD may impact the clinical effect or safety profile of your product as compared to the RLD when your product is substituted for the RLD.
- c. If your assessment identifies design differences as not being minor, please provide your proposal to evaluate the acceptability of the differences in device and labeling resulting from these differences in user interface.

4.1.3 Firm's Response to Agency's Follow-Up Question (Background)

Mylan's goal remains to work with the Agency to provide a more affordable, therapeutically equivalent version of the RLD to patients. Consistent with this goal and Mylan's continued commitment to meaningfully engage the agency in scientific discussion regarding our proposed products, Mylan has undertaken a thorough comparative analyses assessment of the RLD and Wixela Inhub in line with this new draft guidance. The results of our assessment are described in more detail below in our responses to FDA Comments 1A – 1C.

With regard to our Wixela Inhub device, our many discussions with the Agency and the resulting development plan relied on sound and current Human Factor engineering principles to show that users of the RLD could also use Wixela Inhub without the need for retraining or other intervention from a health care professional. The scientific and statutory standards governing our discussions with the Agency over the years have not changed since we began discussing the data needed to satisfy the "sameness" standard applicable to ANDAs. The draft guidance does not (and could not) purport to change the statutory standard for approval. Thus, as expected, the evidence generated as part of our development program is fully consistent with both the statute

and the draft guidance and supports the conclusion that our Wixela Inhub is substitutable for the RLD.

At a high level, the results from performing the threshold analyses (labeling comparison, comparative task analysis, and physical comparison of the delivery device constituent part) outlined in the draft guidance, show that:

- All differences identified in the user-interface of Wixela Inhub when compared to the RLD were assessed as minor.*
- None of the design differences identified impact the clinical effect or safety profile of Wixela Inhub as compared to the RLD;*
- Based on all identified differences being categorised as minor, no additional comparative use Human Factors studies are required.*
- Orientation of use was assessed as a minor difference in the Threshold Analyses as use of the Inhub inhaler in the vertical orientation is not identified as a critical task in order to achieve a successful dose. In addition, the in-vitro orientation study confirms that there is no risk associated with the use of the device in the horizontal orientation. Prior to the issue of the draft 2017 guidance OGD identified the orientation of use as a difference from the RLD and directed Mylan to conduct the Human Factors Device Orientation Study. Mylan complied precisely with this request. This was one component of the comprehensive Device Development Program agreed during the course of many discussions with the Agency.*
- In conclusion, and as expected, the evidence generated as part of our development program is fully consistent with both the previous guidance provided by the agency and the draft guidance and supports the conclusion that Wixela Inhub is substitutable for the RLD.*

Notwithstanding these results, and consistent with all discussions with the Agency during the development program, Mylan still believes that, regardless of any design difference, a comprehensive Human Factors program assessing the ability of intended users, inclusive of both RLD and naïve users, to safely and effectively use the Inhub inhaler to deliver the intended dose without any training or intervention, is the most appropriate way to ensure acceptable use. These considerations led to our comprehensive Human Factors device orientation study to explore whether the difference in orientation made a difference to users and to otherwise support our product as an ANDA.

The protocol for our study is consistent with current Human Factor engineering principles, FDA guidances related to Human Factors, generally, and this product, specifically, and detailed OGD feedback. In particular, and in accordance with FDA's advice (Scientific Advice Meeting December 3rd 2009 and Scientific Advice Meeting December 12th 2012), Wixela Inhub is intended to be substitutable for Advair Diskus and additionally be available for use for newly diagnosed patients. Development of the Inhub inhaler therefore considered the RLD inhaler, and

assessed any potential opportunities for incorporation of design features that would add capability for safe and effective use by intended users whilst still maintaining substitutability. A risk-based approach to the device development program was undertaken, underpinned by a risk management plan consistent with EN ISO 14971:2012 Medical Devices - Application of Risk Management to Medical Devices, to ensure all aspects of potential risk were considered with the aim of ensuring successful delivery of the intended therapeutic dose and elimination or reduction of potential harm that has the potential to compromise medical care.

Inherent in the device development program was the aim to eliminate or minimise any potential hazards, and ensure that end users could perform critical tasks using the product-user interface without making unintentional medication errors and without being exposed to unnecessary safety hazards. The characteristics of users that could affect their ability to use the product correctly were considered and fed into the design proactively. Examples of this include consideration of differentiating colour of the actuation lever and a thumb grip feature to the mouthpiece cover to provide visual cues to the users. Safety was proactively considered in the design of the inhaler, with regard to improving detectability or readability of controls, labels and displays (e.g. incorporation of a larger dose counter to that of the RLD, for improved user awareness of doses remaining within the inhaler), and incorporating safety mechanisms in the device itself (e.g. introducing a lock-out feature to ensure that users were aware that there are no remaining doses at the end of inhaler life). This approach is entirely consistent with two of the Agency's recent final guidances, Applying Human Factors and Usability Engineering to Medical Devices (Final, February 2016) and Safety Considerations for Product Design to Minimise Medication Errors (Final, April 2016).

Further, the Inhub inhaler meets the requirements set out in the FDA Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate (Sep, 2013) inclusive of the requirement that the inhaler-interface consists of four (4) external operating procedures ((1) Open, (2) Click, (3) Inhale, and (4) Close). A comparison of these 4 steps for the Diskus and Inhub inhalers was provided in the ANDA Module 1, 1.14 Labelling. Consistent with this draft guidance, the numerous discussions with FDA on the device development program during pre-submission, and existing standards and guidances (including Human Factors & Usability Engineering to Optimise Medical Device Design, (September 2011, draft), EN ISO 62366:2007 Application of Usability Engineering to Medical Devices, AAMI/ANSI HE-75:2009(R)2013 Human factors engineering – Design of medical devices) Mylan applied the very latest in thinking to the development and validation of the user interface. A 'task' was defined as an action or set of actions performed by a user to achieve the required goal and a 'critical task' defined as one which if performed incorrectly or not performed at all (e.g. push the lever to enable the dose to be made available to the airway path) could cause serious 'harm', to include compromised medical care. This assessment was undertaken regardless of any design differences between the RLD and Inhub to ensure that under all intended use scenarios, both for substitution and with consideration of the potential for newly diagnosed patients (or those transferring from a pMDI), all aspects of the user-interface that have the potential to impact safe and effective use were assessed. This is also consistent with another recent human factors draft guidance, Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development (Draft, February 2016).

These critical tasks informed the protocol for the definitive Human Factors Usability Study, (Device Orientation Study MGR000-1004), and the final protocol followed discussions with OGD on the study design to be sure that the horizontal orientation of Inhub does not introduce a risk that has the potential to impact safety and/or efficacy as compared to the RLD. (The protocol was developed and submitted to the Agency for review under Request for Special Protocol Assessment, IND: 118769 Sequence: 0009 and controlled correspondence dated February 9, 2015.) In accordance with OGD's direction, this study was also specifically designed to simulate actual use of the device at the point of substitution, i.e. with no provision of training and no HCP intervention.

Finally, OGD advised that the Agency's review and evaluation should be focused on data collected on the Inhub device (Mylan had originally proposed a comparative arm with the RLD, see Item 4, SPA Controlled correspondence February 9, 2014). Notably, in six scientific interactions with the Agency spanning a 7-year period, the threshold analyses approach discussed in FDA's draft guidance were not discussed or proposed, nor was such thinking the subject of presentation in the public domain. Given the difference in device design of the Inhub compared to the RLD, the agency provided clear direction regarding the Human Factors programme of work required to provide evidence that the orientation of the device enables both naïve and current RLD users to achieve a therapeutically effective dose in a safe and effective manner, when substituted for the RLD without training or intervention of a health care professional. Mylan accepted all feedback provided by the FDA on this study protocol was incorporated into the final study design, as outlined in 3.2.P.7.2.6.1.of the ANDA, prior to study execution.

As reflected in our ANDA, the results of this study demonstrated that use of the horizontal orientation for inhalation had no impact on safe and effective use of the device or on dose delivery, including when used by RLD users. This study confirmed that the design difference of orientation of inhalation does not introduce a risk that impacts the safe and effective use or therapeutic dose delivery of the Inhub inhaler when a patient is switched from the RLD without training, instruction or HCP intervention. Additionally, in the period since Mylan's ANDA submission and subsequent filing, Mylan have provided additional information in response to the Agency's Easily Correctable Bioequivalence Deficiency Correspondence (reference #10323634) relating to the outcome of this study to demonstrate that the orientation of the device does not impact the function and performance of the product.

4.1.3.1 Firm's Response to Agency's Follow-Up Question a

As requested, consistent with the draft guidance, please find attached the [threshold analyses report, Attachment 1-0018](#) comparing the user interface of the proposed generic combination product to that of the RLD.

4.1.3.2 Firm's Response to Agency's Follow-Up Question b

Mylan's overall assessment based on the Threshold Analyses, Human Factors Orientation study and the in vitro orientation study, is that there are no differences that affect substitutability with the RLD.

The outcome of the Threshold Analyses of the User Interface of the Inhub, inclusive of i) labelling comparison (to the RLD), ii) comparative task analysis and iii) physical comparison of the delivery device constituent part is provided. The labelling comparison provides a side-by-side, line-by-line comparison of the instructions for use (IFU) of Inhub and Advair Diskus, and provides an assessment of any differences. The comparative task analysis systematically dissects the use processes for Inhub and Diskus, and analyzes and compares the sequential and simultaneous manual and intellectual activities for end-users interacting with each inhaler. A Hierarchal Task Analysis (HTA) has been developed and assessed using the Perception, Cognition, Action (PCA) model to examine the external critical design attributes that directly affect how users perform a critical task necessary to administer a dose safely and effectively. The HTA lists the critical tasks that the user must perform in order to use the device per its intended use. The PCA model then assesses the level of human interaction with the user interface required to fulfil the tasks. The physical comparison provides an assessment of the physical features of the Inhub and the RLD, inclusive of visual and tactile data.

The Threshold Analysis assessment of where there are no design differences, minor design differences, or other design differences was conducted with consideration of overall risk profile of the product, consistent with the risk management program applied throughout the development of the Inhub inhaler described in Section 3.2.P.7.2.7 of the ANDA.

(b) (4)

Human Factors Device Orientation Study

The human factors device orientation study (see Section 3.2.P.7.2.6.1. of the ANDA) that incorporated OGD feedback, assessed all tasks required by the intended users to safely and effectively deliver a dose, including with a specific focus on orientation of use. In addition to the safe and effective use of the inhaler, the study protocol was designed to demonstrate that, regardless of orientation of the inhaler during inhalation (being that the design difference between the RLD and Inhub is identified and agreed as orientation of use), users would be able to inhale with a sufficient inhalation profile to receive the required dose. Peak Inhaled Flow Rate (PIFR) measurements were used to confirm that the orientation of the inhaler at inhalation would not impede the user's ability to receive a therapeutic dose. The study was conducted with 110 representative users - 55 RLD Advair® Diskus® patients and 55 DPI naïve patients. Ten participants (of the 110) inhaled in the horizontal position, with 9 of these 10 achieving a PIFR of >30 L/min and TIV of >1L, therefore confirming that they would have received a full dose. One of the 10 participants who inhaled in the horizontal position did not achieve a PIFR of >30 L/min and TIV of >1L and therefore there is a potential that this participant may not have received a full dose.

(b) (4)

The participant indicated that she had an issue with the 'lung function test' (at her physician's office, this was not part of study inclusion criteria); she achieved a low inhaled flow

rate and total inhaled volume in both orientations of inhalation, thereby demonstrating that this is not due to the orientation of use of the device.

In-vitro testing and orientation of use

(b) (4)

Data demonstrates that device functionality and Uniformity of Emitted Dose are maintained such that the target dose of both fluticasone propionate and salmeterol is delivered regardless of use of the device in vertical or horizontal orientations. In addition, the assessment of the impact of powder build up from doses that were intentionally not evacuated confirmed that device functionality was maintained through-life (i.e. across 60 doses). This data was provided to the Agency on September 28, 2016 in response to the Easily Correctable Bioequivalence Deficiency Correspondence (reference #10323634).

Outcome of Threshold Analyses

The outcome of the three types of Threshold Analyses is that any differences between the RLD and Inhub are considered minor, with consideration of the risk profile of the product, such that the defined design differences do not involve a critical design attribute that impact the substitution of the RLD with the Inhub inhaler where there is no additional training or healthcare intervention. In line with this new draft guidance, these Threshold Analyses therefore do not direct any additional comparative use human factors studies to be conducted.

This outcome is additionally underwritten through the comprehensive Human Factors device orientation study, which considered all critical tasks with a specific focus on orientation of use and the through-life testing of the Inhub inhaler demonstrating that device functionality and Uniformity of Emitted Dose are maintained regardless of orientation. Mylan asserts that the outcome of the device development program is such that the Inhub inhaler has been demonstrated to be substitutable for Advair Diskus.

4.1.3.3 Firm's Response to Agency's Follow-Up Question c

The comparative analyses assessment did not identify any design differences as being other than minor.

4.1.4 Agency's Response:

The Agency will be prepared to discuss the device orientation of the firm's product at the July 13, 2017 meeting. The Agency intends to provide a written response to the firm's question after that meeting.

DBI consulted DMEPA for the question above.⁴ Although DMEPA has not provided their consult response to DBI yet, during the review phases of the current meeting request, there were multiple meetings to discuss about the device orientation issue among multiple divisions/offices

such as OGDG, DBI, DCR, ORS, and/or DMEPA. The response above is provided by OGDG and is concurred by DBI, DMEPA and DCR.

GENERAL

General Deficiencies

4.2 Deficiency Comment #1

The following observations were noted in your 12/29/2015 submission:

- a) According to the certificates of analysis (COAs), the 3 exhibit batches for each of the 100/50 mcg and 500/50 mcg strengths had device configuration (clinical device: (b) (4) different from the proposed commercial device (b) (4). These exhibit batches were used in pharmacokinetic (PK) studies, in vitro studies for the 100/50 mcg and 500/50 mcg strengths, and the clinical endpoint study.
- b) In your batch formula document (12/29/2015 submission, Module 3.2.P.3.2\Batch Formula, p. 1 of 2), you stated that “[i]here are no difference between the batch formula of the registration and commercial batches (b) (4)”. (b) (4)
- c) In your pharmaceutical development report (12/29/2015 submission, Module 3.2.P.2\Pharmaceutical Development, p. 541, 544, 667 and 671 of 676), you stated that the exhibit batch (b) (4) would be provided (12/29/2015 submission, Module 3.2.P.2\Pharmaceutical Development, p. 430, 667, 671 and 675 of 676).
- d) In your 12/29/2016 submission, Module 2.3.P\Drug Product Part 1 – FPSX – Mylan Dublin, p. 97 of 107, you stated that exhibit batches were manufactured (b) (4). (b) (4)

Please provide (b) (4) as mentioned in c) above for each strength of the drug product.

In Controlled Correspondence 844398, based on your statement of (b) (4) difference between batches used in the pivotal clinical studies and commercial batches, the Agency recommended you to demonstrate in vitro bioequivalence (BE) according to the *Draft Guidance on Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder at 60 L/min.* (b) (4)

(b) (4)
, please conduct in vitro BE studies [single actuation content (SAC) and aerodynamic particle size distribution (APSD) studies] comparing reference listed drug (RLD) product and the test product with final commercial formulation (b) (4), device (b) (4), and manufacturing process (b) (4) and manufactured (b) (4) as bridging studies. These studies should be conducted for each strength of the product, and should be conducted according to *Draft Guidance on Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder* (recommended September 2013, will be referred to as product-specific guidance in the rest of this deficiency letter) at **30, 60, and 90 L/min**, and use at least 3 batches each of T and unexpired R products with no fewer than 10 units from each batch.

In the above APSD studies, please include a standard curve and quality control (QC) samples with three validated concentrations in the range of expected study concentrations with each analytical batch, as outlined in the *Guidance for Industry - Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal sprays for Local Actions* (posted April 2003).

4.2.1 Firm's Discussion with Respect to Conducting Studies at Additional Flow Rates

Mylan asserts that the changes cited in the CR letter Bioequivalence Question 1 between the commercial product and drug product used in pivotal clinical studies have no impact on drug product performance.

The three changes between the exhibit batches and the commercial batches cited in the FDAs CR letter question are discussed below. For the commercial demonstration batches manufactured and used to demonstrate IVBE with RLD, these 'changes', as discussed were either minor with no impact on the performance of the product, or as in the case of overages there was no change:

Change from clinical device configuration to commercial configuration.

The commercial device configuration (b) (4) was used in the manufacture of 250/50 exhibit batches (used in pivotal clinical and in vitro equivalence studies). Hence these are directly comparable to the batches manufactured (b) (4).

The clinical device configuration used in the manufacture of the 100/50 mcg and 500/50 mcg pivotal batches are also fully representative of batches manufactured using the commercial device configuration. (b) (4)

(b) (4) therefore the factors affecting pharmaceutical performance and user experience of inhalation remain constant between the two device configurations.

These changed¹⁰ are discussed in greater detail in 3.2.P.7.2.3.4.1 Description of the Design Change of ANDA 208891 Sequence 0000), submitted Dec 2015.

Potency adjustment

(b) (4)

In fact, there was negligible change in the dispensed quantities between the exhibit batches presented in the ANDA and the batches

(b) (4)

Mylan asserts that this small adjustment has no impact on the equivalence demonstrated between the MGR001 product and RLD at 60 L/min as agreed with FDA at the pre-ANDA meeting and no impact on bioequivalence at 30 and 90 L/min as requested in the CRL.

(b) (4)

(b) (4)

There is no change between the exhibit batches and commercial demonstration batches.

(b) (4)

There is no change between the exhibit batches and commercial demonstration batches. This information is provided in the amendment update; section 3.2.P.3.3 Manufacturing Process and Controls

In summary the changes between the exhibit batches and commercial demonstration batches cited in Bioequivalence Question 1 as giving rise to the request for additional IVBE studies have no impact on the performance of the product, hence Mylan asserts that the FDAs original request to demonstrate in vitro bioequivalence between batches manufactured (b) (4) and RLD at 60 L/min flow rate only remains valid. Mylan have provided these data in the amendment update, ANDA 208891 Sequence 0015, Section 3.2.P.3.3 Manufacturing Process and Controls, submitted Dec 2015).

¹⁰ The firm stated “changed” here, but the reviewer considers that they meant “changes”.

Firm's Question

Does the agency agree with Mylan's assertion that the changes in potency factor and device design have no impact on product performance hence the FDAs original request to demonstrate in vitro bioequivalence between batches manufactured using (b) (4) and RLD at 60 L/min flow rate only remains valid.

4.2.2 Agency's Response:

Based on the additional information provided by the firm as well as the Agency's additional evaluation, the Agency considers the firm's in vitro bridging studies at 60 L/min flow rate may suffice at this moment (please note that this bridging data has not yet been reviewed, so the acceptability of this data is to be determined), but the Agency reserves the right to ask for data at 30 L/min and 90 L/min flow rates if in the future it is determined that the device difference impacts product performance.

(b) (4)

.¹³ However, it is noted that for the PK studies, the 2 individual PK studies (MGR001-1005 and MGR001-1014 for the 250/50 mcg strength) that used commercial device did not meet BE criteria; whereas the 2 PK studies (MGR001-006 for the 100/50 mcg strength and MGR001-1007 for the 500/50 mcg strengths) that used clinical device met BE criteria. Therefore, in order to ensure that the device design difference would not impact the product performance at each of the 3 flow rates, the firm was asked to provide bridging studies at 3 flow rates (30, 60 and 90 L/min) in the CR letter.

According to the Office of Testing and Research (OTR)'s report¹⁴, (b) (4) devices are similar to each other. Therefore, it is possible that this device design change does not have significant impact on product performance.

(b) (4)

Based on this data, the reviewer considers that this difference in potency

¹¹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.7\Container Closure System, p. 66-67 of 229).

¹² GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 2.3.P\Drug Product Part 2 _ FPSX – Mylan Dublin, p. 58 of 103).

¹³ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 2.5\Clinical Review, p. 12 of 21).

¹⁴ GDRP: ANDA-208891-ORIG-1, OTR Report-Phase 2-17-037_Generic Advair.pdf, 2/1/2017.

adjustment between the exhibit and commercial demonstration batches does not have significant impact on product performance.

(b) (4)

Based on the above information, the firm will be informed that the in vitro bridging studies at 60 L/min flow rate may suffice at this moment (the firm will also be informed that this bridging data has not yet been reviewed, so the acceptability of this data is to be determined), but the Agency reserve the right to ask for data at 30 L/min and 90 L/min flow rates if in the future it was determined that the device difference impacts product performance.

4.2.3 Firm's Discussion with Respect to Including A Standard Curve and Quality Control of Samples at Three Validated Concentrations

Mylan has completed and submitted (sequence 0015, March 2017) the IVBE studies between batches manufactured (b) (4) and RLD at 60 L/min as originally requested in Controlled Correspondence 844398 (October 2015). Multipoint calibration was not used in these studies, nevertheless Mylan asserts that the approach adopted was adequate to provide accuracy based on linearity demonstrated during experimentation and confirmed by Validation.

Mylan notes the Agency request, in respect of future APSD equivalence studies, to include a standard curve and quality control (QC) samples with three validated concentrations in the range of expected study concentrations with each analytical batch, as outlined in the Guidance for Industry - Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal sprays for Local Actions (posted April 2003). Mylan was not previously aware of the applicability of this nasal product guidance to studies for this product, and will comply with this requirement for future studies, as requested.

However, in relation to the specific IVBE studies between batches manufactured (b) (4) (b) (4) and RLD referred to in the above Agency request, Mylan has recently completed and submitted these studies at 60L/min as originally requested. Mylan has carried out the same approach to calibration and quantification in these studies as in the studies using registration batches presented in the ANDA, i.e. single point calibration supported by linearity demonstrated during validation together with checks on consistency of UV response and LOQ during the study analytical runs. As expected for UV response, a very high degree of linearity was demonstrated during validation, with $r^2 \geq 0.99997$ and calibrators not deviating by more than 8 % from nominal concentration for both actives. Consistent linearity is also demonstrated by the responses obtained for the calibration and check solutions during each analytical run.

Firm's Question

On the basis of the above information does the Agency agree that the accuracy of the data generated during these studies is adequate?

4.2.4 Agency's Response:

The acceptability of data accuracy in the firm's in vitro BE studies between batches manufactured [REDACTED] ^{(b) (4)} and RLD at 60 L/min will be determined when the study data is reviewed.

The acceptability of this depends on the actual study data. The firm will be informed that the acceptability of the data accuracy in these studies will be determined based on the actual study data (this study data has not been reviewed).

IN VITRO STUDIES

Deficiencies Related to Information Common to In Vitro Studies MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093 (4 kPa fixed pressure drop)

Both SAC and APSD Studies

4.3 Deficiency Comment #31

Each of the SAC and APSD studies at 4 kPa fixed pressure drop was conducted on 3 lots of test and 3 lots of RLD product. For each lot, 3 test and 3 RLD devices were tested, with 3 replicates of SAC (beginning, middle, and end lifestages), and 2 replicates of APSD (beginning and end lifestages) collected from each device. You then conducted statistical comparison of geometric mean ratios at 4 kPa vs. 60 L/min. Please repeat the study with 10 test and 10 RLD devices per lot, using 3 lots of test and 3 lots of unexpired RLD product. SAC study should be tested at beginning, middle and end lifestages, while APSD studies should be tested at beginning and end lifestages. Please conduct statistical comparison of test vs. RLD product at 4 kPa pressure drop using population bioequivalence (PBE) analysis. Please refer to *Draft Guidance on Budesonide Inhalation Suspension* for step-wise procedure of the PBE analysis.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf>

Please note that other deficiencies (deficiency #s 10-18, 22, 23, 32, and 33) related to the in vitro studies MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093 (4 kPa fixed pressure drop) are also identified and listed in the current section for IN VITRO STUDIES. Please take them into consideration when you repeat your in vitro studies (4 kPa fixed pressure drop).

4.3.1 Firm's Discussion

Throughout development of MGR001 CRC749, Mylan has worked with the Agency to define the appropriate path for product approval. The difference in resistance between CRC749 and Diskus® devices was explicit throughout these discussions, including that in which the

submission route was defined as 505(j) on the basis of the similarity of the products (as agreed with the agency at Sept 27 2013 Scientific Advice Meeting). The pivotal clinical and in vitro studies required for approval (defined through these discussions, and confirmed via the FDA's Draft Guidance on FP/Salmeterol, 2013) included in vitro equivalence studies at fixed flow rates (30, 60 and 90 L/min) interpreted by population bioequivalence statistics.

As recommended by FDA (September 2013 meeting), Mylan carried out supportive studies comparing the SAC and APSD of test and reference product at a fixed pressure drop of 4kPa, in addition to the pivotal in vitro studies carried out at 30, 60 and 90 L/min. These studies were intended to support the assessment of comparability of resistance between test and reference. The test product was tested at a mean flow rate of approximately 60 L/min, while the RLD was tested at a mean flow rate of approximately 75 L/min, this difference in flow rates reflecting the difference in device resistance. The data was used to assess whether the mean T/R ratio of the SAC and ISM measured at 4kPa differed significantly from that obtained at 60 L/min through both products. This comparison demonstrated absence of impact of the difference in resistance on the finding of in vitro equivalence in the pivotal in vitro studies.

Mylan wishes to confirm that 4kPa studies are to be viewed as supportive studies rather than pivotal bioequivalence studies. Where the RLD shows any degree of flow rate dependency and there is any difference in device resistance, a product can be formulated to achieve equivalence at fixed flow rates or fixed pressure drops but not both. Mylan has targeted the former, in line with Agency guidance. Furthermore, Mylan contends that fixed pressure drop experiments are not an appropriate basis for determination of bioequivalence. In cases such as MGR001 CRC749 vs Advair® Diskus® where flow rate dependency of APSD is low, the primary driver of difference in ISM comparisons between fixed flow rate and fixed pressure drop experiments is the difference in the cut-offs of the cascade impactor and accessories between the flow rates. This is an artefact of the test apparatus with no clinical relevance. The execution of experiments at fixed pressure drop is complicated by variability of resistance within products. Mylan found that, for the RLD (but not for the test product), there was high variability of the flow rate corresponding to 4kPa pressure drop.

Following clarification of the purpose of these experiments, Mylan wishes to discuss the protocol design in the light of the FDA request to test a minimum of 10 inhalers per batch. Three inhalers from each of 3 batches of each product were used in the 4kPa study presented in the ANDA. This number of inhalers was considered appropriate to adequately estimate the mean T/R ratios used in the data assessment, based on Mylan's understanding that between-device variance constitutes the minority of the variance in both test and reference products. Mylan wishes to discuss whether this approach is justified for a supportive study.

Firm's Question

Based on the above justification, does the Agency agree that the 4kPa study as presented in the ANDA is sufficient to demonstrate the absence of significant difference between the products as recommended by the Agency at the Sept 27 2013 Scientific Advice Meeting?

4.3.2 Agency's Response:

Upon further consideration, the firm will not be asked to repeat the in vitro studies at 4 kPa fixed pressure drop, provided that the firm could adequately address deficiency #s 10-18, 22, 23, 32, and 33 in the 3/28/2017 CR letter that are related to the in vitro studies MGR-REP-2015-092, MGR-PRO-REP-2015-103, and/or MGR-REP-2015-093 (4 kPa fixed pressure drop) in the CR response.

As mentioned in CC 13-0422, the 4 kPa pressure drop studies are supportive studies, and “[c]omparable emitted dose and fine particle mass measured at 4 kPa pressure drop for both the devices can provide additional confirmation that resistance difference between the RLD and MGR01 is acceptable.” Please note that this quote was for internal use only in CC 13-0422 and was not communicated to the firm.

During the original BE review, it was considered that even though in vitro studies at 4 kPa pressure drop are supportive data, to help the Agency gain more comprehensive and better understanding of how device resistance difference between the test and RLD product would impact product performance, the firm should still provide enough evidence in the study by providing at least 10 units (instead of the firm's 3 units) per batch, using 3 lots of test and 3 lots of unexpired reference product, which is consistent with product-specific guidance's recommendation for in vitro studies of dry powder inhalers (DPIs) as well as for other products such as nasal sprays and metered dose inhalers (MDIs). In addition, the comparison should be made between test and reference product at 4 kPa pressure drop for emitted dose and fine particle mass (FPM) as per CC 13-0422.

Following the firm's meeting request, DBI discussed with ORS about the study. Based on the meeting outcome, it was concluded that PBE analysis will not be used to analyze the emitted dose and FPM data between test and reference product for these in vitro 4 kPa pressure drop studies. Instead, the evaluation will be based on whether the emitted dose and FPM is comparable between test and reference product. Since the firm's current study data did not show a remarkable variability at 4 kPa pressure drop (please note that the firm still needs to address deficiencies related to the in vitro 4 kPa pressure drop studies, thus the data is subject to change upon the firm's CR response), having data from at least 10 units per batch is unlikely to change the mean of these data, but standard deviations. And since test and reference data will be evaluated based on whether they are comparable, instead of whether they meet PBE criteria, asking for data from additional units is unlikely to change the study outcome.

Therefore, the firm will not be asked to repeat the in vitro study at 4 kPa pressure drop if the firm could adequately address other deficiencies related to the 4 kPa fixed pressure drop studies (deficiency #s 10-18, 22, 23, 32, and 33 in the 3/28/2017 CR letter).

PK BE STUDIES

Deficiency Related to Fasting Studies MGR001-1005 and MGR001-1014

4.4 Deficiency Comment #37

For the 2 PK studies you conducted for the 250/50 mcg strength, it is noted that each of the MGR001-1005 and MGR001-1014 studies failed to meet the bioequivalence criteria of 80.00-125.00%. You conducted pooled analysis of these 2 PK studies, and stated that the pooled analysis met the BE criteria. Please be advised that your pooled analysis is not acceptable due to the following reasons:

- a) The pooled analysis consisted of only two studies with opposite findings. It is apparent that by pooling such data together, the differences between the two studies could be balanced out and therefore, yielding a result somewhere toward to the middle and making the pooled study pass bioequivalence.
- b) Study MGR001-1005 failed to show bioequivalence. Study MGR001-1014 also failed to show bioequivalence even though the batch of Advair Diskus® was selected to represent the Advair Diskus® population. Therefore, whether the pooled analysis results can truly represent all the 250/50 mcg strength data is questionable.
- c) The pooled analysis is a post-hoc analysis, not pre-specified in a protocol or a statistical analysis plan. Therefore, the finding from the pooled analysis is viewed as hypothesis generating and is not acceptable from the statistical point of view.
- d) Your statistical model for the pooled analysis included terms for study, subject within study, period within study, treatment, and study by treatment interaction, but did not take sequence-related effects such as sequence within study into consideration. In addition, the batch-to-batch variability was not addressed in the model. Even had the pooled analysis approach/concept been accepted, the suitability of the statistical model is still questionable.

Therefore, the fasting studies MGR001-1005 and MGR001-1014 is unacceptable. Please repeat the PK BE study for the 250/50 mcg strength.

(b) (4)



4.4.4 Agency's Response:



DBI consulted DBVIII for the question above [Error! Bookmark not defined.](#) and the above response is based on DBVIII's consult response⁷ and is concurred by DBVIII and ORS. Please note that DBVIII's consult response also took into consideration of ORS' suggest language based on ORS' previous communication with [\(b\) \(4\)](#) [ORS previously reviewed a similar proposal (using data from one or more failed PK studies to establish BE) from [\(b\) \(4\)](#) thus DBI also consulted ORS to share their experience and provide DBVIII for suggested language [Error! Bookmark not defined.](#)].

Reviewer's note: Please note that the following questions regarding the potential approaches for the repeat 250/50 study are from the firm's 5/19/2017 submission. This would also provide answer to the firm's similar questions in their 4/3/2017 submission.

Firms' Question 2: That a pooled analysis of studies MGR001-1005, 1014 and 1016 pre-specified in the MGR001-1016 clinical protocol (and ultimately Statistical Analysis Plan (SAP)), would be a reasonable and expedient manner to control for Type 2 error and demonstrate PK BE for the 250/50 product strength?

Agency's Response:

Please see the comments in Question 1.

Similar to Agency's response to Firm's Question 1 above, the above response is from DBVIII's consult response⁷ and is concurred by DBVIII and ORS.

Firms' Question 3: That if all 4 primary endpoints fall within standard BE acceptance criteria in the BE analysis of study MGR001-1016 that this will provide adequate demonstration of PK BE for the 250/50 product strength, in the event that a pre-specified pooled analysis is not acceptable to the Agency?

Agency's Response:

If all primary endpoints (C_{max}, AUC) fall within standard BE acceptance criteria in the BE analysis of study MGR001-1016, then this would provide adequate demonstration of PK BE for the 250/50 mcg strength. In addition, the test batches used in this new study should use the commercial device configuration (not the clinical device configuration). Please note that the use

of clinical device configuration for the conduct of the PK study may warrant additional bridging study(ies).

The firm provided the study protocol for their new study MGR001-1016.

Comparing to the study protocol for the failed PK BE study at the 250/50 mcg strength (i.e. MGR001-1005 and MGR001-1014), it is noted that the firm added additional plasma sample collection time points at 3 and 4 mins post-dose. In addition, the firm relaxed the allowable time deviation for time points prior to 5 mins from within 10% of the nominal time to 30 secs. The reviewer considers these changes acceptable.

It is also noted that the firm stated in this protocol that “[i]n the event that any of the primary endpoints are not bioequivalent in this study, a pooled analysis of this study and prior pivotal bioequivalence studies¹⁵ of the 250/50 mcg product will be conducted.” Please note that evaluation of this statement was addressed in the firm’s Question 2 above.

Please note that the above response is consistent with the current DBI’s practice.

In addition, as mentioned in the reviewer’s comments in Section 4.2.2, there are 2 device configurations: clinical device (b) (4) and commercial device (b) (4). The 2 PK studies (MGR001-1005 and 1014 for the 250/50 mcg strength) that used the commercial device failed to meet BE criteria, whereas the 2 PK studies (MGR001-1006 for the 100/50 mcg strength and MGR001-1007 for the 500/50 mcg strength) met BE criteria. For the new BE study (MGR001-1016 for the 250/50 mcg strength), the firm will be recommended that the test batches used in this new study should use the commercial device configuration (not the clinical device configuration). The use of clinical device configuration for the conduct of the PK study may warrant additional bridging study(ies).

Firms’ Question 4: That Mylan’s proposal of using a multi-stage approach to include multiple batches of RLD (and test) product in any future pivotal PK BE study required for the MGR001 program is a novel PK BE study design which would be acceptable to the Agency?

Agency’s Response:

The firm’s multi-stage design in a single PK BE study framework appears to be acceptable. However, the firm’s analysis model does not include batch identifier as a factor since ‘Batch’ is aliased with ‘Stage’ in their two-way crossover, multi-stage design, which treats batches from different stages as replicates of test and reference product in the analysis. For a multiple-batch study design, each batch of test and reference product should be uniquely identified in the analysis and the statistical model should include any batch-related effects. To achieve this, an expanded crossover design (e.g., a 4-sequence, 4-period, 4-treatment crossover) and/or more stages may be needed because the estimate of a batch effect based on a 2-stage 2-way crossover design may not be reliable as noted by the firm.

¹⁵ According to the firm’s 5/19/2017 submission, these studies were the 2 failed pivotal PK studies at the 250/50 mcg strength (MGR001-1005 and MGR001-1014).

In addition, it is important to ensure that the selection of the reference and test batches are adequately justified and the batches are representative of the products. The firm may suggest ways to take into account, in the statistical evaluation, any factors contributing to variability among batches.

Moreover, the test batches used in the study should use the commercial device configuration (not the clinical device configuration). Please note that the use of clinical device configuration for the conduct of the PK study may warrant additional bridging study(ies).

If this is the approach the firm plans to take, the Agency recommends the firm to submit a full protocol containing details of the proposed study design along with a detailed statistical analysis plan well in advance of the conduct of their study, to allow for a thorough assessment and the opportunity for obtaining feedback from the Agency.

Acceptability of using multiple batches

Since ORS has experience reviewing and addressing pre-ANDA communications from different sponsors (b) (4) regarding proposals for inclusion of multiple test and reference batches within PK studies, DBI consulted ORS for whether the firm's reasoning of using multiple batches of reference (and test) product for their 250/50 mcg strength PK BE study is acceptable. [Error! Bookmark not defined.](#)

The firm provided the following rationale to support their proposal of including multiple test and reference batches:

“The reason for exploring the inclusion of additional batches of test and RLD product is that demonstrating PK BE for orally inhaled products, using standard approaches, continues to be a challenge for products that may truly be BE (Burmeister Getz; 2016; 2017). FDA guidance requires that BE is established if the 90% CIs for the geometric mean test and RLD ratios of AUC and Cmax (for both FP and salmeterol) fall within the limits of 80.00–125.00%. This may be straightforward to achieve for a single test (i.e. for a single PK endpoint) but the power for demonstrating BE across all the required 4 endpoints is substantially lower (Fuglsang; 2014)). For a product such as MGR001 with 3 dose strengths, this amounts to 12 separate tests with an associated further reduction in the overall power of demonstrating BE for the product.”

ORS reviewer evaluated the firm's rationale cited above, and considers that the cited publications alone do not adequately support the firm's proposal to conduct a PK BE study for the 250/50 mcg strength using multiple batches of the test and reference product.

ORS reviewer also evaluated in vitro and in vivo performance of Advair Diskus 250/50 from Mylan's (b) (4) submission to assess if high batch-to-batch PK variability exists for the 250/50 mcg strength. The ORS reviewer considered 2 parameters in this assessment:

1) Observed in vitro variability of the 250/50 mcg strength in comparison to that observed for the 100/50 mcg strength

2) Observed PK variability of the 250/50 mcg strength in comparison to that observed for the 100/50 mcg strength

For 1) Observed in vitro variability, ORS provided the following overall statement:

“Overall, it appears that RLD in vitro variability for the 250/50 strength is comparable to that observed for the 100/50 strength. If it is to be believed that FPM and dissolution rate together are predictive of in vivo PK variability, then because the two strengths (100/50 and 250/50) have comparable in vitro batch-to-batch variability, it is possible that the 250/50 strength may also have the same magnitude of PK variability as was observed for 100/50 strength. This observation to some extent supports the proposal of using multiple batches in a PK BE study for the 250/50 strength, since we have a precedent of allowing applicants to use multiple batches in a PK BE study for the 100/50 strength. However, it should be noted that the firm has the advantage of selecting the RLD and the test batches prior to PK BE study based on predictive these in vitro methods, which could mitigate a large portion of uncertainty related to RLD and test batch-to-batch variability during PK BE assessment. Hence, if the firm is allowed to use multiple RLD and test batches, then it is important to ensure that the selections of the RLD and test batches are adequately justified and the batches are representative of the products.”

For 2) Observed PK variability, ORS provided the following overall statement:

“Overall, this reviewer believes that observed PK variability for the 250/50 strength is not as high as that observed for the 100/50 strength. It is worth acknowledging that there were not as many adequately powered PK studies where RLD-to-RLD comparisons were made for the 250/50 strength, as compared to the 100/50 strength. This reviewer cannot assess if more RLD-to-RLD comparisons for the 250/50 strength would have changed the conclusion.”

The overall conclusion by ORS is as follow:

“Currently there are no accepted statistical criteria available to make a determination on whether batch-to-batch PK variability of a product (or a particular strength of the product) is high enough to routinely allow the use of multiple RLD and test batches in a PK BE study. While in vitro data from more than one source indicate likelihood of batch-to-batch PK variability for Advair Diskus 250/50, the currently available PK data for the 250/50 strength product do not provide evidence adequate to reach the same conclusion. Therefore, DTP concludes that it may not be appropriate to reach a determination as to whether or not use of multiple batches of the test and the RLD in a PK BE study would be acceptable for the 250/50 strength at this juncture based on the information provided without further discussion. We would defer and be supportive of DBI to make the final decision, after further internal discussion and evaluation of all available data, in discussion with the Division of Clinical Review (DCR), ORS and DBVIII.”

Study design and statistical approach

DBI also consulted DBVIII about whether the firm’s proposal of using a multi-stage approach to include multiple batches of reference (and test) product in any future pivotal PK BE study

required for the MGR001 program is acceptable; and if yes, whether the firm's statistical method for this study design is acceptable. [Error! Bookmark not defined.](#)

DBVIII provided the following response regarding the questions above:

“The applicant’s multi-stage design in a single PK BE study framework appears to be acceptable from the statistical point of view. However, the applicant’s analysis model does not include batch identifier as a factor since ‘Batch’ is aliased with ‘Stage’ in the applicant’s two-way crossover, multi-stage design, which treats batches from different stages as replicates of Test and RLD in the analysis. For a multiple-batch study design, each batch of Test and RLD should be uniquely identified in the analysis and the statistical model should include any batch-related effects. To achieve this, an expanded crossover design (e.g., a 4-sequence, 4-period, 4-treatment crossover) and/or more stages may be needed because the estimate of a batch effect based on a 2-stage 2-way crossover design may not be reliable as noted by the applicant. In addition, to reduce batch-to-batch variability in RLD (and test) product, the applicant should consider controlling any potential contributing factors (e.g., shelf-life of RLD) during the batch selection process or incorporating the factors into the statistical analysis model.

The applicant should submit a full protocol for the proposed study design along with a detailed statistical analysis plan well in advance to allow for a thorough review and the opportunity for obtaining agreement with the Agency.”

Please note that the response to the firm above is based on ORS’ and DBVIII’s consult responses, as well as the 6/28/2017 meeting discussion among DBI, ORS, and DBVIII, and is concurred by ORS and DBVIII.

FLOW PROFILING STUDY

Deficiencies Related to the Flow Profiling Study (MGR000-1003)

4.5 Deficiency Comment #40

According to p. 40 of 321 of the study report, the reference batch (batch # 547-046) used in this study is Accuhaler™. Therefore, the flow profiling study is unacceptable due to the use of non-US marketed RLD product. Please repeat the flow profiling study using US marketed RLD product.

It is also noted that in the clinical overview (12/29/2015 submission, Module 2.5\Clinical Overview, p. 7 of 21), you stated that “[t]he CRC749 device used in this study was identical in terms of the airway geometry (and therefore airflow paths and device resistance) and the drug-containing discs (and therefore the pharmaceutical performance) remained the same the CRC749 Clinical device used in the pivotal clinical endpoint BE study and PK BE studies with the 100/50 and 500/50 product strengths, and the Commercial device which was included in the

pivotal PK BE studies with the 250/50 product strength.” Based on this statement, it appears that you used test device other than the clinical device (b) (4) and commercial device (b) (4). Please use the commercial device for the test product in your repeat flow profiling study.

4.5.1 Firm’s Discussion

Mylan notes that there is no requirement for a flow profiling study for the test product inhaler device stipulated in the FDA draft guidance FP/Salmeterol, 2013, nor have FDA raised the requirement for such a study for MGR001 device CRC749 specifically at any of the numerous product specific scientific advice / pre-ANDA meetings, including those in which the modest difference between the resistance of the CRC749 and RLD Diskus[®] devices were noted and discussed (primarily December 2012 Meeting).

As the resistance of an inhaler device is the only determinant of airflow through that device, and aware of the modest difference in test and RLD inhaler resistance, Mylan conducted flow profiling study MGR000-1003 in order to satisfy EU requirements (primarily to provide in vitro data at patient relevant flow rates). Mylan maintain that the data provided by study MGR000-1003 is directly applicable to the commercial MGR001 CRC749 device (and Diskus[®] device) as the measured resistance of the test MGR001 device variant (and Accuhaler device) included in the study is equivalent to that measured in the commercial MGR001 device (and Diskus[®] devices), indicating that the airflow pathways through the test (or RLD) device variants have remained conserved.

Mylan reviewed the results of the MGR000-1003 study, specifically the flow-profile data for the test MGR001 CRC749 device, with FDA at the October 2015 pre-ANDA meeting, noting that FDA may wish to consider its relevance to the MGR001 ANDA in two contexts:

- 1. To demonstrate that all patient groups in whom MGR001 would be indicated, in particular those with the poorest lung function either as a result of disease (eg very severe COPD) or age (eg pediatric asthmatics aged > 4 years), could achieve peak inspiratory flow rates (PIFRs) > 30L/min through the CRC749 device. Mylan noted that these data demonstrate that the lowest flow rate achieved in any patient group was above the lower limit of testing at which in vitro equivalence is determined for MGR001 (and US RLD), 30L/min, providing FDA with direct support of the paradigm contained in the draft guidance FP/Salmeterol 2013.*
- 2. To provide patient inhalation profile data for the MGR001 CRC749 device which could be used by FDA, if required, to substitute for the inhalation profile data which is provided for the RLD Diskus[®] device in section 11 of the USPI. To this end, Mylan asked the specific question of FDA “Mylan requests the Agency’s advice regarding the text to be used in the ANDA for section 11 of the USPI to describe the inhalation profiles for the device?” to which the Agency responded: “In principle, description of the inhalation profiles listed in Section 11 of the USPI should be the same as the profiles for the RLD with data included for the Diskus[®] Dry Powder Inhaler. However, once OGD receives and reviews the proposed Prescribing Information as part of an ANDA, additional changes might be warranted and requested, and will be a review issue.”*

Given that the Agency agreed that the data provided by study MGR000-1003, could be useful both to support the range flow rates for determination of in vitro equivalence and for potential use in the USPI of the MGR001 product, it was agreed that the study should be submitted as supportive data to the core (bioequivalence) elements of the MGR001 ANDA.

Mylan wish to discuss with FDA reviewers:

Reviewer's note: The firm had 4 questions, which are addressed individually below.

Firm's Question #1:

- 1. Why there is a now a requirement for a flow-profiling study when such a study was never a requirement of the draft guidance FP/Salmeterol 2013, or raised as a requirement at any of the scientific advice / pre-ANDA meetings held specifically to discuss MGR001?*

4.5.2 Agency's Response for the Firm's Question #1:

The airflow resistance of the firm's device is different from that of the RLD device. An accumulative evidence of data (e.g., in vitro BE, PK, clinical endpoint, in vitro 4 kPa pressure drop, flow profiling, device usability questionnaire) are considered in building up a totality of evidence that such device resistance difference would not impact therapeutic equivalence. Currently there is not enough evidence (e.g. PK study failed at the 250/50 mcg strength, in vitro studies and clinical endpoint study outcome is incomplete) to demonstrate that therapeutic equivalence is not impacted by this device resistance difference. Therefore, to ensure that device resistance difference does not impact therapeutic equivalence, the study was recommended so that it could help with the justification.

(b) (4)

¹⁶ MG001 is the name that the firm refers to for its test product.

¹⁷ CRC749 is the name of the test device.

For the above reasons, the test device is still appropriate for the 505 (j) regulatory pathway. However, to address some residual uncertainties due to the device resistance difference, the Agency recommends the firm to either provide justification/ data **(e.g., comparisons of inspiratory flow rates or profiles generated by relevant patients for the test and reference DPIs)**¹⁸ to support that this difference in the device resistance does not impact therapeutic equivalence of the proposed generic and the RLD, or modify the device to attain similar resistance as the RLD, i.e., $\pm 15\%$ of the RLD.”

¹⁸ Emphasized by the reviewer.

Currently, there are no criteria to routinely review device resistance difference of this degree from BE perspective. For the current ANDA, an accumulative evidence of data (e.g., in vitro BE, PK, clinical endpoint, in vitro 4 kPa pressure drop, flow profiling, device usability questionnaire) are considered in building up our confidence that such device resistance difference would not impact therapeutic equivalence. Currently to this review stage, the firm has not provided adequate evidence (e.g. PK study failed at the 250/50 mcg strength, in vitro studies and clinical endpoint study outcome is incomplete) to demonstrate that therapeutic equivalence is not impacted by this device resistance difference. Therefore, to make sure that device resistance difference does not impact therapeutic equivalence, the study was recommended so that it could help with the justification.

Firm's Question #2:

2. *That the MGR000-1003 study satisfies whatever requirements FDA has determined for flow profile data for the test MGR001 CRC749 device, if Mylan provide data to confirm that the only determinant of airflow, device resistance, of the MGR001 inhaler variant product tested in study MGR000-1003 is equivalent to that of the proposed commercial MGR001 inhaler?*

4.5.3 Agency's Response for the Firm's Questions #2:

If the firm chooses not to repeat the flow profiling study using US marketed product, the firm is recommended to provide adequate evidence (e.g. data to confirm device resistance of the US market product is equivalent to the non-US version of the product used in MGR000-1003) to bridge the US market product with the non-US version product utilized in its Flow Profiling Study (MGR000-1003), in addition, adequate response should be provided to deficiency #s 41-46 in the 3/28/2017 CR letter that are related to the flow profiling study.

If the firm chooses not to repeat the flow profiling study using US marketed product, the firm is recommended to provide adequate evidence (e.g. data to confirm device resistance of the US market product is equivalent to the non-US version of the product used in MGR000-1003) to bridge the US market product with the non-US version product utilized in its Flow Profiling Study (MGR000-1003), which is a supportive study and not a pivotal study. In addition, the firm should provide adequate response to deficiency #s 41-46 in the 3/28/2017 CR letter that are related to the flow profiling study.

Firm's Question #3:

3. *Why Mylan would need to conduct flow-profiling evaluation of the US RLD Diskus[®] device, given there is no requirement for comparison of inhalation profiles through test and RLD product devices, as this data is not relevant to the MGR001 product device which is the subject of the ANDA and in any case is already available in the Advair[®] Diskus[®] USPI?*

4.5.4 Agency's Response for the Firm's Questions #3:

Please see comments in Question #1 above.

Firm's Question #4:

4. ***Furthermore, and in relation to FDA CRL QUESTION: Labelling 2b: “We note that your proposed labeling currently includes the mean peak inspiratory flow (PIF) data of the RLD. Please explain the relevance of the PIF data of the RLD to your ANDA”, Mylan note that this was a question raised with FDA at the pre-ANDA meeting (question 5A) and on which FDA committed to provide advice during their review of the ANDA. In the absence of this advice, Mylan would propose that the following information could be included in the MGR001 USPI to provide information for HCPs:***



Mylan provides this proposed labelling, based on the USPI for the RLD, as an example of how HCPs may be informed of MGR001 product attributes by providing a summary of the in vitro equivalence testing in relation to the flow profiles achieved in patient populations specifically with MGR001 CRC749 device. Mylan requests FDA concordance that such a statement is both warranted and acceptable for the MGR001 USPI.

¹⁹ The firm wrote “8 11”, but the reviewer considers that they meant “8-11”.

4.5.5 Agency's Response for the Firm's Questions 4:

Thank you for your response regarding our request to explain the relevance of the RLD's PIF data to your ANDA. Upon further consideration, we recommend that the description section of your ANDA labeling (section 11) reflect the most recently approved labeling for the RLD (NDA 021077/S-058, approved February 28, 2017).

Please note that the firm's Question 4 is related to Labeling, and the response above is provided by DLR.²⁰

²⁰ V:\DIVISION\BIO\BIO1\Email Reference\208891 Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder\FW Timeline request Mylan DPI ANDA 208891 scientific face to face meeting request.msg

NOTE TO REGULATORY PROJECT MANAGER (RPM): Only the letter at the end of the current document should be incorporated into the written communication to the firm. The remainder of the current document should not be communicated to the firm.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 208891
APPLICANT: Mylan Pharmaceuticals Inc.
DRUG PRODUCT: Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate)
Inhalation Powder, 0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ
0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation

The Division of Bioequivalence I (DBI) has completed its review of your meeting request dated 4/3/2017. Please see the response below:

In your 4/3/2017 Meeting Request, Section 10.1 Device Orientation, you stated:

“Does the Agency agree that the Human Factor Orientation Study (MGR000-1004), designed in collaboration with OGD demonstrates that the horizontal orientation does not introduce a risk that impact the safe and effective use of MGR001 when a patient is switched from the RLD without training or instruction from the healthcare provider.”

Agency’s Response:

The Agency will be prepared to discuss the device orientation of your product at the 7/13/2017 meeting. The Agency intends to provide a written response to your question after that meeting.

In your 4/3/2017 Meeting Request, Section 10.2 In Vitro Bioequivalence Studies at Multiple Flow Rates, you stated:

“Does the agency agree with Mylan’s assertion that the changes in potency factor and device design have no impact on product performance hence the FDAs original request to demonstrate in vitro bioequivalence between batches manufactured [REDACTED] (b) (4) and RLD at 60 L/min flow rate only remains valid.”

Agency’s Response:

Based on the additional information you provided as well as the Agency’s additional evaluation, the Agency considers your in vitro bridging studies at 60 L/min flow rate may suffice at this moment (please note that this bridging data has not yet been reviewed, so the acceptability of this data is to be determined), but the Agency reserves the right to ask for data at 30 L/min and 90 L/min flow rates if in the future it is determined that the device difference impacts product performance.

In the same section 10.2 of the aforementioned document, you also stated:

“On the basis of the above information does the Agency agree that the accuracy of the data generated during these studies is adequate?”

Agency’s Response:

The acceptability of data accuracy in your in vitro BE studies between batches manufactured (b) (4) and RLD at 60 L/min will be determined when the study data is reviewed.

In your 4/3/2017 Meeting Request, Section 10.3 4kPa Study Design, you stated:

“Based on the above justification, does the Agency agree that the 4kPa study as presented in the ANDA is sufficient to demonstrate the absence of significant difference between the products as recommended by the Agency at the Sept 27 2013 Scientific Advice Meeting?”

Agency’s Response:

Upon further consideration, the in vitro studies at 4 kPa fixed pressure drop do not need to be repeated provided that you could adequately address deficiency #s 10-18, 22, 23, 32, and 33 in the 3/28/2017 CR letter that are related to the in vitro studies MGR-REP-2015-092, MGR-PRO-REP-2015-103, and/or MGR-REP-2015-093 (4 kPa fixed pressure drop) in your CR response.

(b) (4)

In your 5/19/2017 submission, you also stated the following questions regarding PK study(ies):

“That a pooled analysis of studies MGR001-1005, 1014 and 1016 pre-specified in the MGR001-1016 clinical protocol (and ultimately Statistical Analysis Plan (SAP)), would be a reasonable and expedient manner to control for Type 2 error and demonstrate PK BE for the 250/50 product strength?”

Agency’s Response:

Please see the comments above for the previous question.

“That if all 4 primary endpoints fall within standard BE acceptance criteria in the BE analysis of study MGR001-1016 that this will provide adequate demonstration of PK BE for the 250/50 product strength, in the event that a pre-specified pooled analysis is not acceptable to the Agency?”

Agency’s Response:

If all primary endpoints (C_{max}, AUC) fall within standard BE acceptance criteria in the BE analysis of study MGR001-1016, then this would provide adequate demonstration of PK BE for the 250/50 mcg strength. In addition, the test batches used in your study MGR001-1016 should use your commercial device configuration (not the clinical device configuration). Please note that the use of clinical device configuration for the conduct of this PK study may warrant additional bridging study(ies).

“That Mylan’s proposal of using a multi-stage approach to include multiple batches of RLD (and test) product in any future pivotal PK BE study required for the MGR001 program is a novel PK BE study design which would be acceptable to the Agency?”

Agency’s Response:

Your multi-stage design in a single PK BE study framework appears to be acceptable. However, your analysis model does not include batch identifier as a factor since ‘Batch’ is aliased with ‘Stage’ in your two-way crossover, multi-stage design, which treats batches from different stages as replicates of test and reference product in the analysis. For a multiple-batch study design, each batch of test and reference product should be uniquely identified in the analysis and the statistical model should include any batch-related effects. To achieve this, an expanded crossover design (e.g., a 4-sequence, 4-period, 4-treatment crossover) and/or more stages may be needed because the estimate of a batch effect based on a 2-stage 2-way crossover design may not be reliable as noted by you.

In addition, it is important to ensure that the selection of the reference and test batches are adequately justified and the batches are representative of the products. You may suggest ways to take into account, in the statistical evaluation, any factors contributing to variability among batches.

Moreover, the test batches used in your study should use your commercial device configuration (not the clinical device configuration). Please note that the use of clinical device configuration for the conduct of the PK study may warrant additional bridging study(ies).

If this is the approach you plan to take, we recommend you submit a full protocol containing details of the proposed study design along with a detailed statistical analysis plan well in advance of the conduct of your study, to allow for a thorough assessment and the opportunity for obtaining feedback from the Agency.

(b) (4)

In your 4/3/2017 Meeting Request, Section 10.10 Flow Profile Study, you stated:

“1. *Why there is a now a requirement for a flow-profiling study when such a study was never a requirement of the draft guidance FP/Salmeterol 2013, or raised as a requirement at any of the scientific advice / pre-ANDA meetings held specifically to discuss MGR001?*”

Agency’s Response:

The airflow resistance of your device is different from that of the RLD device. An accumulative evidence of data (e.g., in vitro BE, PK, clinical endpoint, in vitro 4 kPa pressure drop, flow profiling, device usability questionnaire) are considered in building up a totality of evidence that such device resistance difference would not impact therapeutic equivalence. Currently there is not enough evidence (e.g. PK study failed at the 250/50 mcg strength, in vitro studies and clinical endpoint study outcome is incomplete) to demonstrate that therapeutic equivalence is not impacted by this device resistance difference. Therefore, to ensure that device resistance

difference does not impact therapeutic equivalence, the study was recommended so that it could help with the justification.

2. *That the MGR000-1003 study satisfies whatever requirements FDA has determined for flow profile data for the test MGR001 CRC749 device, if Mylan provide data to confirm that the only determinant of airflow, device resistance, of the MGR001 inhaler variant product tested in study MGR000-1003 is equivalent to that of the proposed commercial MGR001 inhaler?*

Agency's Response:

If you choose not to repeat the flow profiling study using US marketed product, we recommend you provide adequate evidence (e.g. data to confirm device resistance of the US market product is equivalent to the non-US version of the product used in MGR000-1003) to bridge the US market product with the non-US version product utilized in its Flow Profiling Study (MGR000-1003). In addition, adequate response should be provided to deficiency #s 41-46 in the 3/28/2017 CR letter that are related to the flow profiling study in your CR response.

3. *Why Mylan would need to conduct flow-profiling evaluation of the US RLD Diskus® device, given there is no requirement for comparison of inhalation profiles through test and RLD product devices, as this data is not relevant to the MGR001 product device which is the subject of the ANDA and in any case is already available in the Advair® Diskus® USPI?"*

Agency's Response:

Please see comments for your Flow Profile Study Question 1 above.

4. *“Furthermore, and in relation to FDA CRL QUESTION: Labelling 2b: “We note that your proposed labeling currently includes the mean peak inspiratory flow (PIF) data of the RLD. Please explain the relevance of the PIF data of the RLD to your ANDA”, Mylan note that this was a question raised with FDA at the pre-ANDA meeting (question 5A) and on which FDA committed to provide advice during their review of the ANDA. In the absence of this advice, Mylan would propose that the following information could be included in the MGR001 USPI to provide information for HCPs:*



Mylan provides this proposed labelling, based on the USPI for the RLD, as an example of how HPCs may be informed of MGR001 product attributes by providing a summary of the in vitro equivalence testing in relation to the flow profiles achieved in patient populations specifically with MGR001 CRC749 device. Mylan requests FDA concordance that such a statement is both warranted and acceptable for the MGR001 USPI.”

Agency’s Response:

Thank you for your response regarding our request to explain the relevance of the RLD’s PIF data to your ANDA. Upon further consideration, we recommend that the description section of your ANDA labeling (section 11) reflect the most recently approved labeling for the RLD (NDA 021077/S-058, approved February 28, 2017).

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Bing V. Li, Ph.D.
Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.6 Outcome Page

Completed Assignment for 208891 ID: 31365

Reviewer: Ma, Tian

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder, 0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ 0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>		
31365	4/3/2017	BIO	Post CR Meeting Request Review [1]	1	1	Edit	Delete
31365	4/3/2017	BIO	Consult Review (For Consults to Other Office) [1]	1	1	Edit	Delete
31365	4/3/2017	BIO	Consult Review (For Consults to Other Office) [1]	1	1	Edit	Delete
31365	4/3/2017	BIO	Consult Review (For Consults to Other Office) [1]	1	1	Edit	Delete
31365	4/3/2017	BIO	Protocol [1]	1	1	Edit	Delete
31365	4/3/2017	Parallel	Post CR Meeting Request [1]	1	1	Edit	Delete
31365	4/3/2017	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1	Edit	Delete
31365	4/3/2017	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1	Edit	Delete
31365	4/3/2017	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1	Edit	Delete
31365	4/3/2017	Parallel	Protocol or Protocol Amendment [1]	1	1	Edit	Delete
				Total:	10		

DIVISION OF BIOEQUIVALENCE REVIEW FOR DRY POWDER INHALER PRODUCTS

ANDA No.	208891			
Drug Product Name	Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder			
Strength(s)	0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ 0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation			
Applicant Name	Mylan Pharmaceuticals Inc.			
Applicant Address	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310			
US Agent Name and the Mailing Address	Joseph J. Sobecki, Head of Regulatory Affairs - North America joseph.sobecki@mylan.com OR Wayne Talton, Head of Global Regulatory Science & Operations wayne.talton@mylan.com			
US agent's Telephone Number	(304) 599-6429 (JS) 304) 554-6551 (WT)			
US Agent's Fax Number	(304) 285-6407			
Original Submission Date(s)	December 29, 2015			
Submission Date(s) of Amendment(s) Under Review	February 15, 2016 (concentration data, graphs and SAS output for pharmacokinetic studies; tabular listing of all clinical studies; information on unblinding, randomization and datasets for the pharmacodynamic study) August 11, 2016 (Response to ECD/Bioequivalence) [@] September 22, 2016 (Response to ECD/Bioequivalence) September 28, 2016 (Response to ECD/Bioequivalence) [@] January 12, 2017 (Response to ECD/Bioequivalence)			
Primary Reviewer	Tian Ma, Ph.D.			
Secondary Reviewer	Vipra Kundoor, Ph.D.			
Tertiary Reviewer	Bing V. Li, Ph.D.			
Study Number (s)	MGR001-1006	MGR001-1007	MGR001-1005	MGR001-1014
Study Type (s)	Fasting	Fasting	Fasting (failed, but was used in pooled analysis by the firm with MGR001-1014)	Fasting(failed, but was used in pooled analysis by the firm with MGR001-1005)
Strength (s)	100/50 mcg ¹	500/50 mcg	250/50 mcg	250/50 mcg
Clinical Site	Worldwide Clinical Trials Early Phase Services, LLC			
Clinical Site Address	2455 NE Loop 410, Suite 150			

¹ From now on in this review, product strength of “x/y mcg” will be used to indicate the strength of fluticasone propionate and salmeterol xinafoate (EQ y mcg base) per inhalation, respectively.

	San Antonio, Texas 78217		
Analytical Site	Mylan Pharmaceuticals Inc.		
Analytical Site Address	Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505		
Study Number (s)	057755-02-04	MGF-PRO-2015-080	057755-02-07
Study Type (s)	In Vitro BE [single actuation content (SAC) and aerodynamic particle size distribution (APSD)]	In Vitro BE (SAC and APSD)	In Vitro BE (SAC and APSD)
Strength (s)	100/50 mcg	250/50 mcg	500/50 mcg
Analytical Site	(b) (4)	Mylan Global Respiratory Group	(b) (4)
Analytical Site Address	(b) (4)	IPC008, Discovery Park House, Floor 3 Sandwich, Kent. CT13 9ND. UK	(b) (4)
Study Number (s)	MGR-REP-2015-092	MGR-PRO-REP-2015-103	MGR-REP-2015-093
Study Type (s)	Pressure Differential (4 kPa) (SAC and APSD)	Pressure Differential (4 kPa) (SAC and APSD)	Pressure Differential (4 kPa) (SAC and APSD)
Strength (s)	100/50 mcg	250/50 mcg	500/50 mcg
Analytical Site	(b) (4)	Mylan Global Respiratory Group	(b) (4)
Analytical Site Address	(b) (4)	IPC008, Discovery Park House, Floor 3 Sandwich, Kent. CT13 9ND. UK	(b) (4)
Study Number (s)	MGR001-3001		
Study Type (s)	Clinical Endpoint		
Strength (s)	100/50 mcg		
Clinical Site	Site Number	Principal Investigator and Location	Address
	3001001	Idalia A. Acosta, Miami, FL 33015	5941 NW 173 Dr, Ste 1 Miami, FL 33015
	3001002	Niran J. Amar, Waco, TX 76712	333 Londonderry Dr, Ste 110 Waco, TX 76712
	3001003	James W. Baker, Portland, OR 97223	9495 SW Locust St Portland, OR 97223
	3001004	G Daniel Brooks, Bellevue, NE 68123-4303	3503 Samson Way, Ste 108 Bellevue, NE 68123-4303

3001006	Warner W. Carr, Mission Viejo, CA 92691	27800 Medical Center Rd, #240/#244 Mission Viejo, CA 92691
3001007	Jonathan Corren, Los Angeles, CA 90025	10780 Santa Monica Blvd Ste 280 Los Angeles, CA 90025
3001008	David Cypcar, Asheville, NC 28801	14 McDowell St Asheville, NC 28801
3001009	Joseph D. Diaz, San Antonio, TX 78229	2414 Babcock Rd, Ste 108- 109 San Antonio, TX 78229
3001010	Manuel A. Franco, Miami, FL 33133	2720 SW 37 Ave Miami, FL 33133
3001011	Sherwin A. Gillman, Orange, CA 92868	725 West La Veta Ave, Ste 100 Orange, CA 92868
3001012	John T. Given, Canton, OH 44718	Allergy, Respiratory & Sleep Center 4048 Dressier Rd NW, Ste 100 Canton, OH 44718
3001013	Stanley Goldstein, Rockville Centre, NY 11570	242 Merrick Rd, Ste 401 Rockville Centre, NY 11570
3001014	Richard G. Gower, Spokane, WA 99202	324 S Sherman St Spokane, WA 99202
3001015	Leon S. Greos, Centennial, CO 80112	14000 E. Arapahoe Rd, Ste 260 Centennial, CO 80112
3001016	Amina Z. Haggag, Anaheim, CA 92801	Anaheim Clinical Trials, LLC 1085 N. Harbor Blvd Anaheim, CA 92801
3001017	Frank C. Hampel Jr., New Braunfels, TX 78130	705-A Landa St New Braunfels, TX 78130
3001018	Edward Francis Kent Jr., South Burlington, VT 05403	Timber Lane Allergy & Asthma Research, LLC 54 Timber Lane South Burlington, VT 05403
3001019	Phillip E. Korenblat, St. Louis, MO 63141	1040 N Mason Rd, Ste 112 St. Louis, MO 63141
3001020	Craig Fred LaForce, Raleigh, NC 27607	North Carolina Clinical Research 2615 Lake Dr, Ste 301 Raleigh, NC 27607
3001022	Edward E. Lisberg, River Forest, IL 60305	7420 Central Ave, Ste 2020 River Forest, IL 60305
3001023	Stephen Maddock, Lenexa, KS 66219	Analab Clinical Research Inc 15335 W 95th St Lenexa, KS 66219

3001024	Lyndon E. Mansfield, El Paso, TX 79903	2121 Wyoming Ave El Paso, TX 79903
3001025	Jonathan Matz, Baltimore, MD 21236	Chesapeake Clinical Research, Inc 7939 Honeygo Blvd, Ste 219 Baltimore, MD 21236
3001026	Curtis J. Mello, North Dartmouth, MA 02747	370 Faunce Corner Rd 2nd Fl North Dartmouth, MA 02747
3001027	S. David Miller, North Dartmouth, MA 02747	Northeast Medical Research Associates, Inc. 49 State Rd Watuppa Bldg, Ste 202 North Dartmouth, MA 02747
3001028	Anthony Montanaro, Portland, OR 97202	6327 SE Milwaukie Ave, 2nd Floor Portland, OR 97202
3001029	Nancy K. Ostrom, San Diego, CA 92123	5776 Ruffin Rd San Diego, CA 92123
3001031	Amit I. Patel, Riverside, CA 92506	Integrated Research Group, Inc. 4646 Brockton Ave, Ste 202-3 Riverside, CA 92506
3001032	David S. Pearlman, Denver, CO 80230	125 Rampart Way, Ste 150 Denver, CO 80230
3001033	Andrew J. Pedinoff, Skillman, NJ 08558	Montgomery Professional Center 24 Vreeland Dr Skillman, NJ 08558
3001034	Warren William Pleskow, Encinitas, CA 92024	317 N El Camino Real, Ste 506 Encinitas, CA 92024
3001035	Larry S. Posner, Napa, CA 94558	1100 Pear Tree Lane Napa, CA 94558
3001036	Gordon D. Raphael, Bethesda, MD 20814	4915 Auburn Ave, Ste 202 Bethesda, MD 20814
3001037	Paul H. Ratner, San Antonio, TX 78229	7711 Louis Pasteur Dr, Ste 406 San Antonio, TX 78229
3001038	Syed M. Rehman, Toledo, OH 43617	7247 W. Central Ave, Ste A Toledo, OH 43617
3001039	Michael E. Ruff, Dallas, TX 75231	5499 Glen Lakes Dr, Ste 200 Dallas, TX 75231
3001040	Russell A. Settipane, East Providence, RI 02914	450 Veterans Memorial Pkwy #15 East Providence, RI 02914
3001041	Ellen R. Sher, Ocean, NJ 07712	802 West Park Ave, Ste 213 Ocean, NJ 07712

3001042	Lawrence D. Sher, Rolling Hills Estates, CA 90274	550 Deep Valley Dr, Ste 317 Rolling Hills Estates, CA 90274
3001045	Stephen A. Tilles, Seattle, WA 98115	9725 Third Ave NE, Ste 500 Seattle, WA 98115
3001046	Mark L. Vandewalker, Columbia, MO 65203	601 W Nifong Bldg 2-A Columbia, MO 65203
3001047	David P. Chen, Bozeman, MT 59718	950 Stoneridge Dr, Ste 1 Bozeman, MT 59718
*3001048	Patrick H. Win, Shiloh, IL 62269	325 Tamarack Lane Shiloh, IL 62269
3001049	John A. Winder, Sylvania, OH 43560	5800 Monroe St, Ste A-9 Sylvania, OH 43560
3001050	James D. Wolfe, San Jose, CA 95117	4050 Moorpark Ave, Ste 6 San Jose, CA 95117
3001051	Robert N. Wolfe, Los Angeles, CA 90048	Southern California Institute For Respiratory Diseases, Inc. 8635 West 3rd St, Ste 965- W Los Angeles, CA 90048
3001053	Thomas R. Murphy, N. Charleston, SC 29420	7555 Northside Dr N. Charleston, SC 29420
3001054	David I. Bernstein, Cincinnati, OH 45231	Bernstein Clinical Research Center, LLC 8444 Winton Rd Cincinnati, OH 45231
3001055	Charles M. Fogarty, Spartanburg, SC 29303	485 Simuel Rd Spartanburg, SC 29303
3001056	Philip C. Halverson, Minneapolis, MN 55402	825 Nicollet Mall, Ste 1135 Minneapolis, MN 55402
3001057	Sanchayita "Ita" Tripathy, Rolla, MO 65401	509 East 10th St Rolla, MO 65401
3001058	John F. Zwetchkenbaum, Warwick, RI 02886	470 Toll Gate Rd, Ste 203 Warwick, RI 02886
3001059	Dario D. Altamirano, Hialeah, FL 33012	900 W 49th St, Ste 430 Hialeah, FL 33012
3001060	Philip A. Emrie, Wheat Ridge, CO 80033	8550 W 38th Ave, Ste 202 Wheat Ridge, CO 80033
3001061	Timothy Harrison Elder, Gainesville, FL 32607	4343 W Newberry Rd, Ste 17 Gainesville, FL 32607
3001062	Gregory J. Feldman, Spartanburg, SC 29303	141 Harold Fleming Court Spartanburg, SC 29303
3001063	Jason H. Friesen, Eugene, OR 97401	Allergy and Asthma Research Group 1488 Oak St Eugene, OR 97401
3001064	Gregory M. Gottschlich, Cincinnati, OH 45242	9395 Kenwood Rd, Ste 101 Cincinnati, OH 45242

3001065	James Lawrence Pearle, Fullerton, CA 92835	301 W Bastanchury Rd, Ste 220 Fullerton, CA 92835
*3001066	Ronald H. Saff, Tallahassee, FL 32308	Allergy & Asthma Diagnostic Treatment Center 2300 Centerville Rd Tallahassee, FL 32308
3001067	Teresa S. Sligh, North Hollywood, CA 91606	6400 Laurel Canyon Blvd, Ste 300A North Hollywood, CA 91606
3001068	Kurt W. Jensen, Tacoma, WA 98405	Pulmonary Consultants, PLLC 1708 S. Yakima Ave, Ste 300 Tacoma, WA 98405
3001069	Edward M. Kerwin, Medford, OR 97504	Clinical Research Institute of Southern Oregon, PC 3860 Crater Lake Ave, Ste B Medford, OR 97504
3001071	Daniel F. Soteres, Colorado Springs, CO 80907	2709 North Tejon St Colorado Springs, CO 80907
3001074	William R. Lumry, Dallas, TX 75231	10100 N Central Expressway, Ste 125 Dallas, TX 75231
3001075	Mikhail Palatnik, Gold River, CA 95670	2485 Sunrise Blvd Gold River, CA 95670
3001076	Paul Y. Qaqundah, Huntington Beach, CA 92647	17822 Beach Blvd, Ste 278 Huntington Beach, CA 92647
3001077	Weily Soong, Birmingham, AL 35209	504 Brookwood Blvd, Ste 250 Birmingham, AL 35209
3001078	Selwyn Spangenthal, Charlotte, NC 28207	1918 Randolph Rd, Ste 440 Charlotte, NC 28207
*3001079	William W. Storms, Colorado Springs, CO 80907	1625 Medical Center Point, Ste 190 Colorado Springs, CO 80907
3001080	Martha V. White, Wheaton, MD 20902	11002 Veirs Mill Rd, Ste 414 Wheaton, MD 20902
3001081	Isaac R. Melamed, Centennial, CO 80112	6801 S. Yosemite St Centennial, CO 80112
3001082	Vosudesh K. Pai, Lawrenceville, GA 30046	555 Old Norcross Rd, Ste 250 Lawrenceville, GA 30046
3001083	Paul A. Shapero, Bangor, ME 04401	700 Mt. Hope Ave, Ste 430 Bangor, ME 04401

3001084	Daniel Sousa, Fall River, MA 02720	373 New Boston Rd Fall River, MA 02720
3001085	Sheldon Spector, Los Angeles, CA 90025	11645 Wilshire Blvd, Ste 1155 Los Angeles, CA 90025
3001086	Gary C. Steven, Greenfield, WI 53228	8585 W Forest Home Ave, Ste 200 Greenfield, WI 53228
3001087	Manuel A. Fernandez- Gonzalez, Miami, FL 33135	590 SW 27th Ave Miami, FL 33135
3001088	Agustin J. Latorre, Miami, FL 33155	6850 Coral Way, Ste 409 Miami, FL 33155
3001089	Robert S. Call, Henrico, VA 23233	9920 Independence Park Dr, Ste 101 Henrico, VA 23233
3001090	Marcy Jo Gousse, Smithfield, PA 15478	100 Ridge View Dr, Ste 3 Smithfield, PA 15478
3001091	Anoshie Ratnayake, Costa Mesa, CA 92626	3545 Howard Way Costa Mesa, CA 92626
3001092	Marvin Kalafer, Jenkintown, PA 19046	815 Greenwood Ave, Ste 12 Jenkintown, PA 19046
3001093	Santiago Reyes, Oklahoma City, OK 73112	3366 NW Expressway, Bldg D, Ste 330 Oklahoma City, OK 73112
3001095	Karl V. Sitz, Little Rock, AR 72205	18 Corporate Hill, Ste 110 Little Rock, AR 72205
3001096	Stephen G. Basheda, Pittsburgh, PA 15243	1050 Bower Hill Rd, Ste 307 Pittsburgh, PA 15243
3001097	Iftikhar Hussain, Tulsa, OK 74136	7307 S. Yale Ave, Ste 200 Tulsa, OK 74136
3001100	Manav Singla, White Marsh, MD 21162	Asthma Allergy & Sinus Center 5430 Campbell Blvd, Ste 103 White Marsh, MD 21162
3001102	Daniel Rodriguez, New Port Richey, FL 34653	Advanced Research Institute, Inc. 7114 Congress St New Port Richey, FL 34653
3001104	Edward Joseph Campbell, Provo, UT 84604	2230 North at University Pkwy Cottontree Square, Bldg 6A Provo, UT 84604
3001107	Stephen Ryan, Tacoma, WA 98405	316 Martin Luther King Jr. Way, Ste 401 Tacoma, WA 98405
3001108	Tonny Tanus, Bakersfield, CA 93301	2116 17th St Bakersfield, CA 93301

	3001109	Carl Thornblade, Missoula, MT 59808	2683 Palmer St, Ste B Missoula, MT 59808
	3001111	Miguel E. Trevino, Clearwater, FL 33756	1573 South Fort Harrison Ave Clearwater, FL 33756
	3001112	Steven F. Weinstein, Huntington Beach, CA 92647	Allergy and Asthma Specialists Medical Group 17742 Beach Blvd, Ste 310 Huntington Beach, CA 92647
	3001114	David Fuentes, Boerne, TX 78006	1420 River Rd, Ste 100 Boerne, TX 78006
	3001115	Susan L. Andrew, Dickinson, TX 77539	914 FM 517 Road West Dickinson, TX 77539
	*3001116	William L. Ebbeling, Fresno, CA 93720	1646 E. Herndon Ave, Ste 106 Fresno, CA 93720
	3001119	Bruce A. DeCotiis, Brick, NJ 08724	1673 Hwy 88 West Brick, NJ 08724
	3001120	Ernesto Diaz, Coral Gables, FL 33134	5200 SW 8th St, Ste 119- 120 Coral Gables, FL 33134
	3001122	Lawrence P. Landwehr, Warrensburg, MO 64093	407A East Russell Ave, Ste 3 Warrensburg, MO 64093
Clinical Site Address	Please see table above		
Study Number (s)	MGR000-1003		
Study Type (s)	Flow Profiling		
Strength (s)	N/A (empty inhaler which did not contain drug or placebo)		
Clinical Site	Site	Principal Investigator	Address
	1	Dominik Kappeler	Inamed Clinical Unit, 82131 Gauting, Germany
	2	Isabelle Schenkenberger	Clinical Research Berlin GbR; 10787 Berlin, Germany
	3	Prof. Dr. med. Walter Dorsch	Practice for Child and Adolescent Medicine, Allergy, Pediatric Pulmonology, Naturopathic, 81379 Munich, Germany
	4	Dr. med. Manfred Praun	Practice for Child and Adolescent Medicine Dr. Praun & Dr. Stiebing, 82205 Gilching, Germany
	5 (not activated)	Prof. Dr. med. Stefan Zielen	University Hospital Johann Wolfgang Goethe-Universität Frankfurt/Main,

			Centre for children and adolescents, Departement of paediatric pneumology, allergology and cystic fibrosis, 60590 Frankfurt/Main, Germany
Clinical Site Address	Please see table above		
Study Number (s)	MGR000-1004		
Study Type (s)	Device Orientation		
Strength (s)	N/A (empty inhaler which did not contain drug or placebo)		
Market Research Facilities^S	(b) (4)		
Market Research Facilities^S Address	Please see table above		
OSI Status	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete ☐ N/A (Waiver) ²	<u>Post October 1, 2014 ANDAs</u> ☐ To Be Determined by OSIS ☐ Pending ☒ Complete	
Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☐ Not granted ☒ N/A		
QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ N/A		
Formulation	☒ Adequate ☐ Inadequate		
Will Response to CR Result in a Reformulation?	☐ Possibly ☒ No ☐ N/A		
BE Guidance Version Used for Evaluation of Current ANDA	Draft Guidance on Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder (Recommended Sep 2013)		
Deficiency Classification	☒ Major (Deficiencies to be communicated by CR) ☐ Minor ☐ N/A (Review is Adequate)		
Overall Review Result	☐ Adequate ☒ Inadequate		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		

² Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1,2,10,14	Fasting	100/50 mcg	INCOMPLETE
1,2,10,14	Fasting	500/50 mcg	INCOMPLETE
1,2,10,14	Fasting (Failed, but was used in pooled analysis by the firm with MGR001-1014)	250/50 mcg	UNACCEPTABLE
1,2,10,14	Fasting (Failed, but was used in pooled analysis by the firm with MGR001-1005)	250/50 mcg	UNACCEPTABLE
1,10,14	In Vitro BE (SAC and APSD)	100/50 mcg	INCOMPLETE
1,10,14	In Vitro BE (SAC and APSD)	250/50 mcg	INCOMPLETE
1,10,14	In Vitro BE (SAC and APSD)	500/50 mcg	INCOMPLETE
1,10,14	Pressure Differential (4 kPa) (SAC and APSD)	100/50 mcg	UNACCEPTABLE
1,10,14	Pressure Differential (4 kPa) (SAC and APSD)	250/50 mcg	UNACCEPTABLE
1,10,14	Pressure Differential (4 kPa) (SAC and APSD)	500/50 mcg	UNACCEPTABLE
1,2	Clinical Endpoint	100/50 mcg	INCOMPLETE
1,2,10	Flow Profiling	N/A (empty inhaler which did not contain drug or placebo)	UNACCEPTABLE
1,8 [@] ,11 [@] ,14	Device Orientation	N/A (empty inhaler which did not contain drug or placebo)	UNACCEPTABLE

[@] Submission in response to Office of Surveillance and Epidemiology (OSE)/ Division of Medication Error Prevention and Analysis (DMEPA)'s ECD [issued through Division of Bioequivalence I (DBI)], which is reviewed by DMEPA for their response to DBI's consult request for evaluation of the firm's device orientation study.

* The firm stated that these sites screened subjects but did not enroll any subjects.

[§] The firm stated that these sites provided the facility in which user handling sessions were conducted; these facilities provided no other function or resource in the user handling assessment

1 EXECUTIVE SUMMARY

This is the *first generic* drug application.

Mylan Pharmaceuticals Inc. has submitted the current application for Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder, 0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ 0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation. The test product, also referred to as MGR001 by the firm, contains fluticasone propionate (FP) and salmeterol xinafoate (SX) inhalation powder in CRC749 inhaler device. The reference-listed drug (RLD) is Advair Diskus® 100/50 (fluticasone propionate and salmeterol xinafoate), 0.1 mg/EQ 0.05 mg base per inhalation; Advair Diskus® 250/50 (fluticasone propionate and salmeterol xinafoate), 0.25 mg/EQ 0.05 mg base per inhalation; and Advair Diskus® 500/50 (fluticasone propionate and salmeterol xinafoate), 0.5 mg/EQ 0.05 mg base per inhalation manufactured by GLAXO GRP LTD (approved on August 24, 2000 under NDA 021077).

Consistent with the current Draft Bioequivalence (BE) Guidance on Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder (recommended Sep 2013)³ (product-specific guidance), the firm submitted results of the following studies comparing the test and RLD products:

- Four fasting pharmacokinetic (PK) BE studies (#MGR001-1006 for the 100/50 mcg strength, #s MGR001-1005 and MGR001-1014 for the 250/50 mcg strength, and #MGR001-1007 for the 500/50 mcg strength)
- One clinical endpoint study (#MGR001-3001 at the 100/50 mcg strength)
- Two types [single actuation content (SAC) and aerodynamic particle size distribution (APSD)] of in vitro BE studies for each of the three strengths of the drug product (#057755-02-04 for the 100/50 mcg strength, #MGR-PRO-2015-080 for the 250/50 mcg strength, and #057755-02-07 for the 500/50 mcg strength)

In addition, as recommended by the Agency to the firm during pre-ANDA communications^{4,5} due to difference in device resistance and device orientation as compared to the RLD product, the firm also submitted the following studies:

- Two types (SAC and APSD) of in vitro studies at 4 kPa fixed pressure drop for each of the three strengths of the drug product (#MGR-REP-2015-092 for the 100/50 mcg strength, # MGR-PRO-REP-2015-103 for the 250/50 mcg strength, and #057755-02-08 for the 500/50 mcg strength) comparing the test and RLD products
- One flow profiling study (#MGR000-1003) comparing the empty test and RLD devices
- One device orientation study (#MGR000-1004) using empty test device

The findings and outcome of the studies are summarized as follows:

³<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM367643.pdf> Last accessed: 12/16/2016.

⁴<\\cdsnas\OGDS6\CONTROLS\2012-docs\12-0731.pdf>

⁵<\\cdsnas\OGDS6\CONTROLS\2013-docs\13-0422.pdf>

Fasting studies

Each of the fasting BE studies was designed as a single-dose, two-way crossover study on healthy male and female subjects. And fasting studies were conducted on all strengths of the drug products.

100/50 mcg strength

The firm's fasting BE study for the 100/50 mcg strength is **inadequate** due to method validation deficiencies. The reviewer's results are summarized in the table below.

Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder 3 x 100/50 mcg Fasting Bioequivalence Study, Study No. MGR001-1006, N=64 (Male=36 and Female=28) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
FP							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
<u>Group 1</u>							
LAUCT (hr *pg/ml)	567.02	20	581.56	20	0.98	91.27	104.16
LAUCI (hr *pg/ml)	592.74	20	607.71	20	0.98	91.39	104.10
LCMAX (pg/ml)	99.92	20	107.96	20	0.93	86.12	99.47
<u>Group 2</u>							
LAUCT (hr *pg/ml)	611.59	20*	557.84	20*	1.10	102.38	117.40
LAUCI (hr *pg/ml)	637.68	20*	579.28	20*	1.10	102.94	117.72
LCMAX (pg/ml)	104.88	20*	110.89	20*	0.95	87.75	101.96
<u>Group 3</u>							
LAUCT (hr *pg/ml)	702.22	22	657.49	22	1.07	100.47	113.53
LAUCI (hr *pg/ml)	733.11	22	685.59	22	1.07	100.78	113.46
LCMAX (pg/ml)	111.69	22	122.54	22	0.91	83.36	99.66
SA							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
<u>Group 1, 2 and 3</u>							
LAUCT (hr *pg/ml)	712.40	60^	659.12	60^	1.08	104.81	111.46
LAUCI (hr *pg/ml)	745.82	60^	692.05	60^	1.08	104.65	110.98
LCMAX (pg/ml)	347.94	60^	349.15	60^	1.00	94.35	105.26

* Subjects (b) (6) were excluded by the reviewer due to missing samples that potentially affect Cmax.
^ Subjects (b) (6) were excluded by the reviewer due to missing samples that potentially affect Cmax.

Note: The subjects were dosed in 3 groups. For FP, the treatment*group interaction was statistically significant ($p < 0.1$) for LAUC_{0-t} and LAUC_{0-∞}, and was not statistically significant ($p > 0.1$) for LCmax, thus the reviewer calculated 90% CIs of PK parameters for each group separately as per the current Division of Bioequivalence (DB) practice. For SA, the treatment*group interaction was not statistically significant ($p > 0.1$) for LAUC_{0-t}, LAUC_{0-∞} and LCmax, thus the reviewer combined three groups for statistical analysis as per the current DB practice.

250/50 mcg strength

The firm conducted 2 PK studies for the 250/50 mcg strength. The first study MGR001-1005 did not meet the BE criteria, and the firm repeated the study in MGR001-1014 using a different RLD batch, which also failed to meet BE criteria. The firm then conducted a pooled analysis of these 2 failed studies, and stated that the pooled analysis met the BE criteria. According to the consult response⁶ from Office of Translational Science (OTS)/ Office of Biostatistics (OB)/ Division of Biostatistics VIII (DBVIII) on this issue, the firm's pooled analysis is not acceptable from the statistical point of view. Therefore, both of the 2 PK studies are **unacceptable** because they each failed to meet the BE criteria of 80.00-125.00%. The reviewer's results are summarized in the table below.

MGR001-1005

Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder 3 x 250/50 mcg Fasting Bioequivalence Study, Study No. MGR001-1005, N=66 (Male=35 and Female=31) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
FP							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
Group 1							
LAUCT (hr *pg/ml)	1882.22	22	1493.75	22	1.26	115.59	137.36
LAUCI (hr *pg/ml)	1966.71	22	1548.13	22	1.27	116.35	138.70
LCMAX (pg/ml)	242.69	22	201.03	22	1.21	110.85	131.47
Group 2							
LAUCT (hr *pg/ml)	1901.97	21*	1460.99	21*	1.30	123.85	136.85
LAUCI (hr *pg/ml)	2007.77	21*	1516.38	21*	1.32	126.20	138.91
LCMAX (pg/ml)	253.74	21*	209.02	21*	1.21	114.12	129.13
Group 3							
LAUCT (hr *pg/ml)	1963.37	20^	1628.03	20^	1.21	113.35	128.31
LAUCI (hr *pg/ml)	2079.71	20^	1689.37	20^	1.23	115.82	130.85
LCMAX (pg/ml)	263.01	20^	242.29	20^	1.09	103.34	114.02
SA							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
Group 1, 2 and 3							
LAUCT (hr *pg/ml)	851.86	62#	708.72	62#	1.20	115.51	125.07
LAUCI (hr *pg/ml)	893.17	62#	744.37	62#	1.20	115.44	124.72
LCMAX (pg/ml)	485.94	62#	401.57	62#	1.21	114.44	127.96

* Subject (b) (6) was excluded by the reviewer due to missing samples that potentially affect Cmax.
 ^ Subjects (b) (6) were excluded by the reviewer due to missing samples that potentially affect Cmax.
 # Subjects (b) (6) were excluded by the reviewer due to missing samples that potentially affect Cmax.

⁶ GDRP: ANDA 208891, Documents, A208891_Statistical_PK.doc, 12/13/2016.

Note: The subjects were dosed in 3 groups. For FP, the treatment*group interaction was statistically significant (p<0.1) for LCmax, and was not statistically significant (p>0.1) for LAUC_{0-t} and LAUC_{0-∞}, thus the reviewer calculated 90% CIs of PK parameters for each group separately as per the current Division of Bioequivalence (DB) practice. For SA, the treatment*group interaction was not statistically significant (p>0.1) for LAUC_{0-t}, LAUC_{0-∞} and LCmax, thus the reviewer combined three groups for statistical analysis as per current DB practice.

MGR001-1014

Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder 3 x 250/50 mcg Fasting Bioequivalence Study, Study No. MGR001-1014, N=65 (Male=35 and Female=30) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
FP							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
Group 1, 2 and 3							
LAUCT (hr *pg/ml)	1449.73	63*^#	1516.15	63*^#	0.96	91.43	100.00
LAUCI (hr *pg/ml)	1531.99	63*^#	1581.09	63*^#	0.97	92.60	101.39
LCMAX (pg/ml)	189.23	63*^#	228.89	63*^#	0.83	79.03	86.48
SA							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
Group 1, 2 and 3							
LAUCT (hr *pg/ml)	723.85	61^#@	745.80	61^#@	0.97	93.78	100.45
LAUCI (hr *pg/ml)	758.82	61^#@	782.61	61^#@	0.97	93.77	100.26
LCMAX (pg/ml)	329.05	61^#@	400.73	61^#@	0.82	76.87	87.71

* Subject (b) (6) was excluded by the reviewer due to missing samples that potentially affect Cmax.
 ^ Subject (b) (6) was excluded by the reviewer due to carryover blank issue in the corresponding bioanalytical run.
 # The last 2 time points (36 and 48 hrs) for Subject (b) (6) Period 2 was treated as missing by the reviewer due to administration of laxative with unknown ingredient.
 @ Subjects (b) (6) were excluded by the reviewer due to missing samples that potentially affect Cmax.

Note: The subjects were dosed in 3 groups. For both FP and SA, the treatment*group interaction was not statistically significant (p>0.1) for LAUC_{0-t}, LAUC_{0-∞} and LCmax, thus the reviewer combined three groups for statistical analysis as per the current DB practice.

500/50 mcg

The firm’s fasting BE study for the 500/50 mcg strength is **inadequate** due to method validation deficiencies. The reviewer’s results are summarized in the table below.

Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder 3 x 500/50 mcg Fasting Bioequivalence Study, Study No. MGR001-1007, N=65 (Male=24 and Female=41) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
FP							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
Group 1, 2 and 3							
LAUCT (hr *pg/ml)	2763.22	64*	2865.93	64*	0.96	92.43	100.58
LAUCI (hr *pg/ml)	2947.30	64*	3004.17	64*	0.98	94.09	102.30
LCMAX (pg/ml)	253.89	64*	283.06	64*	0.90	86.15	93.38
SA							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
Group 1, 2 and 3							
LAUCT (hr *pg/ml)	686.10	61^	684.20	61^	1.00	96.13	104.61
LAUCI (hr *pg/ml)	716.94	61^	717.53	61^	1.00	95.95	104.05
LCMAX (pg/ml)	335.10	61^	387.72	61^	0.86	81.57	91.58

* Subject ^{(b) (6)} was excluded by the reviewer due to missing samples that potentially affect Cmax.

^ Subject #s ^{(b) (6)} were excluded by the reviewer due to missing samples that potentially affect Cmax.

Note: The subjects were dosed in 3 groups. For both FP and SA, the treatment*group interaction was not statistically significant ($p>0.1$) for LAUC_{0-t}, LAUC_{0-∞} and LCmax, thus the reviewer combined three groups for statistical analysis as per the current DB practice.

Two types of in vitro BE studies (SAC and APSD) for each of the 3 strengths

All of the in vitro BE studies are **incomplete** due to multiple deficiencies.

Clinical endpoint study

The study was designed as a randomized, double-blind, double-dummy, placebo-controlled, parallel group design consisting of a 4 week run-in period followed by a 4-week treatment period. The clinical endpoint study is **incomplete** due to missing information on study design and Office of Study Integrity and Surveillance (OSIS) inspectional deficiencies. In addition, Division of Clinical Review (DCR)'s per-protocol set (PPS) recommendation, which is required for the Agency's statistical analysis of the current study, is pending the firm's response to the current complete response (CR). The firm's results are summarized in the table below. Please note that these results are subject to change upon evaluation of the firm's CR response.

Per Sponsor			
Primary Endpoint 1 (continuous endpoint)			
	Test	Reference	Placebo
PP Population	Endpoint: Change from baseline AUEC ₀₋₁₂ FEV ₁ on Day 1		
N	502	502	101
LS Mean	3.9734 (L.hr)	3.5411 (L.hr)	0.8400 (L hr)
90% CI for Test and Reference for Mean Response (e.g., test/reference or test-reference)	Ratio of LS means (test/reference): 1.120 90% CI: 1.016, 1.237		Not applicable
90% CI for Test and Reference for Median Response (e.g., test/reference or test-reference)	Not applicable		Not applicable
mITT* Population			
N	508	510	102
LS Mean	3.9534 (L.hr)	3.4964 (L.hr)	0.8191 (L hr)
(Test or Reference) vs. Placebo (p-value)	3.1343 (L.hr) (p<0.0001)	2.6773 (L.hr) (p<0.0001)	Not applicable

* The term 'Full Analysis Set (FAS)' is used in place of 'mITT' in the MGR001-3001 Clinical Study Report.

Per Sponsor			
Primary Endpoint 2 (continuous endpoint)			
	Test	Reference	Placebo
PP Population	Endpoint: Change from baseline Trough FEV ₁ on Day 29 (± 2 days)		
N	498	497	99
LS Mean	0.2911 (L)	0.2728 (L)	0.0574 (L)
90% CI for Test and Reference for Mean Response (e.g., test/reference or test-reference)	Ratio of LS means (test/reference): 1.069 90% CI: 0.938, 1.220		Not applicable
90% CI for Test and Reference for Median Response (e.g., test/reference or test-reference)	Not applicable		Not applicable
mITT* Population			
N	504	505	100
LS Mean	0.2927 (L)	0.2720 (L)	0.0575 (L)
(Test or Reference) vs. Placebo (p-value)	0.2352 (L) (p<0.0001)	0.2145 (L) (p<0.0001)	Not applicable

* The term 'Full Analysis Set (FAS)' is used in place of 'mITT' in the MGR001-3001 Clinical Study Report.

Two types of in vitro studies (SAC and APSD) at 4 kPa fixed pressure drop for each of the 3 strengths

All of the in vitro studies at 4 kPa fixed pressure drop are **unacceptable** due to insufficient number of units used in the study.

Flow Profiling Study

The flow profiling study was designed as an open label two-way crossover study using empty devices on healthy adult subjects, children with asthma (aged 4-7 years), children with asthma (aged 8-11 years), adult subjects with severe asthma, and adult subjects with severe chronic obstructive pulmonary disease (COPD). The flow profiling study is **unacceptable** due to the use of non-US reference product.

Device orientation study

The device orientation study was designed as an open label study using empty test devices on adolescent (aged 12 years old or older) and adult patients diagnosed with asthma and/or COPD. The firm's device orientation study is **unacceptable**. According to the consult response from the Office of Surveillance and Epidemiology (OSE)/ Division of Medication Error Prevention and Analysis (DMEPA),⁷ the firm conducted a non-comparative HFS. The firm has not provided data, such as data from a comparative use human factors study that assesses the differences in use error rates between the proposed product and the RLD. Such data may be warranted to assess the acceptability of the differences in device and labeling resulting from these differences in user interface between the proposed product and the RLD and to help evaluate whether the proposed product can be substituted for the RLD with the full expectation that the proposed product will produce the same clinical effect and safety under the conditions specified in labeling.

Formulation

The formulation of firm's test product is quantitatively (Q1) and qualitatively (Q2) the same as that of the RLD product. The formulation is considered acceptable from BE perspective. It should be noted that the firm did not provide information on (b) (4), and thus will be asked to provide so. The acceptability of (b) (4) is deferred to Office of Product Quality (OPQ).⁸

OSIS inspection

OSIS inspection is complete for the clinical and analytical sites used in PK studies, clinical sites used in clinical endpoint studies, as well as analytical sites used in in vitro BE studies.

For the PK studies, OSIS issued a decline-to-inspect memo for the clinical site (Worldwide Clinical Trials Early Phase Services, LLC, San Antonio, TX), and the OSIS

⁷ DARRTS: ANDA 208891, REV-SURVEPI-24(Human Factors Review), 3/16/2017.

⁸ V:\DIVISION\BIO\BIO1\Email Reference\208891 Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder\ RE API (b) (4) for Mylan's fluticasonesalmeterol DPI A208891.msg

outcome was voluntary action indicated (VAI) for the analytical portion of the study. OSIS findings at the analytical site (Mylan Pharmaceuticals Inc., Morgantown, WV) are not expected to have impact on the outcome of the inspected studies (MGR001-1006, MGR001-1007, and MGR001-1014) in the current ANDA. For the in vitro studies, OSIS issued a decline-to-inspect memo for one of the analytical sites (Mylan Global Respiratory Group, Kent, UK), and the OSIS outcome was VAI for the other analytical site (b)(4). The firm will be asked to provide additional information based on OSIS findings. For the clinical endpoint study, out of 16 inspected sites, the OSIS outcome was VAI for 7 sites, and no action indicated (NAI) for the other 9 sites. The firm will be asked to provide additional information based on OSIS findings.

Please note that on 3/2/2017, the firm submitted in vitro BE study data conducted using test products manufactured (b)(4) and the corresponding strength of the RLD products. This is to support the firm's proposal of (b)(4)

(b)(4). Please note that this 3/2/2017 submission is submitted during the late stage of the current review cycle (GDUFA goal date of 3/28/2017), and thus is not reviewed in the current BE review. The firm will be notified that the BE-related deficiencies communicated to them in the current CR letter are based on their BE-related submissions prior to this 3/2/2017 submission.

The application is **inadequate** with deficiencies.

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3 BACKGROUND

3.1 Background about the Firm's Pre-ANDA Communications

The firm (Mylan) acquired MGR001 in 12/2011 from Pfizer Inc. (Pfizer).⁹ Prior to ANDA submission, the Agency had 2 meetings with Pfizer and 3 meetings with Mylan:

- 12/3/2009 face-to-face meeting with Pfizer [control correspondence (CC) 09-0478] (regarding FP monotherapy in CRC749 inhaler device)
- 5/12/2010 face-to-face meeting with Pfizer (DARRTS meeting ID 028726)
- 12/12/2012 teleconference with Mylan (CCs 12-0731 and 12-0850)
- 9/27/2013 face-to-face meeting with Mylan (CCs 13-0422 and 13-0422A)
- 10/22/2015 face-to-face meeting with Mylan (GDRP Meeting Request 844398)

The firm also submitted other pre-ANDA communications:

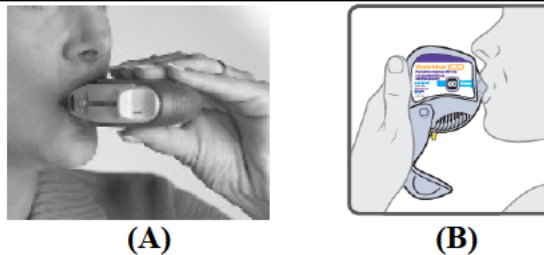
- CC 26230 (for device orientation study protocol)
- IND 118769 (for PK study, device orientation study, trade name review request, etc.)

In some of these pre-ANDA communications, the Agency recommended additional justification/study data to be provided in addition to the studies recommended by the product-specific guidance. The Agency's concerns and recommended additional studies are detailed below.

According to CC 12-0731¹⁰, there are 2 key device differences between the MGR001 and the RLD:

- 1) MGR001 **device airflow resistance** is almost $\frac{(b)}{(4)}\%$ ¹¹ higher than that of RLD.
- 2) The proposed **orientation** of the use of MGR001 is vertical while of RLD is horizontal (please see figure below).

Orientation of use of Advair® Diskus® (A) and the test product MGR001 (B).



According to this CC12-0731¹², the Agency considers the test device still appropriate for the 505(j) regulatory pathway.

⁹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 2.5\Clinical Overview, p. 3 of 21).

¹⁰ \\cdsnas\OGDS6\CONTROLS\2012-docs\12-0731.pdf, p. 9 of 34.

¹¹

(b) (4)

(b) (4)

However, to address some residual uncertainties due to **device resistance differences**, the Agency, according to CC12-0731¹³, recommends the firm to *either*:

- i) Modify the device to attain similar resistance as the RLD, i.e., $\pm 15\%$ of the RLD,
or
- ii) Provide justification/data [e.g., comparisons of inspiratory flow rates or profiles generated by relevant patients for the test and reference dry powder inhalers (DPIs)] to support that this difference in the device resistance does not impact therapeutic equivalence of the proposed generic and the RLD.

Additionally in CC13-0422¹⁴, the Agency recommends the firm to provide:

- iii) The SAC and APSD results for MGR001 and RLD measured at flow rates that produce 4 kPa pressure drop¹⁵ across the corresponding inhalers.
and
- iv) Justification that the airflow resistance difference between MGR001 and RLD does not impact the usability of their proposed generic product. This may be achieved by conduct of a patient survey as part of the clinical endpoint BE study to evaluate/capture patients' experience with the use of MGR001.

In the current application, the firm provided information on ii), iii) and iv) above, which include:

- A flow profiling study in healthy subjects and patients (Study MGR000-1003, which is evaluated in Section 5.5),
- Justification to support that this difference in the device resistance does not impact therapeutic equivalence of the test and RLD product (evaluated in Section 5.3.1.2),
- In vitro study at 4 kPa fixed pressure drop (Studies MGR-REP-2015-092, MGR-PRO-REP-2015-103 and 057755-02-08, which are evaluated in Section 5.3.3), and
- Device questionnaire in the clinical endpoint study (evaluated in Section 5.4.9).

According to CC12-0731¹⁶, the Agency is also concerned about the **difference in the orientation** of use between the MGR001 and the RLD product. Some patients may use MGR001 in the horizontal orientation (i.e., the orientation that patients use for Advair® Diskus®). Such an error may result in incomplete lip sealing around the mouthpiece and lead to different air flow pattern through the inhaler compared to when the test product is

¹² [\\cdsnas\OGDS6\CONTROLS\2012-docs\12-0731.pdf](#), p. 13 and 33 of 34.

¹³ [\\cdsnas\OGDS6\CONTROLS\2012-docs\12-0731.pdf](#), p. 13 of 34 (Question 3a).

¹⁴ [\\cdsnas\OGDS6\CONTROLS\2013-docs\13-0422.pdf](#) p. 28 of 28.

¹⁵ According to CC13-0422 (p. 21 of 28), “[i]n literature, it has been reported that patients produce around 4 kPa pressure drop across the inhaler when inhale against resistances typical for the marketed DPIs. Comparable emitted dose and fine particle mass measured at 4kPa pressure drop for both the devices can provide additional confirmation that resistance difference between the RLD and MGR001 is acceptable.”

¹⁶ [\\cdsnas\OGDS6\CONTROLS\2012-docs\12-0731.pdf](#), p. 16-17 of 34 (Question 8).

used correctly (i.e. vertically). The Agency recommends that the firm to demonstrate *one of the following*:

- i) Low likelihood of the orientation-related errors when MGR001 is used by the patients including prior Advair® Diskus® users.
- ii) Inhalation profiles through inhaler (i.e. peak inhalation flow rate (PIFR) and total inhalation volume through inhaler)¹⁷ when used by the patients and the device retention (i.e. amount of drug retains in the device and air channel following inhalation) are comparable at both the (vertical and horizontal) orientations.

In the current application, the firm provided information on i) above, which is a

- Device orientation study (Study MGR000-1004, which is evaluated in Section 5.6).

3.2 Background about Review-Related Information

On 6/6/2016, Division of Bioequivalence I (DBI) sent consult request to OT/OB/DBVIII for statistical evaluation of the firm's clinical endpoint study data.¹⁸ On 8/12/2016, OTS provided their consult response to DBI.¹⁹

On 6/30/2016, DBI sent consult request to OSE/DMEPA for evaluation of the firm's device orientation study.²⁰ On 3/16/2017, DMEPA provided their consult response to DBI.²¹

On 6/30/2016, DBI met with the Office of Pharmaceutical Quality (OPQ) to discuss the approach for evaluating information submitted in this ANDA. It was determined that OPQ will review the device robustness study and DBI will review the device orientation study. In addition, DBI will review BE-related documents (e.g. in vitro BE studies) that were submitted in Module 3, as well as multiple pages that contain BE-related information (e.g. summary of PK studies, device orientation study) in pharmaceutical development report and container closure system in Module 3.

On 8/10/2016, DMEPA issued ECD to the firm through DBI. The firm's response was received on 8/11/2016.

On 8/16/2016, DBI met with DCR and it was determined that DCR will make per-protocol set (PPS) recommendation for the clinical endpoint study. This will be a separate

¹⁷ Footnote as in the CC review: "In the event of incomplete lip sealing around the mouthpiece of the inhaler, the patient may draw some portion of from the unsealed area around the mouthpiece. As a result, the amount and flow rate of air drawn through the inhaler by the patient may be less compared to the situation when the patient has complete lip sealing around the mouthpiece."

¹⁸ GDRP: ANDA 208891, Bioequivalence Primary Review, A208891_Consult to DBVIII.doc, 6/6/2016.

¹⁹ GDRP: ANDA 208891, Documents, A208891_Statistical.doc, 8/12/2016.

²⁰ GDRP: ANDA 208891, Documents, A208891_Consult to DMEPA.doc, 6/30/2016.

²¹ DARRTS: ANDA 208891, REV-SURVEPI-24(Human Factors Review), 3/16/2017.

review instead of a consult. Once DCR makes PPS recommendation, biostatistics reviewer will use this PPS to conduct statistical analysis, and statistical results will be sent to DBI.

On 8/29/2016, 8/30/2016 and 9/8/2016, DBI met with the Office of Regulatory Science (ORS), DCR and OTS to discuss questions regarding the clinical endpoint study for the current ANDA (b) (4) for FP/SX DPI (b) (4).²² Questions regarding the PK studies and in vitro studies in the current ANDA were also discussed.

On 9/9/2016, DBI issued an ECD to the firm. On 9/15/2016, the firm sent an email seeking clarification regarding one of the comments for this ECD. On the same day (9/15/2016), DBI responded to the firm's clarification email. The firm's ECD response was received on 9/22/2016.

On 10/21/2016, DBI sent consult request to OTS/OB/DBVIII for evaluation of whether the firm's pooled analysis of the 2 failed PK studies at the 250/50 mcg strength are acceptable.²³ On 12/13/2016, OTS provided their consult response to DBI.²⁴

On 12/29/2016, DBI issued another ECD to the firm. The firm's response was received on 1/12/2017.

On 1/17/2017, DBI sent OSIS inspection request consult to OSIS for routine inspection request of in vitro BE study sites, as it was not previously listed as a task in Generic Drug Review Platform (GDRP).²⁵ On 3/15/2017, OSIS provided the inspection report for one of the in vitro study sites (b) (4).²⁶ On 3/16/2017, OSIS issued decline to inspect memo for the other invitro study site (Mylan Global Respiratory Group).²⁷

On 1/18/2017, 1/19/2017 and 3/20/2017, DBI met with the Office of Bioequivalence (OB) management to discuss issues identified in the review.²⁸

Currently there are 2 citizen petitions related to the FP/SX DPI. On 12/16/2009, Ropes & Gray LLP, on behalf of GlaxoSmithKline, submitted a citizen petition to FDA (Docket No. FDA-2009-P-0597) regarding applications that reference generic copies of oral inhalation products containing fluticasone propionate and/or salmeterol xinafoate. (b) (4)

(b) (4)
The issues raised by these petitions are currently under review by the Agency, and FDA has not made a final

²² V:\DIVISION\BIO\BIO1\Meeting Minutes\DBI non-Bio Management Meeting\2016\ 08292016-09082016 ANDA 208891_(b) (4) Fluticasone_salmeterol DPI.doc.

²³ GDRP: ANDA 208891, Documents, A208891_Conult to DBVIII - PK.doc, 10/21/2016.

²⁴ GDRP: ANDA 208891, Documents, A208891_Statistical_PK.doc, 12/13/2016.

²⁵ GDRP: ANDA 208891, Documents, A208891_Conult to OSIS.doc, 1/17/2017.

²⁶ GDRP: ANDA 208891, In Vitro BE Sites, EIR Review (b) (4)_ANDA208891_final, 3/15/2017.

²⁷ GDRP: ANDA 208891, In Vitro BE Sites, Decline to Inspect_ANDA 208891_Mylan UK_Analy, 3/16/2017.

²⁸ V:\DIVISION\BIO\BIO1\Meeting Minutes\DBI non-Bio Management Meeting\2016\01182017-03202017 ANDA 208891_(b) (4) Fluticasone_salmeterol DPI.doc.

decision on these issues. The reviewer's comments and deficiency comments in this review reflect only our current thinking.

APPEARS THIS WAY ON
ORIGINAL

4 SUBMISSION SUMMARY

4.1 Drug Product Information²⁹

Test Product	Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder, 0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ 0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation
Reference Product	Advair Diskus® 100/50 (fluticasone propionate and salmeterol xinafoate), 0.1 mg/EQ 0.05 mg base per inhalation; Advair Diskus® 250/50 (fluticasone propionate and salmeterol xinafoate), 0.25 mg/EQ 0.05 mg base per inhalation; and Advair Diskus® 500/50 (fluticasone propionate and salmeterol xinafoate), 0.5 mg/EQ 0.05 mg base per inhalation
RLD Manufacturer	GLAXO GRP LTD
NDA No.	021077
RLD Approval Date	August 24, 2000
Indication³⁰	ADVAIR DISKUS is a combination product containing a corticosteroid and a LABA indicated for: • Treatment of asthma in patients aged 4 years and older. • Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). Important limitation: • Not indicated for the relief of acute bronchospasm.

4.2 PK/PD Information³⁰

Bioavailability	<u>Fluticasone Propionate</u> <u>Healthy subjects</u> Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Trials using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed. Absolute bioavailability of fluticasone propionate was 5.5% following administration of ADVAIR DISKUS. <u>Salmeterol Xinafoate</u> <u>Healthy Subjects</u> Salmeterol acts locally in the lung; therefore, plasma levels do not

²⁹ Online Orange Book:

http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021077&TABLE1=OB_Rx
Last accessed: 7/17/2016.

³⁰ DailyMed: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4eeb5f6a-593f-4a9e-9692-adea2caf8fc> Last accessed: 7/17/2016.

	predict therapeutic effect.
Food Effect	Not specified in the RLD labeling.
Tmax	<u>Fluticasone Propionate</u> <u>Healthy subjects</u> Following administration of ADVAIR DISKUS to healthy adult subjects, peak plasma concentrations of fluticasone propionate were achieved in 1 to 2 hours. <u>Salmeterol Xinafoate</u> <u>Healthy Subjects</u> Following administration of ADVAIR DISKUS to healthy adult subjects, peak plasma concentrations of salmeterol were achieved in about 5 minutes. <u>Subjects With Asthma</u> Following chronic administration of an inhaled dose of 50 mcg of salmeterol inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7 subjects with asthma.
Metabolism	<u>Fluticasone Propionate</u> The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the CYP3A4 pathway. This metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man. <u>Salmeterol Xinafoate</u> Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominantly in the feces. No significant amount of unchanged salmeterol base was detected in either urine or feces. An in vitro study using human liver microsomes showed that salmeterol is extensively metabolized to α-hydroxysalmeterol (aliphatic oxidation) by CYP3A4. Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of α-hydroxysalmeterol in vitro.
Excretion	<u>Fluticasone Propionate</u> Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites. <u>Salmeterol Xinafoate</u> In 2 healthy adult subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days.
Half-life	<u>Fluticasone Propionate</u> Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours.

	Terminal half-life estimates of fluticasone propionate for ADVAIR HFA, ADVAIR DISKUS, and fluticasone propionate CFC inhalation aerosol were similar and averaged 5.6 hours. <u>Salmeterol Xinafoate</u> The terminal elimination half-life was about 5.5 hours (1 volunteer only). The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (greater than 99%) and has a long elimination half-life of 11 days. No terminal half-life estimates were calculated for salmeterol following administration of ADVAIR DISKUS.
Dosage and Administration	ADVAIR DISKUS should be administered as 1 inhalation twice daily by the orally inhaled route only. After inhalation, the patient should rinse his/her mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis. More frequent administration or a greater number of inhalations (more than 1 inhalation twice daily) of the prescribed strength of ADVAIR DISKUS is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. Patients using ADVAIR DISKUS should not use additional LABA for any reason. <u>Asthma</u> If asthma symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate relief. <u>Adult and Adolescent Patients Aged 12 Years and Older:</u> For patients aged 12 years and older, the dosage is 1 inhalation twice daily, approximately 12 hours apart. The recommended starting dosages for ADVAIR DISKUS for patients aged 12 years and older are based upon patients' asthma severity. The maximum recommended dosage is ADVAIR DISKUS 500/50 twice daily. Improvement in asthma control following inhaled administration of ADVAIR DISKUS can occur within 30 minutes of beginning treatment, although maximum benefit may not be achieved for 1 week or longer after starting treatment. Individual patients will experience a variable time to onset and degree of symptom relief. For patients who do not respond adequately to the starting dosage after 2 weeks of therapy, replacing the current strength of ADVAIR DISKUS with a higher strength may provide additional improvement in asthma control. If a previously effective dosage regimen fails to provide adequate improvement in asthma control, the therapeutic regimen should be reevaluated and additional therapeutic options (e.g., replacing the current strength of ADVAIR DISKUS with a higher strength, adding additional

	inhaled corticosteroid, initiating oral corticosteroids) should be considered. <u>Pediatric Patients Aged 4 to 11 Years:</u> For patients with asthma aged 4 to 11 years who are not controlled on an inhaled corticosteroid, the dosage is 1 inhalation of ADVAIR DISKUS 100/50 twice daily, approximately 12 hours apart. <u>Chronic Obstructive Pulmonary Disease</u> The recommended dosage for patients with COPD is 1 inhalation of ADVAIR DISKUS 250/50 twice daily, approximately 12 hours apart. If shortness of breath occurs in the period between doses, an inhaled, short-acting beta -agonist should be taken for immediate relief.
Maximum Daily Dose	1 mg/EQ 0.1 mg base (ADVAIR DISKUS 500/50 twice daily).
Drug Specific Issues (if any)	WARNING: ASTHMA-RELATED DEATH Long-acting beta -adrenergic agonists (LABA), such as salmeterol, one of the active ingredients in ADVAIR DISKUS, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of salmeterol with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 subjects on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

4.3 OGD Recommendations for Drug Product

Number of studies recommended:	2 in vitro studies for each strengths of the product, 1 fasting PK BE studies for each strength of the product, and 1 clinical endpoint study for the lowest strength of the product

In vitro studies

The following in vitro studies are recommended to be conducted for all strengths of the T and R products. For each strength, these in vitro studies should be conducted using at least 3 batches each of T and R products with no fewer than 10 units from each batch.

1.	Type of study:	Single actuation content (SAC)
	Design:	The SAC test should be performed at the beginning (B), middle (M), and end (E) lifestages ³¹ of the product using flow rates of 30 L/min, 60 L/min and 90 L/min. The USP <601> Apparatus B or another appropriate apparatus may be used to determine the SAC using a validated assay. The number of actuations per determination should be one. The volume of air drawn through the delivery system should be 2 L.
	Equivalence based on:	Population bioequivalence (PBE) analysis of SAC. Please refer to the draft Budesonide Inhalation Suspension BE Guidance for additional information regarding PBE. ³²

2.	Type of study:	Aerodynamic particle size distribution (APSD)
	Design:	The APSD test should be performed at the B and E lifestages of the product using flow rates of 28.3 L/min or 30 L/min, 60 L/min and 90 L/min. The USP <601> Apparatus 3, Apparatus 5, or another appropriate method may be used to determine APSD using a validated assay. The APSD determination of each unit should be performed with a minimum number of inhalations justified by the sensitivity of the validated assay. The volume of air drawn through the delivery system should be 4 L.
	Equivalence based on:	PBE analysis of impactor-sized mass (ISM). ³³ The CI profiles representing drug deposition on the individual stages of the CI along with the mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle mass (FPM) should be submitted as supportive evidence for equivalent APSD.
	Additional Comments:	Drug deposition on individual sites, including the mouthpiece adapter, the induction port, the pre-separator, and each stage of the cascade impactor (CI) and the filter, is requested. Mass balance accountability should be reported based on the sum of all deposition sites. For electronic submission of the individual CI data for the T and R products, please provide a table using the format in the appendix, and send them as part of the abbreviated new drug application (ANDA) submission for BE evaluation.

PK BE Study

The following PK BE study is recommended to be conducted for all strengths of the T and R products.

³¹ Based on the labeled number of actuations, the terms, B lifestage, M lifestage, and E lifestage represent the first actuation(s), the actuation(s) corresponding to 50 percent of the labeled number of actuations, and the actuation(s) corresponding to the labeled number of actuations, respectively.

³² <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf>

³³ ISM is defined as a sum of the drug mass on all stages of the CI plus the terminal filter, but excluding the top CI stage because of its lack of a specified upper cutoff size limit.

3.	Type of study:	Fasting
	Design:	Single-dose, two-way crossover
	Dose:	Minimum number of inhalations that is sufficient to characterize a PK profile by using a sensitive analytical method.
	Subjects:	Normal healthy males and non-pregnant females, general population.
	Additional Comments:	Subjects should adhere to labeling as follows: “Rinse your mouth with water after breathing-in the medicine. Spit the water out. Do not swallow.”

Analytes to measure (in plasma/serum/blood):	Fluticasone propionate and salmeterol in plasma
Bioequivalence based on:	AUC and C _{max} for fluticasone propionate and salmeterol. The 90% confidence intervals (CIs) for the geometric mean T/R ratios of AUC and C _{max} should fall within the limits of 80.00–125.00%.

Clinical endpoint study

The following BE study with a clinical endpoint is recommended to be conducted for the lowest strength of the T and R products.

4.	Type of study:	Clinical endpoint study
	Design:	A randomized, multiple-dose, placebo-controlled, parallel group design consisting of a 2 week run-in period followed by a 4-week treatment period of the placebo, T or R product
	Strength:	100/50 (fluticasone propionate 100 mcg and salmeterol 50 mcg powder for inhalation)
	Dose:	100/50, twice daily
	Subjects:	Males and non-pregnant females with asthma
	Additional Comments:	• Inclusion criteria should, at minimum, include: a. Male or female subjects (≥ 12 years of age) of non-child bearing potential or of child bearing potential committing to consistent and correct use of an acceptable method of birth control. b. Diagnosed with asthma as defined by the National Asthma Education and Prevention Program (NAEPP)³⁴ at least 12 weeks prior to screening. c. Pre-bronchodilator FEV₁ of $\geq 40\%$ and $\leq 85\%$ of the predicted value during the screening visit and on the first day of treatment. d. Currently non-smoking; had not used tobacco products (i.e., cigarettes, cigars, pipe tobacco) within the past year, and had ≤ 10 pack-years of historical use. e. $\geq 15\%$ reversibility of FEV₁ within 30 minutes following 360 mcg of albuterol inhalation (pMDI). f. Able to discontinue their asthma medications (inhaled corticosteroids and long-acting β agonists) during

³⁴ Guidelines for the Diagnosis and Management of Asthma: Expert Panel Report 3. National Asthma Education and Prevention Program; National Institute of Health; National Heart, Lung, and Blood Institute. 2007, Publication No. 07-4051.

		the run-in period and for remainder of the study. g. Able to replace current short-acting β agonists (SABAs) with salbutamol/albuterol inhaler for use as needed for the duration of the study (subjects should be able to withhold all inhaled SABAs for at least 6 hours prior to lung function assessments on study visits). h. Able to continue the following medications without a significant adjustment of dosage, formulation, dosing interval for the duration of the study, and judged able by the investigator to withhold them for the specified minimum time intervals prior to each clinic visit: ▪ short-acting forms of theophylline 12 hours ▪ twice-a-day controlled-release forms of theophylline 24 hours ▪ once-a-day controlled-release forms of theophylline 36 hours i. Able to discontinue the following medications for the specified minimum time intervals prior to the run-in period and for the remainder of the study, if the study is conducted in the US: ▪ oral corticosteroids 1 month ▪ parenteral corticosteroids 1 month ▪ oral short-acting β-agonists 12 hours j. Willingness to give their (and in the case of a minor their parent/guardian was able to give) written informed consent to participate in the study. • Exclusion criteria should, at minimum, include: a. Life-threatening asthma, defined as a history of asthma episode(s) requiring intubation, and/or associated with hypercapnoea; respiratory arrest or hypoxic seizures, asthma related syncopal episode(s), or hospitalizations within the past year or during the run-in period. b. Evidence or history of clinically significant disease or abnormality including congestive heart failure, uncontrolled hypertension, uncontrolled coronary artery disease, myocardial infarction, or cardiac dysrhythmia. In addition, historical or current evidence of significant hematologic, hepatic neurologic, psychiatric, renal, or other diseases that in the opinion of the investigator, would put the patient at risk through study participation, or would affect the study analyses if the disease exacerbated during the study. c. Hypersensitivity to any sympathomimetic drug (e.g., salmeterol or albuterol) or any inhaled, intranasal, or systemic corticosteroid therapy. d. Medication(s) with the potential to affect the course of asthma or to interact with sympathomimetic amines, e.g.: ▪ β-blockers ▪ oral decongestants ▪ benzodiazepines ▪ digitalis ▪ phenothiazines ▪ polycyclic antidepressants ▪ Monoamine oxidase inhibitors e. Viral or bacterial, upper or lower respiratory tract

		infection or sinus or middle ear infection within 4 weeks prior to the screening visit or during the run-in period. f. Factors (e.g., infirmity, disability or geographic location) that the investigator felt would likely limit the patient's compliance with the study protocol or scheduled clinic visits. • The study is recommended to begin with a placebo run-in period (at least 2 weeks in duration) to wash out any pre-study corticosteroids/ long acting bronchodilators and to establish FEV₁ baseline values. • The study protocol should provide a definition of compliant subjects (e.g., used at least 75% and no more than 125% of study drug doses) and specify how compliance will be verified (e.g., by the use of subject diaries). • To ensure adequate study sensitivity, the T and R products should both be statistically superior to placebo ($p < 0.05$) with regard to the BE study primary endpoints. • It is the sponsor's responsibility to enroll a sufficient number of subjects for the study to demonstrate BE of the T to the R product. • The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both. • All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the T and R products.

BE study endpoints:	(i) Area under the serial FEV₁-time curve calculated from time zero to 12 hours (AUC_{0-12h}) on the first day of the treatment, and (ii) FEV₁ measured in the morning prior to the dosing of inhaled medications on the last day of a 4-week treatment. The above two primary endpoints should be baseline adjusted (change from baseline). A FEV₁ baseline is defined as the average of pre-dose FEV₁ values of at least two time points measured in the morning of the first day of a 4 week treatment period. Sampling is recommended to correspond to the same time of day as used on the last day of a 4-week treatment. On the first day of the treatment, FEV₁ should be determined at 0, 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 hour post-dose.
Equivalence based on:	T/R ratio for the primary endpoints. The 90% CIs for the T/R ratios for the primary endpoints should fall within the limits of 80.00-125.00%.

Source of most recent recommendations:	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM367643.pdf (Recommended Sep 2013)
Summary of OGD or DB History (for details, please see table below):	Please see table below

Document Type and Number	Received Date	Description	Agency's Response
CC 09-0478 ³⁵ (Pfizer ³⁶)	9/15/2009	Meeting request for guidance on the proposed product of FP Inhalation Powder in CRC749 inhaler (to obtain agency's feedback and concurrence regarding the acceptability of the proposed regulatory and development strategy to support an ANDA for FP Inhalation Powder in CRC749 inhaler FP products)	Face-to-face meeting on 12/3/2009.
DARTS Meeting # 028726 ^{37,38} (Pfizer ³⁶)	3/3/2010	Inquiry of guidance on the FP and SX Inhalation Powder in CRC749 inhaler [to seek agency's advice and concurrence on the firm's strategy for in vivo local delivery and systemic exposure (PK) studies, as well as in vitro studies for BE submission.]	Face-to-face meeting on 5/12/2010. The Agency made several recommendations (e.g., PK of FP and SX should be conducted on all strengths of the combination product; for device resistance, the firm should provide pressure drop as a function of flow rate.)
CC 12-0731 ³⁹	7/30/2012	Meeting request to confirm their understanding of previous discussions and to seek direction from the agency on this product and to discuss the pharmaceutical development program, as well as to provide an update on the clinical development program.	Teleconference on 12/12/2012 The Agency made several recommendations (e.g., regarding studies/justifications to address the difference in device orientation and device resistance as compared to the RLD product)
CC 12-0850 ⁴⁰	9/14/2012	Pre-meeting information package	Teleconference on 12/12/2012 (same as CC12-0731)
CC 13-0422 ⁴¹	5/22/2013	Meeting request (to seek guidance on issues including clinical study to show	Face-to-face meeting on 9/27/2013 The Agency made several

³⁵ <http://cdsogd1/controls/DOCForm.asp?ID=13640>

³⁶ According to CC 12-0731³⁹, the drug product (MGR001: FP and SX inhalation powder in CRC749 inhaler device) was acquired from Pfizer Inc. by Mylan in December 2011.

³⁷ DARTS: Meeting-028726, FRM-MINUTES-01 (Internal Meeting Minutes), 3/15/2010.

³⁸ DARTS: Meeting-028726, FRM-MINUTES-01 (Internal Meeting Minutes), 9/22/2010.

³⁹ <\\cdsnas\OGDS6\CONTROLS\2012-docs\12-0731.pdf>

⁴⁰ <\\cdsnas\OGDS6\CONTROLS\2012-docs\12-0850.pdf>

⁴¹ <\\cdsnas\OGDS6\CONTROLS\2013-docs\13-0422.pdf>

		in vivo equivalence, and demonstration that difference of device resistance does not impact therapeutic equivalence)	recommendations (e.g., regarding the clinical endpoint study, and difference in device resistance as compared to the RLD product)
CC 13-0422A ⁴²	7/16/2013	Amendment to the meeting request of CC-130422	Face-to-face meeting on 9/27/2013 (same as CC13-0422)
CC 26230 ^{43,44}	8/27/2014	Protocol assessment request for the device orientation study	The Agency provided comments in written response
Meeting Request 844398 ⁴⁵	7/2/2015	Meeting request to discuss submission-related issues	Face-to-face meeting 10/22/2015
IND118769 ⁴⁶	Multiple submissions (original submission: 8/1/2013)	Submissions for PK study (250/50 mcg strength) using 3 inhalations, device orientation study, trade name review request, etc.	PK study (250/50 mcg strength) using 3 inhalations reasonably safe to proceed from the clinical standpoint. Comments provided to the firm regarding device orientation study protocol, and proposed proprietary name conditionally accepted.

4.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	4 (including 2 failed studies that the firm used for pooled analysis)
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	No	--
Waiver requests	No	--
BCS Waivers	No	--
Clinical Endpoints	Yes	1
Other Studies	Yes	3 in vitro BE studies 3 pressure differential (4 kPa) studies 1 flow profiling study 1 device orientation study
Failed Studies	Yes	2, as mentioned above, the firm used these 2 failed studies for pooled analysis
Amendments	No	--

⁴² [\\cdsnas\OGDS6\CONTROLS\2013-docs\13-0422A.pdf](#)

⁴³ GDRP: Correspondence 26230, Primary Review, 26230_Review_V2.docx, 1/8/2015.

⁴⁴ GDRP: Correspondence 26230, Primary Review, Attachment Mylan follow up internal discussion.pdf, 2/23/2015.

⁴⁵ GDRP: Meeting Request 844398, Primary Review, 844398_Review.doc, 10/19/2015.

⁴⁶ DARRTS: IND 118769.

4.5 Pre-Study Bioanalytical Method Validation

Information Requested	Analyte	Location in Report (Module, Section, Page ⁴⁷)
Bioanalytical method validation report location	12/29/2015 submission, Module 5.3.1.4. 15-006 – Validation Study Tagging File: A. Project 15-006 Validation Report B. Project 15-006 Validation Report Appendix 1 – Tables and Attachments C. Project 15-006 Validation Report Addendum 1 D. Project 15-006 Validation Report Addendum 1 – Tables and Attachments E. Project 15-006 Validation Report Addendum 2 F. Project 15-006 Validation Report Addendum 2 Appendix 1 – Tables and Attachments G. Project 15-006 Validation Report Addendum 3 H. Project 15-006 Validation Report Addendum 3 Appendix 1 – Tables and Attachments I. Project 15-006 Validation Report Addendum 4 J. Project 15-006 Validation Report Addendum 4 Appendix 1 – Tables and Attachments	--
Study Report Number	15-006	A1
Analyte	Fluticasone Propionate (FP) and Salmeterol (SA)	A1
Internal standard (IS)	Fluticasone Propionate-d ₅ (DFLU) and Salmeterol-d ₃ (DSAL)	A6
Method description	Solid phase extraction followed by liquid- liquid extraction; LC/MS/MS – ESI	A6
Limit of quantitation	1.0 pg/mL (FP and SA)	A7
Anticoagulant Used	K2EDTA	A6
LLOQ Intraday precision (%)	6.26% - 7.78% (FP) ^a 2.68% - 6.90% (SA) ^a	B19 B21
LLOQ Intraday accuracy (%)[^]	98.84% - 108.00% (FP) ^a 101.10% - 107.90 (SA) ^a	B19 B21
LLOQ Interday precision (%)	7.65% (FP) ^a 5.42% (SA) ^a	B19 B21
LLOQ Interday accuracy (%)[^]	102.30% (FP) ^a 104.40% (SA) ^a	B19 B21
% recovery (and %CV) at each concentration tested	<u>FP</u> ^a : LQC1: 56% MQC2: 57%	B81-82

⁴⁷ Since there are multiple method validation report files (e.g. appendix, addendum) as indicated in Row 2 Column 2 of this table, the page number listed below composed of a file number that corresponds to a specific method validation report file (please refer to Row 2 Column 2 of this table), and the page number of in that file. For example, information found on p. 6 of A. Project 15-006 Validation Report will be listed as A6.

	HQC: 58% Average: 57% <u>SA</u> ^a : LQC1: 43% MQC2: 41% HQC: 45% Average: 43%	
Average recovery of IS (%)	63% (DFLU) ^a 46% (DSAL) ^a	B83-84
Standard curve concentrations (units/mL)	1, 2, 3, 10, 30, 100, 300, 400, 500, 600 pg/mL (FP) 1, 2, 3, 10, 30, 100, 300, 400, 500, 600 pg/mL (SA)	B16-18
QC concentrations (units/mL)	For each of FP ^a and SA ^a : LQC1: 3 pg/mL LQC2: 15 pg/mL MQC1: 90 pg/mL MQC2: 240 pg/mL HQC: 450 pg/mL	B19-22
QC Intraday precision range (%)	<u>FP</u> ^a : LQC1: 1.39% - 7.41% LQC2: 1.62% - 2.71% MQC1: 0.79% - 2.64% MQC2: 1.07% - 2.27% HQC: 1.37% - 2.53% <u>SA</u> ^a : LQC1: 1.62% - 2.81% LQC2: 1.13% - 2.57% MQC1: 1.39% - 2.35% MQC2: 0.87% - 1.39% HQC: 1.29% - 2.16%	B19-22
QC Intraday accuracy range (%)[^]	<u>FP</u> ^a : LQC1: 95.90% - 100.60% LQC2: 97.07% - 104.00% MQC1: 96.11% - 102.21% MQC2: 99.62% - 102.83% HQC: 99.64% - 101.67% <u>SA</u> ^a : LQC1: 96.67% - 103.20% LQC2: 99.20% - 104.73% MQC1: 99.29% - 103.41% MQC2: 103.25% - 103.79% HQC: 102.42% - 102.96%	B19-22
QC Interday precision range (%)	<u>FP</u> ^a : LQC1: 4.73% LQC2: 3.99% MQC1: 3.27% MQC2: 2.13% HQC: 2.13% <u>SA</u> ^a :	B19-22

	LQC1: 3.45% LQC2: 3.21% MQC1: 2.50% MQC2: 1.03% HQC: 1.78%										
QC Interday accuracy range (%)[^]	<u>FP</u> ^a : LQC1: 98.53% LQC2: 99.67% MQC1: 99.37% MQC2: 101.13% HQC: 100.38% <u>SA</u> ^a : LQC1: 100.33% LQC2: 101.07% MQC1: 101.43% MQC2: 103.50% HQC: 102.73%	B19-22									
Bench-top stability (hrs)	18.4 hours @ room temperature (FP) ^a 18.4 hours @ room temperature (SA) ^a	A10, B57-58									
Stock stability (days)	FP Stock Solution 32 days @ room temperature ^d SA Stock Solution 32 days @ 4°C ^d FP /SA Working Solution 32 days @ 4°C ^d DFLU Internal Standard Stock Solution 32 days @ room temperature ^d DSAL Internal Standard Stock Solution 32 days @ 4°C ^d DFLU/DSAL Internal Standard Working Solution 32 days @ 4°C ^d SA Stock Solution 23 hours @ room temperature ^a FP/SA Working Solution 23 hours @ room temperature ^a DSAL Internal Standard Stock 23 hours @ room temperature ^a DFLU/DSAL Internal Standard Working 23 hours @ room temperature ^a	H10-11 H11-13 H14-17 H18-19 H20-21 H22-25 B39-40 B41-44 B45-46 B47-50									
Processed stability (hrs)	29 hours @ room temperature (FP/SA) ^a 74 hours @ 4°C (FP/SA) ^a	A11, B65-66 A10-11, B61-64									
Freeze-thaw stability (cycles)	3 cycles @ -70°C and -15°C FP ^a 3 cycles @ -70°C and -15°C SA ^a	A10, B55-56									
Long-term storage stability (days)	26 days @ -15°C (FP/SA) ^b 132 days @ -70°C (FP/SA) ^d	C6-7, D9-10 G7, H26-27									
Dilution integrity (concentration, percent CV) dilution factor, accuracy	2400 pg/mL (4 x highest standard), diluted 1:5 ^a <table border="1"> <thead> <tr> <th></th> <th>%CV</th> <th>%Accuracy[^]</th> </tr> </thead> <tbody> <tr> <td>FP</td> <td>2.45%</td> <td>93.62%</td> </tr> <tr> <td>SA</td> <td>2.08%</td> <td>96.46%</td> </tr> </tbody> </table>		%CV	%Accuracy [^]	FP	2.45%	93.62%	SA	2.08%	96.46%	B67-68
	%CV	%Accuracy [^]									
FP	2.45%	93.62%									
SA	2.08%	96.46%									
Selectivity	No interfering peaks noted in blank plasma samples for FP or SA ^a	A6, B266-267									
For combination products: Did the matrix include all analytes and show that one analyte does not interfere with the	No (see comments below)	--									

other?		

^a Generated in FLSA_v15006 Validation

^b Generated in FLSA_v15006 Validation Addendum 1

^c Generated in FLSA_v15006 Validation Addendum 2

^d Generated in FLSA_v15006 Validation Addendum 3

[^] Reviewer calculated values based on firm-provided %Error using formula: % accuracy= 100% + %Error.

SOPs submitted	Yes MGWBIO-SOP-BIO-GEN-0016 Bioanalytical Methods Validation (version 3.0, effective 5/7/2013); and MPI-SOP-BIO-GEN-0016 Bioanalytical Methods Validation (version 4.0, effective 4/30/2015)
Was the % recovery consistent across QC concentrations?	Yes
Is the same anticoagulant used in the pre-method validation study used in the sample assay?	Yes (K2EDTA)
If not, was cross validation study conducted?	N/A
Was the dilution factor adequate for the current study sample analysis?	Yes
Was the same dilution medium (plasma/solvent) used during validation and sample analysis?	Yes (K2EDTA plasma)
Does the duration of the each of the stability parameters support the sample preparation and assay dates	Yes
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	No (please see comments below)

Comments on the Pre-Study Method Validation:

1. The firm conducted partial method validation to validate the removal of a guard column preceding the analytical column. They also conducted partial method validation to validate the preparation of the standard curve calibrators using an (b) (4) repeater pipet (or equivalent) which prompted changes to diluent and matrix standard volumes used.
2. It is noted that the firm performed pre-study method validation on instruments (b) (4), (b) (4). However, additional instruments were used in the pivotal PK study (b) (4) was used in fasting study MGR001-1014; and (b) (4) was used in fasting studies MGR001-1005, MGR001-1006 and MGR001-1014). The firm did not provide detailed information of these additional instruments used. Therefore, the firm will be asked to provide this information, and the firm will be advised that according to Guidance for Industry – Bioanalytical Method Validation (draft guidance recommended September 2013), partial validation needs to be conducted for change(s) in instruments and/or software platforms.
3. The pre-study method validation for the determination of FP and salmeterol (SA) was conducted in human plasma containing K₂EDTA, which is the same anti-coagulant used in the fasting BE studies.

4. The firm conducted long term storage stability (LTSS) testing of 132 days at -70°C, which exceeds the storage period of 23 days, 37 days, 26 days and 19 days at -70°C for the fasting BE studies MGR001-1006, MGR001-1007, MGR001-1005 and MGR001-1014, respectively.
5. The firm stated that assay selectivity was evaluated in 6 sources of human plasma.⁴⁸ However, the firm only provided representative chromatography to show selectivity. The firm will be asked to provide selectivity results for each of the 6 sources of human plasma.
6. Since the proposed test product has two analytes, the firm should provide evidence that one analyte does not interfere with analysis of the other analyte (e.g. LQC and HQC samples of FP fortified with SA show no effect on determination of FP, and vice versa).
7. In pre-study method validation, dilution integrity was validated using DQC of 2400 pg/mL and dilution factor of 1:5, which covered the dilution factors (1:2 and 1:4) used in the pivotal fasting studies. Same dilution medium (K₂EDTA plasma) was used during pre-study method validation and pivotal fasting studies.
8. The firm stated in the original validation report that during the validation study, a minor modification was made to the final reconstitution solvent composition whereby the mobile phase buffer (b) (4) (b) (4) was substituted for water in order to provide higher and more consistent recovery of SA. The aqueous:methanol ratio remained at 75:25. The recovery experiments were performed using the buffered reconstitution solvent. The accuracy and precision study were performed using both the unbuffered reconstitution solvent and the buffered solvent, and met the acceptance criteria (%CV and %error should be ≤15%, except for LLOQ, which should be ≤20%) in each reconstitution solvent condition.

The pre-study method validation is **incomplete**.

⁴⁸ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.1.4. 15-006 – Validation Study Tagging File\ Project 15-006 Validation Report, p. 6 of 16).

4.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

PK BE Study MGR001-1006

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route), [Product ID]	Subjects Number (M/F), Type, Age (yrs.), Mean (Range)	Mean Parameters (SD)*						Study Report Location	
					Treatment Group	C _{max} (pg/mL)	T _{max} (hr)	AUC _{last} (pg/mL•hr)	AUC _{inf} (pg/mL•hr)	T _{1/2} (hr)		Kel (hr ⁻¹)
MGR001-1006	To confirm the systemic pharmacokinetic BE of both FP and salmeterol after oral inhalation of single doses of MGR001 (Test) vs Advair® Diskus® (Reference)	Open-label, Randomized 2-way crossover study	A=MGR001 Batch No. 631-002 100/50 mcg, (Single dose, 3 inhalations) [Test] B= Advair® Diskus® Lot No. 4ZP3863 100/50 mcg, (Single dose, 3 inhalations) [Reference]	66 Dosed 64 Completed (M:36/F:28) Healthy Subjects Mean Age**: 33.8 (19 to 53)	Fluticasone Propionate						Section 5.3.1.2	
					A [Test]	109.7 (36.19)	0.75 (0.08-1.50)	637.8 (200.8)	656.0 (201.3)	10.18 (2.46)		0.0737 (0.0315)
					B [Reference]	118.6 (35.46)	0.75 (0.08-1.50)	608.7 (178.5)	625.4 (178.4)	9.95 (2.77)		0.0777 (0.0354)
					Salmeterol							
					A [Test]	385.4 (162.8)	0.08 (0.03-1.50)	727.3 (223.2)	764.3 (229.8)	11.87 (1.54)		0.0594 (0.0077)
B [Reference]	379.3 (143.9)	0.08 (0.03-2.00)	677.4 (245.2)	709.9 (255.2)	12.21 (1.93)	0.0580 (0.0085)						

*Arithmetic mean (SD) for all parameters except median (range) for Tmax

**Mean Age (Range) presented for all subjects (n=66),

PK BE Study MGR001-1007

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route), [Product ID]	Subjects Number (M/F), Type, Age (yrs.), Mean (Range)	Mean Parameters (SD)*							Study Report Location
					Treatment Group	C _{max} (pg/mL)	T _{max} (hr)	AUC _{last} (pg/mL•hr)	AUC _{inf} (pg/mL•hr)	T _{1/2} (hr)	Kel (hr ⁻¹)	
MGR001-1007	To confirm the systemic pharmacokinetic BE of both FP and salmeterol after oral inhalation of single doses of MGR001 (Test) vs Advair® Diskus® (Reference)	Open-label, Randomized 2-way crossover study	A=MGR001 Batch No. 631-006 500/50 mcg, (Single dose, 3 inhalations) [Test] B= Advair® Diskus® Lot No. 4ZP5917 500/50 mcg, (Single dose, 3 inhalations) [Reference]	66 Dosed 65 Completed (M:24/F:41) Healthy Subjects Mean Age**: 35.7 (19 to 53)	Fluticasone Propionate							Section 5.3.1.2
					A [Test]	261.6 (69.13)	1.50 (0.33 – 4.00)	2851 (970.1)	3009 (1018)	12.23 (2.68)	0.0590 (0.0112)	
					B [Reference]	290.9 (73.98)	1.50 (0.33 – 4.00)	2919 (831.3)	3051 (874.4)	10.57 (1.90)	0.0675 (0.0112)	
					Salmeterol							
					A [Test]	376.6 (181.3)	0.08 (0.03 – 1.00)	723.7 (297.0)	753.2 (303.1)	11.21 (2.01)	0.0638 (0.0113)	
					B [Reference]	418.0 (145.8)	0.08 (0.03 – 1.50)	707.7 (236.0)	739.9 (243.1)	11.56 (1.86)	0.0614 (0.0091)	

*Arithmetic mean (SD) for all parameters except median (range) for Tmax

**Mean Age (Range) presented for all subjects (n=66)

PK BE Study MGR001-1005

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route), [Product ID]	Subjects Number (M/F), Type, Age (yrs.), Mean (Range)	Mean Parameters (SD)*							Study Report Location
					Treatment Group	C _{max} (pg/mL)	T _{max} (hr)	AUC _{last} (pg/mL•hr)	AUC _{inf} (pg/mL•hr)	T _{1/2} (hr)	Kel (hr ⁻¹)	
MGR001-1005	To confirm the systemic pharmacokinetic BE of both FP and salmeterol after oral inhalation of single doses of MGR001 (Test) vs Advair® Diskus® (Reference)	Open-label, Randomized 2-way crossover study	A=MGR001 Batch No. 631-009 250/50 mcg, (Single dose, 3 inhalations) [Test] B=Advair® Diskus® Lot No. 5ZP9304 250/50 mcg, (Single dose, 3 inhalations) [Reference]	66 Dosed 66 Completed (M:35/F:31) Healthy Subjects Mean Age: 33.5 (19 to 53)	Fluticasone propionate							Section 5.3.1.2
					A [Test]	258.7 (67.27)	1.00 (0.25-2.00)	1934 (478.2)	2034 (520.2)	11.87 (1.84)	0.0598 (0.0097)	
					B [Reference]	223.8 (59.04)	1.00 (0.50-3.00)	1562 (411.0)	1632 (409.4)	10.55 (1.86)	0.0677 (0.0120)	
					Salmeterol							
					A [Test]	513.6 (173.8)	0.08 (0.03-0.10)	875.2 (260.4)	918.3 (274.4)	12.24 (1.82)	0.0579 (0.0084)	
B [Reference]	432.4 (166.6)	0.08 (0.03-0.12)	744.4 (252.4)	782.2 (269.3)	11.96 (2.23)	0.0599 (0.0109)						

*Arithmetic mean (SD) for all parameters except median (range) for Tmax

PK BE Study MGR001-1014

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route), [Product ID]	Subjects Number (M/F), Type, Age (yrs.), Mean (Range)	Mean Parameters ($\pm$ SD)*							Study Report Location
					Treatment Group	C _{max} (pg/mL)	T _{max} (hr)	AUC _{last} (pg/mL•hr)	AUC _{inf} (pg/mL•hr)	T _{1/2} (hr)	Kel (hr ⁻¹)	
MGR001-1014	To confirm the systemic pharmacokinetic BE of both FP and salmeterol after oral inhalation of single doses of MGR001 Test) vs Advair® Diskus® (Reference)	Open-label, Randomized 2-way crossover study	A=MGR001 Batch No. 631-009 250/50 mcg, (Single dose, 3 inhalations) [Test] B=Advair® Diskus® Lot No. 5ZP9882 250/50 mcg (Single dose, 3 inhalations) [Reference]	66 Dosed 65 Completed (M:31/F:35) Healthy Subjects Mean Age**: 36.4 (18 to 54)	Fluticasone propionate							Section 5.3.1.2
					A [Test]	193.6 (56.10)	1.00 (0.25-2.00)	1472 (475.5)	1569 (502.3)	12.01 (2.01)	0.0592 (0.0094)	
					B [Reference]	231.9 (61.78)	0.79 (0.17-2.00)	1509 (391.1)	1580 (409.0)	10.77 (2.26)	0.0671 (0.0135)	
					Salmeterol							
					A [Test]	362.9 (160.3)	0.08 (0.03-1.00)	779.1 (318.9)	814.9 (335.8)	11.59 (1.60)	0.0609 (0.0081)	
					B [Reference]	430.8 (157.1)	0.08 (0.03-0.10)	800.4 (307.8)	837.8 (321.6)	11.68 (1.86)	0.0607 (0.0089)	

*Arithmetic mean (SD) for all parameters except median (range) for Tmax

**Mean Age (Range) presented for all subjects (n=66)

Clinical Endpoint Study MGR001-3001

Study no.	Study objective	Study design	Primary endpoint (s)	Treatment (dose, dosage form, dosing regimen, route, application site)	Subject no., age: mean (range)	Mean (LS mean, %) parameters			90% CI	P value	
						Test	Reference	Placebo/ vehicle			
MGR001-3001	To confirm the local bioequivalence of MGR001 100/50 (Test) versus Advair® Diskus® 100/50 (RLD) after oral inhalation of single and multiple doses (4 weeks, twice a day [BID]) using clinical endpoints.	Randomized, double-blind, double-dummy, placebo-controlled, parallel group	Change from baseline in FEV ₁ area under the effect curve (AUEC) over 12 hours postdose (FEV ₁ AUEC ₀₋₁₂) on Day 1. Change from baseline in trough FEV ₁ at Week 4 (Day 29).	Test: MGR001 100/50 Reference: Advair® Diskus® 100/50 Placebo for MGR001 and Advair® Diskus®	# enrolled (received at least 1 dose of double-blind treatment): 1127 #M/#F: 448/679 Mean age (range): 42.6 (18-84) years	PRIMARY ENDPOINT 1 (BIOEQUIVALENCE) Change from baseline AUEC₀₋₁₂ FEV₁ on Day 1 (PP population):					
						3.9734 L.hr	3.5411 L hr	0.8400 L.hr	N/A	N/A	
						Ratio of LS means (test/reference): 1.120			N/A	1.016, 1.237	N/A
						PRIMARY ENDPOINT 1 (ASSAY SENSITIVITY) Change from baseline AUEC₀₋₁₂ FEV₁ on Day 1 (mITT population*):					
						3.9534 L.hr	3.4964 L hr	0.8191 L.hr	N/A	N/A	
						Test vs. placebo: 3.1343 L.hr Reference vs. placebo: 2.6773 L.hr			N/A	p<0.0001 p<0.0001	
						PRIMARY ENDPOINT 2 (BIOEQUIVALENCE) Change from baseline Trough FEV₁ on Day 29 (PP population):					
						0.2911 L	0.2728 L	0.0574 L	N/A	N/A	
						Ratio of LS means (test/reference): 1.069			N/A	0.938, 1.220	N/A
						PRIMARY ENDPOINT 2 (ASSAY SENSITIVITY) Change from baseline Trough FEV₁ on Day 29 (mITT population*):					
						0.2927 L	0.2720 L	0.0575 L	N/A	N/A	
						Test vs. placebo: 0.2352 L Reference vs. placebo: 0.2145 L			N/A	p<0.0001 p<0.0001	

* The term 'Full Analysis Set (FAS)' is used in place of 'mITT' in the MGR001-3001 clinical study report by the firm.

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer
Fasting PK BE Study MGR001-1006 (100/50 mcg strength)

Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder 3 x 100/50 mcg Fasting Bioequivalence Study, Study No. MGR001-1006, N=64 (Male=36 and Female=28) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
FP							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
Group 1							
LAUCT (hr *pg/ml)	567.02	20	581.56	20	0.98	91.27	104.16
LAUCI (hr *pg/ml)	592.74	20	607.71	20	0.98	91.39	104.10
LCMAX (pg/ml)	99.92	20	107.96	20	0.93	86.12	99.47
Group 2							
LAUCT (hr *pg/ml)	611.59	20*	557.84	20*	1.10	102.38	117.40
LAUCI (hr *pg/ml)	637.68	20*	579.28	20*	1.10	102.94	117.72
LCMAX (pg/ml)	104.88	20*	110.89	20*	0.95	87.75	101.96
Group 3							
LAUCT (hr *pg/ml)	702.22	22	657.49	22	1.07	100.47	113.53
LAUCI (hr *pg/ml)	733.11	22	685.59	22	1.07	100.78	113.46
LCMAX (pg/ml)	111.69	22	122.54	22	0.91	83.36	99.66
SA							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
Group 1, 2 and 3							
LAUCT (hr *pg/ml)	712.40	60^	659.12	60^	1.08	104.81	111.46
LAUCI (hr *pg/ml)	745.82	60^	692.05	60^	1.08	104.65	110.98
LCMAX (pg/ml)	347.94	60^	349.15	60^	1.00	94.35	105.26

* Subjects (b) (6) were excluded by the reviewer due to missing samples that potentially affect Cmax.

^ Subjects (b) (6) were excluded by the reviewer due to missing samples that potentially affect Cmax.

Note: The subjects were dosed in 3 groups. For FP, the treatment*group interaction was statistically significant (p<0.1) for LAUC_{0-t} and LAUC_{0-∞}, and was not statistically significant (p>0.1) for LCmax. For SA, the treatment*group interaction was not statistically significant (p>0.1) for LAUC_{0-t}, LAUC_{0-∞} and LCmax.

Fasting PK BE Study MGR001-1007 (500/50 mcg strength)

Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder 3 x 500/50 mcg Fasting Bioequivalence Study, Study No. MGR001-1007, N=65 (Male=24 and Female=41) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
FP							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
<u>Group 1, 2 and 3</u>							
LAUCT (hr *pg/ml)	2763.22	64*	2865.93	64*	0.96	92.43	100.58
LAUCI (hr *pg/ml)	2947.30	64*	3004.17	64*	0.98	94.09	102.30
LCMAX (pg/ml)	253.89	64*	283.06	64*	0.90	86.15	93.38
SA							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
<u>Group 1, 2 and 3</u>							
LAUCT (hr *pg/ml)	686.10	61^	684.20	61^	1.00	96.13	104.61
LAUCI (hr *pg/ml)	716.94	61^	717.53	61^	1.00	95.95	104.05
LCMAX (pg/ml)	335.10	61^	387.72	61^	0.86	81.57	91.58

* Subject (b) (6) was excluded by the reviewer due to missing samples that potentially affect Cmax.

^ Subject #s (b) (6) were excluded by the reviewer due to missing samples that potentially affect Cmax.

Note: The subjects were dosed in 3 groups. For both FP and SA, the treatment*group interaction was not statistically significant (p>0.1) for LAUC_{0-t}, LAUC_{0-∞} and LCmax.

Fasting PK BE Study MGR001-1005 (250/50 mcg strength)

Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder 3 x 250/50 mcg Fasting Bioequivalence Study, Study No. MGR001-1005, N=66 (Male=35 and Female=31) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
FP							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
Group 1							
LAUCT (hr *pg/ml)	1882.22	22	1493.75	22	1.26	115.59	137.36
LAUCI (hr *pg/ml)	1966.71	22	1548.13	22	1.27	116.35	138.70
LCMAX (pg/ml)	242.69	22	201.03	22	1.21	110.85	131.47
Group 2							
LAUCT (hr *pg/ml)	1901.97	21*	1460.99	21*	1.30	123.85	136.85
LAUCI (hr *pg/ml)	2007.77	21*	1516.38	21*	1.32	126.20	138.91
LCMAX (pg/ml)	253.74	21*	209.02	21*	1.21	114.12	129.13
Group 3							
LAUCT (hr *pg/ml)	1963.37	20^	1628.03	20^	1.21	113.35	128.31
LAUCI (hr *pg/ml)	2079.71	20^	1689.37	20^	1.23	115.82	130.85
LCMAX (pg/ml)	263.01	20^	242.29	20^	1.09	103.34	114.02
SA							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
Group 1, 2 and 3							
LAUCT (hr *pg/ml)	851.86	62#	708.72	62#	1.20	115.51	125.07
LAUCI (hr *pg/ml)	893.17	62#	744.37	62#	1.20	115.44	124.72
LCMAX (pg/ml)	485.94	62#	401.57	62#	1.21	114.44	127.96

* Subject (b) (6) was excluded by the reviewer due to missing samples that potentially affect Cmax.

^ Subjects (b) (6) were excluded by the reviewer due to missing samples that potentially affect Cmax.

Subjects (b) (6) were excluded by the reviewer due to missing samples that potentially affect Cmax.

Note: The subjects were dosed in 3 groups. For FP, the treatment*group interaction was statistically significant (p<0.1) for LCmax, and was not statistically significant (p>0.1) for LAUC_{0-t} and LAUC_{0-∞}. For SA, the treatment*group interaction was not statistically significant (p>0.1) for LAUC_{0-t}, LAUC_{0-∞} and LCmax.

Fasting PK BE Study MGR001-1014 (250/50 mcg strength)

Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder 3 x 250/50 mcg Fasting Bioequivalence Study, Study No. MGR001-1014, N=65 (Male=35 and Female=30) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
FP							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
<u>Group 1, 2 and 3</u>							
LAUCT (hr *pg/ml)	1449.73	63*^#	1516.15	63*^#	0.96	91.43	100.00
LAUCI (hr *pg/ml)	1531.99	63*^#	1581.09	63*^#	0.97	92.60	101.39
LCMAX (pg/ml)	189.23	63*^#	228.89	63*^#	0.83	79.03	86.48
SA							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
<u>Group 1, 2 and 3</u>							
LAUCT (hr *pg/ml)	723.85	61^#@	745.80	61^#@	0.97	93.78	100.45
LAUCI (hr *pg/ml)	758.82	61^#@	782.61	61^#@	0.97	93.77	100.26
LCMAX (pg/ml)	329.05	61^#@	400.73	61^#@	0.82	76.87	87.71

* Subject (b)(6) was excluded by the reviewer due to missing samples that potentially affect Cmax.

^ Subject (b)(6) was excluded by the reviewer due to carryover blank issue in the corresponding bioanalytical run.

The last 2 time points (36 and 48 hrs) for Subject (b)(6) Period 2 was treated as missing by the reviewer due to administration of laxative with unknown ingredient.

@ Subjects (b)(6) were excluded by the reviewer due to missing samples that potentially affect Cmax.

Note: The subjects were dosed in 3 groups. For both FP and SA, the treatment*group interaction was not statistically significant (p>0.1) for LAUC_{0-t}, LAUC_{0-∞} and LCmax.

Are the PK parameters within the acceptance limits for the 90% CI and meeting BE?

Yes for fasting PK studies MGR001-1006 (100/50 mcg strength) and MGR001-1007 (500/50 mcg strength).

No for fasting PK studies MGR001-1005 and MGR001-1014 (both at 250/50 mcg strength).

Table 3. Reanalysis of Study Samples

Fasting Study, Study No. <u>MGR001-1006</u> (Pivotal BE study with MGR001 100/50 mcg vs Advair® Diskus® 100/50 mcg)								
Repeat Analysis Results for FP								
Additional Information in Table 6A of Appendix 1 of the MGR001-1006 Bioanalytical Study Report								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Reason A	0	2	0.00%	0.08%	0	2	0.00%	0.08%
Reason B	3	0	0.12%	0.00%	3	0	0.12%	0.00%
Reason C	2	1	0.08%	0.04%	2	1	0.08%	0.04%
Reason D	2	3	0.08%	0.12%	2	3	0.08%	0.12%
Reason E	0	1	0.00%	0.04%	0	0	0.00%	0.00%
Reason F	0	1	0.00%	0.04%	0	1	0.00%	0.04%
Reason G	0	1	0.00%	0.04%	0	1	0.00%	0.04%
Total	7	9	0.28%	0.37%	7	8	0.28%	0.32%

Reason A = Poor Chromatography

Reason B = Abnormal Internal Standard (IS) Response

Reason C = Documented Sample Processing Error – broken vial, sample lost

Reason D = Sample outside Limits of Curve Range (BLQ)

Reason E = Documented Sample Processing Error – sample was not transferred to collection plate

Reason F = Documented Sample Processing Error – insufficient volume in Aliquot 1, Aliquot 2 was utilized for re-assay in Run 78

Reason G = Documented Sample Processing Error – sample would not pass through extraction plate, Aliquots 1 and 2 combined for re-assay in Run 78

Fasting Study, Study No. MGR001-1006 (Pivotal BE study with MGR001 100/50 mcg vs Advair® Diskus® 100/50 mcg)

Repeat Analysis Results for SA

Additional Information in Table 6B of Appendix 1 of the MGR001-1006 Bioanalytical Study Report

Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Reason A	0	2	0.00%	0.08%	0	2	0.00%	0.08%
Reason B	3	0	0.12%	0.00%	3	0	0.12%	0.00%
Reason C	2	1	0.08%	0.04%	2	1	0.08%	0.04%
Reason D	7	5	0.28%	0.20%	7	5	0.28%	0.20%
Reason E	2	2	0.08%	0.08%	2	2	0.08%	0.08%
Reason F	0	1	0.00%	0.04%	0	0	0.00%	0.00%
Reason G	0	1	0.00%	0.04%	0	1	0.00%	0.04%
Total	14	12	0.57%	0.49%	14	11	0.57%	0.45%

Reason A = Poor chromatography

Reason B = Abnormal Internal Standard (IS) Response

Reason C = Documented Sample Processing Error – broken vial, sample lost

Reason D = Sample Outside Limits of Curve Range (ALQ)

Reason E = Sample Outside Limits of Curve Range (BLQ)

Reason F = Documented Sample Processing Error – sample was not transferred to collection plate

Reason G = Documented Sample Processing Error – insufficient sample volume in Aliquot 1, Aliquot 2 was utilized for re-assay in Run 78

Fasting Study, Study No. <u>MGR001-1007</u> (Pivotal BE study with MGR001 500/50 mcg vs Advair® Diskus® 500/50 mcg)								
Repeat Analysis Results for FP								
Additional Information in Table 6A of Appendix 1 of the MGR001-1007 Bioanalytical Study Report								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Reason A	2	2	0.08%	0.08%	2	2	0.08%	0.08%
Reason B	2	4	0.08%	0.16%	2	4	0.08%	0.16%
Reason C	1	1	0.04%	0.04%	1	1	0.04%	0.04%
Total	5	7	0.20%	0.28%	5	7	0.20%	0.28%

Reason A = Measurable Concentration in Subject Zero Sample
Reason B = Documented Sample Processing Error – broken vial
Reason C = Abnormal Internal Standard (IS) Response

Fasting Study, Study No. <u>MGR001-1007</u> (Pivotal BE study with MGR001 500/50 mcg vs Advair® Diskus® 500/50 mcg)								
Repeat Analysis Results for SA								
Additional Information in Table 6B of Appendix 1 of the MGR001-1007 Bioanalytical Study Report								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Reason A	8	9	0.32%	0.36%	8	9	0.32%	0.36%
Reason B	2	5	0.08%	0.20%	2	5	0.08%	0.20%
Reason C	1	0	0.04%	0.00%	1	0	0.04%	0.00%
Total	11	14	0.44%	0.56%	11	15	0.44%	0.56%

Reason A = Sample Outside Limits of Curve Range (ALQ)
Reason B = Documented Sample Processing Error – broken vial
Reason C = Abnormal Internal Standard (IS) Response

Fasting Study, Study No. MGR001-1005 (Pivotal BE study with MGR001 250/50 mcg vs Advair® Diskus® 250/50 mcg)

Repeat Analysis Results for **FP**

Additional Information in Table 6A of Appendix 1 of the MGR001-1005 Bioanalytical Study Report

Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Reason A	3	2	0.12%	0.08%	3	2	0.12%	0.08%
Reason B	1	0	0.04%	0.00%	1	0	0.04%	0.00%
Reason C	0	3	0.00%	0.12%	0	3	0.00%	0.12%
Reason D	0	1	0.00%	0.04%	0	1	0.00%	0.04%
Total	4	6	0.16%	0.24%	4	6	0.16%	0.24%

Reason A = Abnormal Internal Standard (IS) Response

Reason B = Documented sample processing error – cracked vial

Reason C = Documented sample processing error – insufficient sample volume

Reason D = Poor Chromatography

Fasting Study, Study No. MGR001-1005 (Pivotal BE study with MGR001 250/50 mcg vs Advair® Diskus® 250/50 mcg)								
Repeat Analysis Results for SA								
Additional Information in Table 6B of Appendix 1 of the MGR001-1005 Bioanalytical Study Report								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Reason A	22	10	0.88%	0.40%	21	11	0.84%	0.44%
Reason B	1	0	0.04%	0.00%	1	0	0.04%	0.00%
Reason C	13	6	0.52%	0.24%	12	7	0.48%	0.28%
Reason D	0	3	0.00%	0.12%	0	3	0.00%	0.12%
Reason E	0	1	0.00%	0.04%	0	1	0.00%	0.04%
Total	36	20	1.40%	0.84%	35	21	1.40%	0.84%

Reason A = Sample outside Limits of Curve Range (ALQ)

Reason B = Documented sample processing error – cracked vial

Reason C = Abnormal Internal Standard (IS) response

Reason D = Documented processing sample error – insufficient sample volume

Reason E = Poor chromatography

Fasting Study, Study No. MGR001-1014 (Pivotal BE study with MGR001 250/50 mcg vs Advair® Diskus® 250/50 mcg)								
Repeat Analysis Results for FP								
Additional Information in Table 6A of Appendix 1 of the MGR001-1014 Bioanalytical Study Report								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Reason A	2	2	0.08%	0.08%	2	2	0.08%	0.08%
Total	2	2	0.08%	0.08%	2	2	0.08%	0.08%

Reason A = Documented sample processing error – Insufficient volume for full analysis from the primary aliquot

Fasting Study, Study No. <u>MGR001-1014</u> (Pivotal BE study with MGR001 250/50 mcg vs Advair® Diskus® 250/50 mcg) Repeat Analysis Results for SA Additional Information in Table 6B of Appendix 1 of the MGR001-1014 Bioanalytical Study Report								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Reason A	2	2	0.08%	0.08%	2	2	0.08%	0.08%
Reason B	9	9	0.36%	0.32%	9	9	0.36%	0.32%
Total	11	11	0.44%	0.44%	11	11	0.44%	0.44%

Reason A = Documented sample processing error – Insufficient volume for full volume analysis from the primary aliquot

Reason B = Sample outside limits of curve range (ALQ)

Table 4. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
<i>All PK BE Studies</i>		
MPI-SOP-BIO-GEN-0019 (v. 2.0)	2/4/2015	Chromatography Acceptance Criteria
<i>Studies MGR001-1006 and MGR001-1007 only</i>		
MGWBIO-SOP-BIO-GEN-0018 (v. 3.0)	9/3/2013	Evaluation and Acceptance Criteria for Analytical Runs
MGWBIO-SOP-BIO-GEN-0020 (v. 3.0)	9/3/2013	Re-assay or Re-injection of Clinical Samples
<i>Studies MGR001-1005 and MGR001-1014 only</i>		
MPI-SOP-BIO-GEN-0018 (v. 4.0)*	8/27/2015	Evaluation and Acceptance Criteria for Analytical Runs
MPI-SOP-BIO-GEN-0020 (v. 4.0)*	8/27/2015	Re-assay or Re-injection of Clinical Samples

* Please see details about this SOP version update in reviewer's comments of Section 5.1.3.3.

Reanalysis SOPs submitted?	Yes
Do you agree that the reassay criteria: analytical and pharmacokinetic	Yes
If not, list the criteria that you don't agree and provide additional comment below	N/A
Are the data in the summary table consistent with the data in the full analytical report?	Yes
If not, provide comment below	N/A
Did reviewer reanalyze study results?	Yes

Was the study outcome changed based on reviewer reanalysis?	No
Did the firm provide a comprehensive table of repeat samples in the format recommended by the DB?	Yes
Did the firm provide numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log)?	Yes

Comments from the Reviewer:

Reviewer's note: For each of the fasting study, the firm assigned each subject with both a subject number (b) (4)

It appears that the firm's clinical study reports prefer to refer to subjects using their subject numbers, whereas the bioanalytical report prefers to refer to subjects using their randomization numbers. Therefore, to be consistent with the firm's report, the clinical portion of the review will refer to a subject mostly using subject number, whereas the analytical portion of the review will mostly use randomization number. For subjects with clinical-related issues that may impact PK analysis (e.g. protocol deviations), the reviewer will list out both subject number and randomization number in reviewer's comments. For details about each subject's subject number and randomization number, please refer to the randomization scheme in the Study Design section under each individual fasting study.

4.6.1 Fasting Study MGR001-1006

Fasting Study MGR001-1006 - Fluticasone Propionate (FP)

Poor Chromatography

Two (2) samples were reassayed due to poor chromatography. For information on poor chromatography, SOP MGWBIO-SOP-BIO-GEN-0020 "Re-assay or Re-injection of Clinical Samples" referred to SOP MPI-SOP-BIO-GEN-0019 "Chromatography Acceptance Criteria". Relevant information in SOP MPI-SOP-BIO-GEN-0019 on poor chromatography of study samples included following statement: "*Chromatograms may be rejected for 'poor chromatography' in cases where a significant time shift occurred for the analyte or internal standard.*" Additionally, according to the aforementioned SOP, samples reassayed due to poor chromatography should be reassayed in singlet.

The rejected chromatograms of these 2 samples (Subject (b) (6), Period 2, 3 hrs; and Subject (b) (6), Period 1, 24 hrs) both had retention time shift for both the analyte and internal standard (IS). Therefore, the reviewer considers these repeats identified as per SOP. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Abnormal Internal Standard (IS) Response

Three (3) samples were reassayed due to abnormal IS response. SOP MGWBIO-SOP-BIO-GEN-0020 states: “For each batch run, the mean internal standard peak area (or height) of all acceptable calibrators will be calculated. A clinical sample having an internal standard peak area (or height) < 40% or > 180% of this mean will be re-assayed due to abnormal internal standard response.” Additionally, according to the aforementioned SOP, samples reassayed due to abnormal IS response should be reassayed in singlet. The reviewer verified that reassay and final reporting of all samples were in accordance with SOP (see table below).

Subject	Period	Time (hr)	Original Run				Repeated Run			
			IS Response	Mean IS Response of the Respective Batch	Beyond 40%-180% of Mean IS Response	Original Concentration (pg/mL)	IS Response	Mean IS Response of the Respective Batch	Within 40%-180% of Mean IS Response	Repeated Concentration (pg/mL)
(b) (6)	2	48	112022	329084	Yes	3.052	119201	128920	Yes	BLQ
	1	0.03	0	~375000	Yes	No peak detected	112405		Yes	35.71
	2	0	0	~320000	Yes	No peak detected	128878		Yes	BLQ

Documented Sample Processing Error – broken vial, sample lost

Three (3) samples were reassayed due to documented sample processing error – broken vial, sample lost. SOP MGWBIO-SOP-BIO-GEN-0020 states that “documented sample processing error or analyst error” should be reassayed in singlet, but did not specify detailed conditions that could be classified as sample processing error. According to the numerical raw data, All of these 3 samples (Subject (b) (6), Period 1, 3 hrs; Subject (b) (6), Period 1, 0.75 hr and Subject (b) (6), Period 1, 12 hrs) had 0 response for both analyte and IS. Therefore, the reviewer considers these samples identified per SOP. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Documented Sample Processing Error – sample was not transferred to collection plate

One (1) sample (Subject (b) (6) Period 1, 0.08 hr) was reassayed due to documented sample processing error – sample was not transferred to collection plate. According to the numerical raw data, this sample had 0 response for both analyte and IS. Therefore, the reviewer considers these samples identified per SOP. The first reassay of this sample failed (and reassay concentration listed as “not reportable”) due to documented sample processing error – insufficient volume in Aliquot 1, Aliquot 2 was utilized for re-assay in Run 78, which is evaluated below.

Documented Sample Processing Error – insufficient volume in Aliquot 1, Aliquot 2 was utilized for re-assay in Run 78

As mentioned above, the reassay of sample (Subject (b) (6), Period 1, 0.08 hr) due to “documented sample processing error – sample was not transferred to collection plate” failed due to “documented sample processing error – insufficient volume in Aliquot 1, Aliquot 2 was utilized for re-assay in Run 78”. According to the numerical raw data, although this sample had 0 response for analyte, the response for IS was acceptable (within 40%-180% of mean IS of its run). In the firm’s 9/22/2016 ECD response, the firm stated that during the reassay of this sample, the analyst documented the following on the sample plate map during plasma sample aliquotting step: “*Sample is QNS⁴⁹ for assay. Sample will be re-assayed using aliquot 2 at a later time. 800 µL water will be added to this well.*” The reviewer verified the above documentation based on the sample plate map provided by the firm. The firm also stated that the reason why this sample exhibited a normal IS response is because IS was added to all 96 wells in the plate using the (b) (4) handling workstation. Because this well received the normal amount of IS, and the extraction proceeded as per the method procedure, the resultant IS peak area was in the acceptable range. Therefore, the reviewer considers this sample identification acceptable. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Documented Sample Processing Error – sample would not pass through extraction plate, Aliquots 1 and 2 combined for re-assay in Run 78

One (1) sample (Subject (b) (6), Period 2, 1.5 hr from the repeated run for Subject (b) (6)) was reassayed due to documented sample processing error – sample would not pass through extraction plate, Aliquots 1 and 2 combined for re-assay in Run 78. According to the numerical raw data, this sample had 0 response for both analyte and IS. Therefore, the reviewer considers these samples identified per SOP. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Sample outside Limits of Curve Range (BLQ)

Five (5) samples were reassayed due to BLQ. SOP MGWBIO-SOP-BIO-GEN-0020 states: “*If the LLOQ of the standard curve is deactivated: Any samples that are BLQ after the LLOQ is deactivated*” should be reassayed. Additionally, according to the aforementioned SOP, samples reassayed due to BLQ should be reassayed in singlet. All of these 5 samples were from Subject (b) (6), which were originally analyzed in Run 34. According to the numerical raw data, the LLOQ of this Run 34 had 0 response for both analyte and IS. Therefore, the reviewer agrees that this LLOQ is not acceptable. The reviewer verified from the firm’s original concentration of these samples (provided in the firm’s 9/22/2016 ECD response) that all of these 5 samples had their concentration below the concentration of the next acceptable CS (2 pg/mL). Therefore, the reviewer considers these samples identified per SOP. The reviewer also verified that final reporting of these samples were in accordance with SOP.

⁴⁹ According to the firm, QNS = quantity not sufficient.

Rejected Run (not listed under repeat analysis)

Five (5) runs were rejected and 1 additional run (Run 63) was listed as “N/A”. Please see detail and reviewer’s comments below.

Subject #	Run ID	Firm’s Reason for Run Rejection	Run Repeated?	Run Rejected?	Reviewer’s Comments
(b) (6)	38	Instrument malfunction (deteriorated guard column)	--	Yes	Please see comments below
	40	Unacceptable FP standard curve	Yes	--	Agree (rejected per SOP)
	41	Instrument malfunction (LC/MS system paused on sample 56)	--	Yes	Agree (b) (6)
	63	Run was “not imported into (b) (4) due to analyst error (incorrect plate was injected)”.	--	--	Please see comments below
	56	Unacceptable FP QCs	Yes	--	Agree (rejected per SOP)
	68	Unacceptable FP QCs	Yes	--	Agree (rejected per SOP)

For Subject (b) (6) (Run ID 38) that was rejected due to “instrument malfunction (deteriorated guard column)”, there are no apparent issues in the firm’s numerical raw data of the original run. Therefore, it is difficult to verify the reason of this run rejection. However, since the whole run was re injected, and all samples had their re injected concentration within 15% of their original injection concentration except 1 sample at the elimination phase (Subject (b) (6), Period 1, 48 hr, with original injection concentration as BLQ and re injection concentration as 1.681 pg/mL), the reviewer will not pursue this issue further. The time interval between the start of the original injection to the end of the re injection is 15.5 hrs, which is adequately covered by validated processed stability of 74 hrs at 4°C (autosampler temperature).

For Subject (b) (6) re injection (Run 63) that had a run status as “N/A”, the firm stated that the run was “not imported into (b) (4) due to analyst error (incorrect plate was injected)”. In the 9/22/2016 ECD response, the firm further stated that when the results from this run were reviewed, it was observed that the chromatograms at the end of the run contained no peaks. Because

no apparent reason for the lack of peaks was found, the location of the Subject (b) (6) 96-well plate in the autosampler was checked. It was found that the plate containing Subject (b) (6), not Subject (b) (6), was in the autosampler position specified in the Run 63 acquisition sequence, meaning that Subject (b) (6) had inadvertently been reinjected instead of Subject (b) (6). The firm also provided an incident report form that documented these observations and conclusions. The reviewer noticed from the raw data that the last 3 samples of the Run 63 had analyte peak area of 0, and Subject (b) (6) had 3 fewer samples as compared to Subject (b) (6). This is consistent with the firm's statement that the last 3 chromatograms of this run contained no peaks and the plate containing Subject (b) (6) was analyzed in place of Subject (b) (6). Therefore, the reviewer considers the firm's reason for not accepting this run acceptable. The firm reinjected Subject (b) (6) in Run 65. And as mentioned above, the time interval between the start of the original injection of this subject (Run 41) to the end of the reinjection of this subject (Run 65) is adequately covered by validated processed stability.

Fasting Study MGR001-1006 - Salmeterol (SA)

Poor Chromatography

Two (2) samples were reassayed due to poor chromatography. The rejected chromatograms of these 2 samples (Subject (b) (6), Period 2, 3 hrs; and Subject (b) (6), Period 1, 24 hrs) both had retention time shift for both the analyte and IS. Therefore, the reviewer considers these repeats identified as per SOP. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Abnormal IS Response

Three (3) samples were reassayed due to abnormal IS response. The reviewer verified that reassay and final reporting of all samples were in accordance with SOP (see table below).

Subject	Period	Time (hr)	Original Run				Repeated Run			
			IS Response	Mean IS Response of the Respective Batch	Beyond 40%-180% of Mean IS Response	Original Concentration (pg/mL)	IS Response	Mean IS Response of the Respective Batch	Within 40%-180% of Mean IS Response	Repeated Concentration (pg/mL)
(b) (6)	2	48	260637	974856	Yes	4.208	264524	311284	Yes	1.474
	1	0.03	0	~1010000	Yes	No peak detected	251868		Yes	259.5
	2	0	3769	~975000	Yes	No peak detected	303298		Yes	BLQ

Documented Sample Processing Error – broken vial, sample lost

Three (3) samples were reassayed due to documented sample processing error – broken vial, sample lost. According to the numerical raw data, all of these 3 samples (Subject (b) (6), Period 1, 3 hrs; Subject (b) (6), Period 1, 0.75 hr and Subject (b) (6), Period 1, 12 hrs) had 0 response for both analyte and IS. Therefore, the reviewer considers these samples identified per SOP. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Documented Sample Processing Error – sample was not transferred to collection plate

One (1) sample (Subject (b) (6), Period 1, 0.08 hr) was reassayed due to documented sample processing error – sample was not transferred to collection plate. According to the numerical raw data, this sample had 0 response for both analyte and IS. Therefore, the reviewer considers these samples identified per SOP. The first reassay of this sample failed (and reassay concentration listed as “not reportable”) due to documented sample processing error – insufficient volume in Aliquot 1, Aliquot 2 was utilized for re-assay in Run 78, which is evaluated below.

Documented Sample Processing Error – insufficient volume in Aliquot 1, Aliquot 2 was utilized for re-assay in Run 78

As mentioned above, the reassay of sample (Subject (b) (6), Period 1, 0.08 hr) due to “documented sample processing error – sample was not transferred to collection plate” failed due to “documented sample processing error – insufficient volume in Aliquot 1, Aliquot 2 was utilized for re-assay in Run 78”. According to the numerical raw data, although this sample had 0 response for analyte, the response for IS was acceptable (within 40%-180% of mean IS of its run). As detailed in the FP section above for this study sample, the firm provided additional supporting information in their 9/22/2016 ECD response, and the reviewer considers this sample identification acceptable. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Sample outside Limits of Curve Range (BLQ)

Four (4) samples were reassayed due to BLQ. All of these 4 samples were from Subject (b) (6), which were originally analyzed in Run 34. According to the numerical raw data, the LLOQ of this Run 34 had 0 response for both analyte and IS. Therefore, the reviewer agrees that this LLOQ is not acceptable. The reviewer verified from the firm’s original concentration of these samples (provided in the firm’s 9/22/2016 ECD response) that all of these 4 samples had their concentration below the concentration of the next acceptable CS (2 pg/mL). Therefore, the reviewer considers these samples identified per SOP. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Sample Outside Limits of Curve Range (ALQ)

Twelve (12) samples were reassayed due to ALQ. These samples were correctly identified based on pre-established criterion in the SOP, and all reassayed values were higher than the highest CS (600.0 pg/mL). Final reporting of these samples were in accordance with SOP. All of the 12 reassayed values were greater than the highest CS after adjusting for dilution factor.

Rejected Run (not listed under repeat analysis)

Two (2) runs were rejected and 1 run was listed as “N/A”. Please see detail and reviewer’s comments in the table below.

Subject #	Run ID	Firm’s Reason for Run Rejection	Run Repeated?	Run Rejected?	Reviewer’s Comments
(b) (6)	38	Instrument malfunction (deteriorated guard column)	--	Yes	Justifiable (please see reviewer’s comments for the same run in the FP section above. In addition, similar to FP, all SA samples had their reinjected concentration within 15% of their original injection concentration)
	41	Instrument malfunction (LC/MS system paused on sample 56)	--	Yes	Agree (please see reviewer’s comments for the same run in the FP section above)
	63	Run was “not imported into (b) (4) due to analyst error (incorrect plate was injected)”.	--	--	Agree (please see reviewer’s comment for the same run in the FP section above)

4.6.2 Fasting Study MGR001-1007

Fasting Study MGR001-1007 - FP

Measurable Concentration in Subject Zero Sample

Four (4) samples were reassayed due to measurable concentration in subject zero sample. SOP MGWBIO-SOP-BIO-GEN-0020 states: “If the assayed concentration in a pre-dose sample is $\geq$ LLOQ (i.e., a measurable concentration), the sample will be re-assayed in triplicate (volume permitting) to confirm the original results.” The reviewer verified that the original concentration of these 4 samples were all greater than LLOQ (1.0 pg/mL), thus these samples were identified per SOP. The firm repeated in these samples in singlet, likely due to insufficient sample volume. For reporting of the final concentration, the aforementioned SOP states that if all re-assay replicates are $\geq$ LLOQ, and “if the CV of all the results (including the original) is $\leq$ 25%, then the mean of all determinations will be reported.” All of these samples had repeated concentration $\geq$ LLOQ, and

the %CV of their repeat and the original concentration is $\leq 7.22\%$. The reviewer verified that final reporting of these samples were in accordance with SOP (mean value of the original and repeated concentration were reported).

Documented Sample Processing Error – broken vial

Six (6) samples were reassayed due to documented sample processing error – broken vial. According to the numerical raw data, 1 sample (Subject (b) (6), Period 2, 36 hrs) had both analyte and IS response $\leq 10\%$ as compared to those of the adjacent samples; 4 samples (Subject (b) (6), Period 1, 6 hrs; Subject (b) (6), Period 2, 0.75 hr; Subject (b) (6), Period 2, 48 hrs; and Subject (b) (6), Period 1, 0.33 hr) had 0 response for both analyte and IS. Therefore, the reviewer considers these 5 samples identified per SOP.

For Subject (b) (6), Period 2, 3 hrs, both analyte and IS response are about 30%-40% lower than adjacent samples, but this sample still meets acceptance criteria for IS. In the firm’s 9/22/2016 ECD response, the firm stated that during the extraction of this sample, the analyst documented the following on the sample plate map: “*Cracked vial observed following the execution of program FLSA_15006_Transfer_v1_OP_SP23HTA⁵⁰.*” The reviewer verified the above documentation based on the sample plate map provided by the firm. The firm also stated that the IS response for this sample, while acceptable, was on the low end of the acceptance range (the reviewer verified that the IS response of this sample is 43% of mean IS response of this run, whereas the acceptable criteria for IS response is 40%-180%), and the relatively low IS response for this sample was consistent with the loss of a portion of the extract volume due to the cracked vial in the extraction step. Therefore, the reviewer considers this sample identification acceptable.

The reviewer also verified that final reporting of these samples were in accordance with SOP.

Abnormal IS Response

Two (2) samples were reassayed due to abnormal IS response. The reviewer verified that reassay and final reporting of all samples were in accordance with SOP (see table below).

Subject	Period	Time (hr)	Original Run				Repeated Run			
			IS Response	Mean IS Response of the Respective Batch	Beyond 40%-180% of Mean IS Response	Original Concentration (pg/mL)	IS Response	Mean IS Response of the Respective Batch	Within 40%-180% of Mean IS Response	Repeated Concentration (pg/mL)
(b) (6)	1	4	162195	531986	Yes	202.9	100183	~150000	Yes	204.1
	2	0.25	55097	~150000	Yes	279.3	276258	~420000	Yes	305.3

Fasting Study MGR001-1007 - SA

Sample Outside Limits of Curve Range (ALQ)

Seventeen (17) samples were reassayed due to ALQ. These samples were correctly identified based on pre-established criterion in the SOP, and all reassayed values were higher than the highest CS (600.0 pg/mL). Final reporting of these subjects were in accordance with SOP. It should be noted that reassay of 1 sample (Subject (b) (6), Period 2, 0.03hr) was rejected due to “documented sample processing error – broken vial”, which will be evaluated below. All of the 17 reassayed values were greater than the highest CS (600 pg/mL) after adjusting for dilution factor.

Documented Sample Processing Error – broken vial

Six (6) samples were reassayed due to documented sample processing error – broken vial. According to the numerical raw data, 1 sample (Subject (b) (6), Period 2, 36 hrs) had both analyte and IS response ≤20% as compared to those of the adjacent samples; 4 samples (Subject (b) (6), Period 1, 6 hrs; Subject (b) (6), Period 2, 0.75 hr; Subject (b) (6), Period 2, 48 hrs; and Subject (b) (6), Period 1, 0.33 hr) had 0 response for both analyte and IS. Therefore, the reviewer considers these 5 samples identified per SOP. For Subject (b) (6) Period 2, 3 hrs, both analyte and IS response are about 70% lower than those of the adjacent samples, and this sample does not meet acceptance criteria for IS. Therefore, the reviewer considers this sample rejection acceptable. The reviewer also verified that final reporting of all these 6 samples were in accordance with SOP.

As mentioned above, Subject (b) (6), Period 2, 0.03hr, which was first reassayed due to ALQ, was rejected due to documented sample processing error – broken vial. According to the numerical raw data, this sample had 0 response for both analyte and IS. Therefore, the reviewer considers these 5 samples identified per SOP. The reviewer also verified that final reporting of this sample was in accordance with SOP.

Abnormal IS Response

One (1) sample was reassayed due to abnormal IS response. The reviewer verified that reassay and final reporting of this sample was in accordance with SOP (see table below).

Subject	Period	Time (hr)	Original Run				Repeated Run			
			IS Response	Mean IS Response of the Respective Batch	Beyond 40%-180% of Mean IS Response	Original Concentration (pg/mL)	IS Response	Mean IS Response of the Respective Batch	Within 40%-180% of Mean IS Response	Repeated Concentration (pg/mL)
(b) (6)	1	4	352071	972722	Yes	26.35	209286	~360000	Yes	25.65

Rejected Run (not listed under repeat analysis)

Three (3) runs were rejected. Please see detail and reviewer’s comments in the table below.

Subject #	Run ID	Firm’s Reason for Run Rejection	Run Repeated?	Run Rejected?	Reviewer’s Comments
(b) (6)	23	Poor chromatography for SA	Yes	--	Please see reviewer’s comment below
	47	Unacceptable SA QCs	Yes	--	Agree (rejected per SOP)
	58	Unacceptable SA QCs	Yes	--	Agree (rejected per SOP)

The firm stated that this Run 23 was rejected due to poor chromatography for SA. According to SOP MPI-SOP-BIO-GEN-0019, “[chromatograms may be rejected for ‘poor chromatography’ in cases where peak shape is aberrant for the analyte or internal standard.” This SOP also states “[p]eak shape is described as aberrant when the peak splits, becomes excessively wide, fronts or tails, relative to the typical chromatographic peaks for a particular assay”. In addition, “[i]f greater than 20% of the samples from a given subject do not meet the acceptance criteria in this SOP, the entire subject will be rejected and re-assayed.” Based on the firm’s rejected chromatograms, it is noticed that most of the analyte and IS peak in this run had aberrant peak shape with tail (please see representative chromatograms below). Therefore, the reviewer considers rejection of this run per SOP. The reviewer also verified that final reporting of this sample was in accordance with SOP.



4.6.3 Fasting Study MGR001-1005

Fasting Study MGR001-1005 - FP

Abnormal IS Response

Five (5) samples were reassayed due to abnormal IS response. The reviewer verified that reassay and final reporting of all samples were in accordance with SOP (see table below).

Subject	Period	Time (hr)	Original Run				Repeated Run				
			IS Response	Mean IS Response of the Respective Batch	Beyond 40%-180% of Mean IS Response	Original Concentration (pg/mL)	IS Response	Mean IS Response of the Respective Batch	Within 40%-180% of Mean IS Response	Repeated Concentration (pg/mL)	
(b) (6)	1	0.5	78855	201478	Yes	173.0	165490	216396	Yes	180.8	
	2	36	80166		Yes	8.755			183562	Yes	9.300
	1	2	53499	152739	Yes	174.0			218001	Yes	170.7
	1	0.5	46856	125273	Yes	232.5			220830	Yes	210.9
	2	15	0	346746	Yes	No peak detected			220403	Yes	185.3

Documented Sample Processing Error – cracked vial

One (1) sample (Subject (b) (6), Period 1, 0.08 hr) was reassayed due to documented sample processing error – cracked vial. According to the numerical raw data, this sample had 0 response for both analyte and IS. Therefore, the reviewer considers this sample identified per SOP. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Documented Sample Processing Error – insufficient sample volume

Three (3) samples (Subject (b) (6), Period 2, 0.03 hr, 0.08 hr and 8 hrs) were reassayed due to “documented sample processing error – insufficient sample volume”. According to the numerical raw data, although these sample had 0 response for analyte, the response for IS was acceptable (within 40%-180% of mean IS of its run). In the 9/22/2016 ECD response, the firm stated that during the sample aliquotting step of the reassay of these 3 samples (the original run of this Subject (b) (6) was rejected, which is evaluated in rejected run below), the analyst noticed that there was insufficient plasma volume in these samples. The firm also provided sample plate map of this run with analyst’s documentation of this observation (“*Insufficient volume in tube. Samples will be analyzed at a later time. 800 µL water added.*”). The firm also stated that the reason these samples exhibited a normal IS response because IS was added to all 96 wells in the plate using the (b) (4) handling workstation. Since these 3 wells received the normal amount of IS, and the extraction proceeded as per the method procedure, the resultant IS peak areas were in the acceptable range. Therefore, the reviewer considers these sample identification acceptable. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Poor Chromatography

One (1) sample (Subject (b) (6), Period 1, 0.08 hr) was reassayed due to poor chromatography. And the firm stated that the poor chromatography determination was based on shifted retention times for the analyte. The reviewer verified that this sample had

retention time shift for both the analyte and IS. Therefore, the reviewer considers these repeats identified as per SOP. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Rejected Run (not listed under repeat analysis)

Two (2) runs were rejected and 2 runs were listed as “N/A”. Please see details and reviewer’s comments below.

Subject #	Run ID	Firm’s Reason for Run Rejection	Run Repeated?	Run Reinjected?	Reviewer’s Comments
(b) (6)	23	Sample processing /analyst error-plate was lost during assay procedure	Yes	--	Agree (please see reviewer’s comments below)
	34		Yes	--	Agree (please see reviewer’s comments below)
	26	QCs did not meet batch acceptance criteria for FP	Yes	--	Agree (rejected per SOP)
	49	Blank samples did not meet batch acceptance criteria	Yes	--	Agree (rejected per SOP)

The firm did not have raw data for Subjects (b) (6) (Run 23) and (b) (6) (Run 34).

For Subject (b) (6) (Run 23), the firm stated in the 9/22/2016 ECD response that during the extraction of this run, the analyst observed a leaking pipettor tip during the addition of IS to the Period 1, 12 h sample. The firm also provided sample plate map of this run with analyst’s documentation of this observation (“*Tip observed dripping during the addition of internal standard. Well appears lower in volume than surrounding wells. It is uncertain which wells were effected by the dripping. Extraction was aborted and sample plate won’t be analyzed.*”). The firm also stated that as documented in the note, the sample plate was not analyzed and thus no raw data was generated. And since the analyst’s observations were clear and well documented, no additional investigation was deemed necessary and this run was repeated. The reviewer considers this run rejection acceptable.

For Subject (b) (6) (Run 24), the firm stated in the 9/22/2016 ECD response that during the extraction of this run, the analyst observed that the vials had broken during the MTBE extract transfer step due to bent tips on the (b) (4) handling workstation. The firm also provided sample plate map of this run with analyst’s documentation of this observation (“*During transfer step, bent tips caused the (b) (4) to pick up vials out of plate holder resulting in broken vials. Extraction will not be completed.*”). The firm also stated that as documented in the note, the extraction was not completed, thus the samples were not analyzed and no raw data was generated. In addition, since the analyst’s observations were clear and well documented, no additional investigation was deemed necessary and this run was repeated. The reviewer considers this run rejection acceptable.

Fasting Study MGR001-1005 - SA

Sample Outside Limits of Curve Range (ALQ)

Thirty-two (32) samples were reassayed due to ALQ. These samples were correctly identified based on pre-established criterion in the SOP, and all reassayed values were higher than the highest CS (600.0 pg/mL). Final reporting of these samples was in accordance with SOP. And all of the 32 reassayed values were greater than the highest CS (600 pg/mL) after adjusting for dilution factor, except for 1 sample that had reassayed value was 96.9% of the highest CS after adjusting for dilution factor.

Abnormal IS Response

Nineteen (19) samples were reassayed due to abnormal IS response. The reviewer verified that reassay and final reporting of all samples were in accordance with SOP (see table below).

Subject	Period	Time (hr)	Original Run				Repeated Run				
			IS Response	Mean IS Response of the Respective Batch	Beyond 40%-180% of Mean IS Response	Original Concentration (pg/mL)	IS Response	Mean IS Response of the Respective Batch	Within 40%-180% of Mean IS Response	Repeated Concentration (pg/mL)	
(b) (6)	1	0.33	83662	218299	Yes	50.01	341048	405306	Yes	50.29	
		0.5	83273		Yes	47.68	541282		Yes	50.39	
		1.5	82212		Yes	38.59	485402		Yes	39.06	
		4	86933		Yes	15.35	508610		Yes	14.60	
		48	85601		Yes	0.4925	358480		Yes	BLQ	
	2	0	85697		Yes	No peak detected	387242		Yes	BLQ	
		0.03	86240		Yes	142.5	417773		Yes	147.4	
		0.25	83103		Yes	102.9	308832		Yes	111.7	
		3	86981		Yes	25.06	456039		Yes	25.65	
		4	82860		Yes	18.89	399770		Yes	18.79	
		12	86770	Yes	6.288	416723	Yes		6.319		
		1	0.5	72426	221094	Yes	130.3		406361	Yes	127.0
		2	15	0	~635000	Yes	No peak detected		411655	Yes	93.60
		2	0.08	1064780	564075	Yes	463.3		680230	Yes	468.6
			0.25	1070908		Yes	186.6		628227	Yes	194.2
	2		1040860	Yes		50.28	624137	Yes	52.46		
	6		1026218	Yes		22.78	645884	Yes	22.91		
	24		1089919	Yes		7.849	548133	Yes	7.639		
	2	0.75	1034276	573659	Yes	113.0	529263	Yes	113.8		

Documented Sample Processing Error – cracked vial

One (1) sample (Subject (b) (6) Period 1, 0.08 hr) was reassayed due to documented sample processing error – cracked vial. According to the numerical raw data, this sample had 0 response for both analyte and IS. Therefore, the reviewer considers this sample identified per SOP. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Documented Sample Processing Error – insufficient sample volume

Three (3) samples (Subject (b) (6), Period 2, 0.03 hr, 0.08 hr and 8 hrs) were reassayed due to “documented sample processing error – insufficient sample volume”. According to the numerical raw data, although these sample had 0 analyte response or <1% analyte response as compared to adjacent samples, the response for IS was acceptable (within 40%-80% of mean IS of its

run). As detailed in the FP section above, the firm stated that insufficient volume was observed during the sample aliquotting step, and provided analyst’s documentation of this observation. The firm also stated that IS was added to all 906 wells in the plate using (b)(4) handling workstation, thus IS peak areas of these 3 samples were in the acceptable range. Therefore, the reviewer considers these sample identification acceptable. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Poor Chromatography

One (1) sample (Subject (b)(6), Period 1, 0.08 hr) was reassayed due to poor chromatography. And the firm stated that the poor chromatography determination was based on shifted retention times for the analyte. The reviewer verified that this sample had retention time shift for both the analyte and IS. Therefore, the reviewer considers these repeats identified as per SOP. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Rejected Run (not listed under repeat analysis)

One (1) run was rejected and 2 runs were listed as “N/A”. Please see details and reviewer’s comments below.

Subject #	Run ID	Firm’s Reason for Run Rejection	Run Repeated?	Run Reinjected?	Reviewer’s Comments
(b)(6)	23	Sample processing /analyst error-plate was lost during assay procedure	Yes	--	Agree (please see reviewer’s comments in the FP section above)
	34		Yes	--	Agree (please see reviewer’s comments in the FP section above)
	49	Blank samples did not meet batch acceptance criteria	Yes	--	Agree (rejected per SOP)

4.6.4 Fasting Study MGR001-1014

Fasting Study MGR001-1014 – FP

Documented sample processing error – Insufficient volume for full volume analysis from the primary aliquot

Four (4) samples were reassayed due to documented sample processing error – Insufficient volume for full volume analysis from the primary aliquot. According to the bioanalytical report, the following incidences occurred to these samples:

1. These 4 samples (Subject (b) (6), Period 1, 0.16 hr; Subject (b) (6), Period 1, 0.16 hr and 0.75 hr, and Period 2, 2 hrs) were originally analyzed in Run 50 (Subjects (b) (6) Period 1).⁵¹ However, the firm stated that this Run 50 was lost during assay procedure due to a leaking in (b) (4) tip (the reviewer agrees with this run rejection as detailed in the rejected run section below). All samples of these run were planned to be reanalyzed in Run 76.⁵²
2. However, these 4 samples had insufficient volume in the primary aliquot for full volume analysis in this whole subject reassay Run 76. And at time, the secondary aliquot had not yet been received from the clinical site.⁵¹
3. Three (3) of these samples (Subject (b) (6), Period 1, 0.16 hr; Subject (b) (6), Period 1, 0.75 hr, and Period 2, 2 hrs) were analyzed at half volume (with dilution factor of 2) in Run 48 using the primary aliquot, along with other miscellaneous samples that required dilution by the same factor.⁵¹ However, the firm stated that this Run 48 did not meet batch acceptance criteria for FP (the reviewer agrees with this run rejection as detailed in the rejected run section below), thus these 3 samples were reassayed in Run 78 at full volume using the secondary aliquot.
4. For sample Subject (b) (6), Period 1, 0.16 hr, the firm stated that it had insufficient volume remaining in primary aliquot for half volume analysis, thus was analyzed in Run 78 at full volume using the secondary aliquot.

The reviewer considers these sample identification acceptable. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Rejected Run (not listed under repeat analysis)

Two (2) runs were rejected and 1 run was listed as “N/A”. Please see detail and reviewer’s comments below.

⁵¹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.1.4. mgr001-1014...\MGR001-1014 Bioanalytical Report, p. 9 of 13).

⁵² GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.1.4. mgr001-1014...\MGR001-1014 Bioanalytical Report Appendix 1... p. 10 of 1846).

Subject #	Run ID	Firm's Reason for Run Rejection	Run Repeated?	Run Rejected?	Reviewer's Comments
(b) (6)	50 (sample extraction date: (b) (6))	Plate was lost during assay procedure (leaking (b) (4) tip)	Yes (whole run repeated in Run 76, with the exception of 3 samples that were reassayed in Run 48 or and 1 sample in Run 78)	--	Agree (please see reviewer's comments below)
(b) (6)	48 (sample extraction date: (b) (6))	Did not meet batch acceptance criteria for FP QCs	Yes (FP samples were reassayed in Run 78)	--	Agree (please see reviewer's comments below)
(b) (6)	74	Instrument malfunction	--	Yes	Agree (b) (6)

The firm did not have raw data for Subject (b) (6) and Subject (b) (6) (Period 1) (Run #50). The firm stated in the 9/22/2016 ECD response that during the extraction of this run, the analyst observed a leaking pipettor tip during transfer of sample to the solid phase extraction plate. The firm also provided sample preparation procedure source document of this run with analyst's documentation of this observation ("Sample 81 (FZD) sample tip observed to be dripping during sample load to solid phase plate. It is unclear as to which well the sample dripped into. Therefore the extraction will not be completed."). The firm also stated that as documented in the note, the extraction was not completed and thus no raw data was generated. And since the analyst's observations were clear and well documented, no additional investigation was deemed necessary and this run was repeated. The reviewer considers this run rejection acceptable.

For Run 48, the firm's reason of run rejection was that this run did not meet batch acceptance criteria for FP QCs. According to the raw data, this run contained a total of 14 QCs, which include 10 QCs that consisted of one at each concentration (3, 15, 90, 240, and 450 pg/mL for FP) injected prior to the study sample and one at each concentration injected after the study samples (the firm referred to them as "bracketing QCs" in the 9/22/2016 ECD response), as well as 4 dilution QCs (all at

concentration of 900 pg/mL)]. According to SOP MPI-SOP-BIO-GEN-0018, “[a]t least 67% QC samples run before, between (if applicable), and after each set of subject samples must calculate within 15% of the theoretical values.” In addition, the firm further stated in the 9/22/2016 ECD response that the dilution QCs was evaluated independently of the 10 QCs that were used to bracket the runs and that served as the bases for batch acceptance or rejection. According to the raw data, 2 “bracketing QCs” (one at 240 pg/mL and one at 450 pg/mL) injected prior to the study samples had more than 15% difference as compared to their respective theoretical values. Since 60% (3 out of 5) QCs run before subject samples were within 15% of the theoretical values, the reviewer considers the firm’s rejection of this run acceptable.

Fasting Study MGR001-1014 - SA

Sample Outside Limits of Curve Range (ALQ)

Eighteen (18) samples were reassayed due to ALQ. These samples were correctly identified based on pre-established criterion in the SOP, and all reassayed values were higher than the highest CS (600.0 pg/mL). Final reporting of these samples was in accordance with SOP. And all of the 18 reassayed values were greater than the highest CS (600 pg/mL) after adjusting for dilution factor, except for 1 sample that had reassayed value was 95.4% of the highest CS after adjusting for dilution factor.

Documented sample processing error – Insufficient volume for full volume analysis from the primary aliquot

Four (4) samples were reassayed due to documented sample processing error – Insufficient volume for full volume analysis from the primary aliquot. These are the same 4 samples that were repeated due to the same reason in the FP section above. According to the bioanalytical report, similar incidences occurred to these samples as compared to their FP counterpart (please note that points 1, 2 and 4 are the same as in the FP section, but point 3 is different):

1. These 4 samples (Subject (b) (6), Period 1, 0.16 hr; Subject (b) (6), Period 1, 0.16 hr and 0.75 hr, and Period 2, 2 hrs) were originally analyzed in Run 50 (Subjects (b) (6) Period 1).⁵³ However, the firm stated that this Run 50 was lost during assay procedure due to a leaking in (b) (4) tip (the reviewer agrees with this run rejection as detailed in the rejected run section for FP above). All samples of these run were planned to be reanalyzed in Run 76.⁵⁴
2. However, these 4 samples had insufficient volume in the primary aliquot for full volume analysis in this whole subject reassay Run 76. And at time, the secondary aliquot had not yet been received from the clinical site.⁵¹

⁵³ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.1.4. mgr001-1014...\MGR001-1014 Bioanalytical Report, p. 9 of 13).

⁵⁴ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.1.4. mgr001-1014...\MGR001-1014 Bioanalytical Report Appendix 1... p. 10 of 1846).

3. Three (3) of these samples (Subject (b) (6), Period 1, 0.16 hr; Subject (b) (6), Period 1, 0.75 hr, and Period 2, 2 hrs) were analyzed at half volume (with dilution factor of 2) in Run 48 using the primary aliquot, along with other miscellaneous samples that required dilution by the same factor.⁵¹
4. For sample Subject (b) (6) Period 1, 0.16 hr, the firm stated that it had insufficient volume remaining in primary aliquot for half volume analysis, thus was analyzed in Run 78 at full volume using the secondary aliquot.

The reviewer considers these sample identification acceptable. The reviewer also verified that final reporting of these samples were in accordance with SOP.

Rejected Run (not listed under repeat analysis)

One (1) run was rejected and 1 run was listed as “N/A”. Please see detail and reviewer’s comments below.

Subject #	Run ID	Firm’s Reason for Run Rejection	Run Repeated?	Run Rejected?	Reviewer’s Comments
(b) (6)	50 (sample extraction date: (b) (6))	Plate was lost during assay procedure (leaking (b) (4) tip)	Yes (whole run repeated in Run 76, with the exception of 4 samples that were reassayed in Run 48 or 78)	--	Agree (please see reviewer’s comments in the FP section above)
	74	Instrument malfunction	--	Yes	Agree (b) (6)

4.7 Formulation

Location in appendix	Section 5.2. Formulation Data
Is the formulation acceptable?	ACCEPTABLE FROM BE PERSPECTIVE (b) (4) (b) (4), the acceptability of which will be evaluated by OPQ ⁸)
If not acceptable, why?	N/A

4.8 In Vitro Dissolution

N/A

4.9 Waiver Request(s) For Immediate Release Dosage Forms

N/A

4.10 Deficiency Comments

Please note that the following deficiencies are based on the firm's submissions dated 12/29/2015, 2/15/2016, 8/11/2016, 9/22/2016, 9/28/2016, and 1/12/2017.

GENERAL

General Deficiencies

1. The following observations were noted in the firm's submission:

- a) According to their certificates of analysis (COAs), the 3 exhibit batches for each of the 100/50 mcg and 500/50 mcg strengths had device configuration (clinical device: (b) (4) different from the proposed commercial device (b) (4). These exhibit batches were used in pharmacokinetic (PK) studies, in vitro studies for the 100/50 mcg and 500/50 mcg strengths, and the clinical endpoint study.
- b) In the batch formula document (12/29/2015 submission, Module 3.2.P.3.2\Batch Formula, p. 1 of 2), the firm stated that "[t]here are no difference between the batch formula of the registration and commercial batches (b) (4)".
- c) In the pharmaceutical development report (12/29/2015 submission, Module 3.2.P.2\Pharmaceutical Development, p. 541, 544, 667 and 671 of 676), the firm stated that the exhibit batch (b) (4).

would be provided (12/29/2015 submission, Module 3.2.P.2\Pharmaceutical Development, p. 430, 667, 671 and 675 of 676).

- d) In the 12/29/2016 submission, Module 2.3.P\Drug Product Part 1 – FPSX – Mylan Dublin, p. 97 of 107, the firm stated that exhibit batches were manufactured (b) (4)

The firm will be asked to provide (b) (4) (b) (4) as mentioned in c) above for each strength of the drug product.

In Controlled Correspondence 844398, based on the firm's statement of (b) (4) (b) (4) difference between batches used in the pivotal clinical studies and commercial batches, the Agency recommended the firm to demonstrate in vitro bioequivalence (BE) according to the *Draft Guidance on Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder at 60 L/min.* (b) (4)

(b) (4) the firm will be asked to conduct in vitro BE studies [single actuation content (SAC) and aerodynamic particle size distribution (APSD) studies] comparing reference listed drug (RLD) product and the test product with final commercial formulation (b) (4) device (b) (4) and manufacturing process (b) (4) and manufactured (b) (4) as bridging studies. These studies should be conducted for each strength of the product, and should be conducted according to *Draft Guidance on Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder* (recommended September 2013, will be referred to as product-specific guidance in the rest of this deficiency letter) **at 30, 60, and 90 L/min**, and use at least 3 batches each of T and unexpired R products with no fewer than 10 units from each batch.

In the above APSD studies, the firm will be asked to include a standard curve and quality control (QC) samples with three validated concentrations in the range of expected study concentrations with each analytical batch, as outlined in the *Guidance for Industry - Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Actions* (posted April 2003).

2. The firm will be asked to provide COAs for the following RLD batches used in the clinical endpoint study or in vitro BE studies: 4ZP4083 (clinical endpoint study), 5ZP8178, 5ZP8397, 5ZP0114, 4ZP7022, and 5ZP8689 (in vitro studies).

IN VITRO STUDIES

Deficiencies Related to Pre-Study Method Validation for In Vitro Studies

Method Validation – Common to Single Actuation Content (SAC) and Aerodynamic Particle Size Distribution (APSD) Studies

3. It is noted that method validation results for SAC Method # MGR-METH-546070 (Section C of this method) is almost the same as method validation results for Method # MDR-RGMETH-0032 (12/29/2015 submission, Module 3.2.P.5.3\Uniformity of delivered dose Validation Report – MDR-RGMETH-0032). The firm will be asked to clarify if these are the same method validation studies.

Similarly, it is noted that method validation results for APSD Method # MGR-METH-546069 (Section C of this method) is almost the same as method validation results for Method # MDR-RGMETH-0031 (12/29/2015 submission, Module 3.2.P.5.3\Aerodynamic Particle Size Distribution Validation Report – MDR-RGMETH-0031). For the former method validation results, the firm also included “achievable LOQ of method” that was not reported in the latter method validation report. The firm will be asked to clarify if these are the same method validation studies.

The firm will be asked to provide street address as well as study dates for their method validation studies for each of aforementioned 4 methods. During Office of Study Integrity and Surveillance (OSIS) inspection at (b) (4), it was found out that the analytical methods performed by (b) (4) were developed and validated by Mylan Global Respiratory Group prior to the transfer to (b) (4), according to (b) (4) method transfer protocol. Since the method validation and in vitro BE studies for the 100/50 and 500/50 mcg strengths were conducted at different sites, the firm will be asked to provide method transfer report for method transfer from Mylan Global Respiratory Group to (b) (4) and from (b) (4), (b) (4). The firm will be advised that if method validation studies were conducted at different sites from any of the in vitro BE studies, then method transfer studies (e.g. precision and accuracy studies for the HPLC method; and precision study for the SAC and APSD methods) are needed to support method transfer between different study sites. The firm will also be advised that method transfer studies for the SAC and APSD methods should be conducted using unexpired RLD product.

4. The firm will be asked to validate accuracy (% recovery at the high and low concentrations) and precision/intermediate precision of the UPLC method that was used in each of the SAC and APSD method. Accuracy and precision should be evaluated with known amounts of fluticasone propionate (FP) and salmeterol (SA) relevant to expected sample concentrations spiked into placebo solution.

Method Validation – SAC Studies only

5. The firm will be asked to provide the flow rate, actuation time and volume of air drawn through the delivery system for the intermediate precision study of SAC.

Method Validation – APSD Studies only

6.  (b) (4)

7. The firm will be asked to provide actuation time and volume of air drawn through the delivery system for the intermediate precision study of APSD.
8. The firm will be asked to provide dose counter number for each of the test and RLD device used in the intermediate precision study of APSD.
9. According to the method validation report of method MDR-RGMETH-0031 (12/29/2015 submission, Module 3.2.P.5.3\Aerodynamic Particle Size Distribution Validation Report – MDR-RGMETH-0031, p. 9 of 26), 3 columns were used in the intermediate precision study of APSD. However, in the firm's test plan table on the same page, only 2 columns were listed. Therefore, the firm will be asked to clarify this discrepancy.

Deficiencies Related to Information Common to All In Vitro Studies (057755-02-04, MGR-PRO-2015-080, 057755-02-07, MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093)

Both SAC and APSD Studies

10. According to the study protocols, the firm used randomization scheme to minimize potential laboratory bias during testing. The firm will be asked to clarify if they used any blinding/unblinding approach during each of the SAC and APSD study. If yes, they will be asked to provide details on what procedures were taken for blinding/unblinding.
11. In Method #s MGR-METH-546070 (Version 7.0, p. 7 of 38) for SAC study and MGR-METH-546069 (Version 6.0, p. 6 of 37) for APSD study, the firm stated that during sample preparation,  (b) (4)
 The firm will also be asked to clarify if they did sealing for the RLD device.

12. According to Method # MGR-METH-546070 (Version 7.0, p. 8 of 38), for emitted dose test set-up, the firm stated that when attaching the mouthpiece adaptor to the (b) (4), “ensuring that the raised notch is pointing downwards at the 6 o’clock position. (Diskus/Accuhaler attach the mouthpiece adaptor to the (b) (4) ensuring that the raised notch is pointing horizontally at the 9 o’clock position.)” The firm also had a similar statement about mouthpiece adapter attachment to the throat in Method # MGR-METH-546069 (Version 6.0, p. 8 of 37) for APSD study. It is unclear what “raised notch” is. Therefore, the firm will be asked to provide picture(s) to illustrate how test and RLD devices were set up with the testing apparatus in SAC and APSD studies.
13. According to the study methods, the approximate retention time for SA in their HPLC analysis is 2.00 min [Method # MGR-METH-546070 (Version 7.0, p. 13 of 38)] for SAC study and 1.8 to 2.2 min [Method # MGR-METH-546069 (Version 6.0, p. 16 of 37)] for APSD study. In addition, the firm also stated in the aforementioned methods that % organic is the main factor affecting SA peak retention time and therefore particular care should be given when diluting the buffer solution component with methanol during preparation of the mobile phase.



In contrast, some other studies had SA retention time around the expected retention time (e.g. study MGR-PRO-REP-2015-103). Therefore, the firm will also be asked to explain for this inconsistency of SA retention time among different studies. In addition, the firm will be asked to specify their approaches taken during sample processing regarding % organic affecting SA peak retention time. Moreover, the firm will be asked to explain for wide range of SA retention time as well as deviation from expected SA retention time observed in aforementioned 3 studies, and justify its impact on reliability of sample analysis.

14. According to the firm’s cover letter (p. 1-2 of 17) in 9/22/2016 submission, (b) (4) methods (b) (4) for APSD determination and (b) (4) for SAC) differ from analytical procedures MDR-RGMETH-0032 and MDR-RGMETH-0031 only in the system suitability requirement for the SA retention time. However, methods MDR-RGMETH-0032 (p. 5 of 8), MDR-RGMETH-0031 (p. 4 of 8), Mylan’s (p. 13 of 41) and (b) (4) (p. 11 of 40) method MGR-METH-546070, Mylan’s (p. 14 of 40) and

(b) (4) (p. 14 of 40) method MGR-METH-546070 all had system suitability requirement for SA retention time (b) (4). Therefore, the firm will be asked to specify the difference they stated in the aforementioned cover letter.

15. According to the study protocols, SAC studies should be conducted on dose counter #s 60, 30 and 1; while APSD studies should be conducted on dose counter #s 59 and 2. The firm will be asked to list out all SAC and APSD samples that were collected on dose counter numbers other than #s 60, 30 and 1 for SAC studies and #s 59 and 2 for APSD studies. For each of these samples, the firm will be asked to provide the detailed reason(s) for using different dose counter numbers, its supporting documents (e.g. investigational report), original actuation data, as well as corrective action taken.
16. The firm will be asked to provide (b) (4) SOP (b) (4) that was effective at the time of the in vitro studies in current application.

APSD Studies

17. According to the study method MGR-METH-546068 (version 6.0, p. 15 of 37), fine particle mass (FPM) is calculated (b) (4) when operated at 60 L/min. However, in study report MGR-REP-2015-096 (version 1.0, p. 14 of 178), the firm stated that FPM (b) (4). Therefore, the firm will be asked to explain why they changed the calculation method for FPM.
18. The firm will be asked to provide detailed calculations for calculating MMAD and GSD.

Deficiencies Related to Information Common to In Vitro Studies 057755-02-04, MGR-PRO-2015-080, and 057755-02-07

Both SAC and APSD Studies

19. It is noted that there are multiple incidences of “alternative blister use” and “replacement device use” in in vitro BE studies. The firm will be asked to explain why there were multiple incidences of them, and the impact of it on in vitro BE studies.

SAC Studies

20. The firm did not provide actual dose counter numbers and % of label claim in the SAS .xpt dataset for their SAC studies. Therefore, the firm will be asked to add a column for actual dose counter number and another column for % of labeled claim in their SAS .xpt file for their SAC studies.

APSD Studies

21. The firm provided mass balance in the study reports, but did not include it in the SAS .xpt file. Therefore, the firm will be asked to add a column for mass balance in their SAS xpt file for APSD studies.

Deficiency Related to Information Common to In Vitro Studies 057755-02-04, 057755-02-07, MGR-REP-2015-092, and MGR-REP-2015-093

22. The firm provided 100% raw analytical data for SAC and APSD testing in their 9/22/2016 submission (Module 3.2.P.2). However, the raw data format provided by the firm for the 4 studies above is rather granular, as each page only contains information for one sample. The firm will be asked to compile the raw data of each run. An example for this compiled raw data format would be the firm’s raw data for study MGR-PRO-2015-080 (9/22/2016 submission, Module 3.2.P.2\Attachment 4-4 – MGR-PRO-2015-080 – 250/50 mcg – APSD Raw Data – Comment 4 – Sequence 0009). The raw data should include all samples (including blank/diluent, standards, etc.) in a run in run sequence order.

Deficiency Related to Information Common to In Vitro Studies MGR-PRO-2015-080, and MGR-PRO-REP-2015-103

23. The firm provided raw data for the above studies in 9/22/2016 submission, Module 3.2.P.2. However, it is noted that these raw data are incomplete, as there are many instances that the result IDs in the run are not consecutive (e.g. 9/22/2016 submission, Module 3.2.P.2\Attachment 4-4 – MGR-PRO-2015-080 – 250/50 mcg – SAC Raw Data – Comment 4 – Sequence 0009, p. 4 of 740, result IDs 30078, 30088-30077 were missing). In addition, it is noted that raw data for blank/diluent, system suitability S1 or S2, standard check S1 and S2 are not included in raw data for SAC studies. Similarly, blank/diluent, system suitability standard SHL, LOQ, standard check SHL and SLL were not included in raw data for APSD studies. Moreover, raw data for stage 7, stage 8 for many samples (e.g. p. 6 of aforementioned document) were not included in the raw data for APSD studies. Therefore, the firm will be asked to submit 100% raw data (including blank/diluent, standards, etc.) in run sequence order.

Deficiencies Related to In Vitro Equivalence Study 057755-02-04 Only

SAC Study

24. The firm did not provide reason and supporting document for the rejection of the following sample (p. 8 of 178 of the firm’s MGR-REP-2015-096 version 1.0). Therefore, the firm will be asked to provide this information.

Product	Batch Number	(b) (4)	Device ID	Mylan Unit	Flow Rate (L/min)
REF	5ZP8397	40		180	60

APSD Study

25. According to study report MGR-REP-2015-096, version 1.0, p. 40 of 178, the firm stated that “No acceptable data generated for both FP and Sal” for the following sample. The firm will be asked to provide the data obtained as well as supporting document for why this data was not acceptable. The firm will also be asked to provide SOP that pre-defines data acceptability.

Product	Batch Number	Unit	Flow Rate (L/min)	Lifestage
REF	5ZP8178	159	60	BOL

Deficiencies Related to In Vitro Equivalence Study MGR-PRO-2015-080 Only

Both SAC and APSD Studies

26. It is noted that the study protocol MGR-PRO-2015-080 provided by the firm is version 3.0. The firm will be asked to provide the effective date of the 2 previous versions of the protocol.

APSD Study

27. The firm will be asked to provide study dates of the repeated APSD study for the 90 L/min flow rate.

28. For the following 3 samples that were repeated using new devices, the firm provided the reason for replacement below in study report MGR-PRO-REP-2015-080 version 1.0 (p. 9, 33, 63 of 192).

Number	Product	Batch Number	Unit	Flow Rate (L/min)	Lifestage	Reason for replacement
1	REF	5ZP0114	91R	30	BOL	Error during sampling. Mouth and throat samples were washed into the same volumetric flask.
2	TEST	631-008	37R	30	BOL	
3	REF	5ZP9882	240R	60	BOL	Stage 5 being sampled instead of stage 4.

- a) For sample #s 1 and 2 above, , mouth and throat samples were to be washed into the same flask for each device according to the study method (MDR-RGMETH-0031, Section 6.2.2, step 1). Therefore, the firm will be asked to explain why this was considered as an error.
- b) For sample #3 above, the firm will be asked to explain how this “stage 5 being sampled instead of stage 4” was found out.

29. For the following sample, the study report showed that it was repeated with a new device [study report MGR-PRO-REP-2015-080 version 1.0 (p. 83 and 95 of 192)], and the firm stated in their 9/22/2016 submission (Module 1.2\Cover Letter..., p. 2 of 17) that original data was generated. However, the firm did not provide reason for device replacement in their study report or in their 9/22/2016 submission. Therefore, the firm will be asked to explain why its original assay was rejected, and provide supporting documents (e.g. investigational report) for this sample rejection.

Product	Batch Number	Unit	Flow Rate (L/min)	Lifestage
REF	5ZP9304	433R	90	EOL

Deficiency Related to In Vitro Equivalence Study 057755-02-07 Only

30. According to the study report MGR-REP-2015-097 (version 1.0, p. 13 of 178), the firm stated that “for units 180 and 221 EOL 60 L/min, no acceptable data will be reported for FP and SA”. The firm will be asked to provide the data obtained as well as supporting document for why this data was not acceptable. As mentioned above, the firm will also be asked to provide SOP that pre-defined data acceptance criteria.

Deficiencies Related to Information Common to In Vitro Studies MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093 (4 kPa fixed pressure drop)

Both SAC and APSD Studies

31. Each of the SAC and APSD studies at 4 kPa fixed pressure drop was conducted on 3 lots of test and 3 lots of RLD product. For each lot, 3 test and 3 RLD devices were tested, with 3 replicates of SAC (beginning, middle, and end lifestages), and 2 replicates of APSD (beginning and end lifestages) collected from each device. The firm then conducted statistical comparison of geometric mean ratios at 4 kPa vs. 60 L/min. The firm will be asked to repeat the study with 10 test and 10 RLD devices per lot, using 3 lots of test and 3 lots of unexpired RLD product. SAC study should be tested at beginning, middle and end lifestages, while APSD studies should be tested at beginning and end lifestages. The firm will be asked to conduct statistical comparison of test vs. RLD product at 4 kPa pressure drop using population bioequivalence (PBE) analysis. The firm will be asked to refer to *Draft Guidance on Budesonide Inhalation Suspension* for step-wise procedure of the PBE analysis.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf>

Please note that other deficiencies (deficiency #s 10-18, 22, 23, 32, and 33) related to the in vitro studies MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093 (4 kPa fixed pressure drop) are also identified and listed in the current section for IN VITRO STUDIES. The firm will be asked to take them into consideration when they repeat the in vitro studies (4 kPa fixed pressure drop).

32. The firm did not provide study results in SAS .xpt format for SAC and APSD studies at 4 kPa fixed pressure drop, and thus will be asked to provide such for their repeated studies. These SAS datasets should include % of label claim for the SAC study, mass balance (% of label claim) for the APSD study, and dose counter number for both SAC and APSD studies.

Deficiency Related to In Vitro Studies MGR-PRO-REP-2015-103 Only

APSD Study

33. Based on chromatograms provided for the APSD study, it is noted that some runs had run time of 6.5 min while others had 3.5 min (9/22/2016 submission, Module 3.2.P.2\Attachment 3-7..., p. 131 of 238). Therefore, the firm will be asked to explain why different run times were used.

PK BE STUDIES

Deficiencies Related to Pre-Study Method Validation

34. It is noted that the firm performed pre-study method validation on instruments (b) (4). However, additional instruments were used in the pivotal PK study (b) (4) was used in fasting study MGR001-1014; and (b) (4) was used in fasting studies MGR001-1005, MGR001-1006 and MGR001-1014). The firm did not provide detailed information of these additional instruments used. Therefore, the firm will be asked to provide this information, and the firm will be advised that according to *Guidance for Industry – Bioanalytical Method Validation* (draft guidance recommended September 2013), partial validation needs to be conducted for change(s) in instruments and/or software platforms.
35. The firm stated that assay selectivity was evaluated in 6 sources of human plasma (12/29/2015 submission, Module 5.3.1.4. 15-006 – Validation Study Tagging File\ Project 15-006 Validation Report, p. 6 of 16). However, the firm only provided representative chromatography to show selectivity. The firm will be asked to provide selectivity results for each of the 6 sources of human plasma.
36. Since the proposed test product has two analytes (i.e., FP and SA), the firm should provide evidence that one analyte does not interfere with analysis of the other analyte (e.g. LQC and HQC samples of FP fortified with SA show no effect on determination of FP, and vice versa).

Deficiency Related to Fasting Studies MGR001-1005 and MGR001-1014

37. For the 2 PK studies the firm conducted for the 250/50 mcg strength, it is noted that each of the MGR001-1005 and MGR001-1014 studies failed to meet the bioequivalence criteria of 80.00-125.00%. The firm conducted pooled analysis of these 2 PK studies, and stated that the pooled analysis met the BE criteria. The firm

will be advised that their pooled analysis is not acceptable due to the following reasons:

- a) The pooled analysis consisted of only two studies with opposite findings. It is apparent that by pooling such data together, the differences between the two studies could be balanced out and therefore, yielding a result somewhere toward to the middle and making the pooled study pass bioequivalence.
- b) Study MGR001-1005 failed to show bioequivalence. Study MGR001-1014 also failed to show bioequivalence even though the batch of Advair Diskus® was selected to represent the Advair Diskus® population. Therefore, whether the pooled analysis results can truly represent all the 250/50 mcg strength data is questionable.
- c) The pooled analysis is a post-hoc analysis, not pre-specified in a protocol or a statistical analysis plan. Therefore, the finding from the pooled analysis is viewed as hypothesis generating and is not acceptable from the statistical point of view.
- d) The firm's statistical model for the pooled analysis included terms for study, subject within study, period within study, treatment, and study by treatment interaction, but did not take sequence-related effects such as sequence within study into consideration. In addition, the batch-to-batch variability was not addressed in the model. Even had the pooled analysis approach/concept been accepted, the suitability of the statistical model is still questionable.

Therefore, the fasting studies MGR001-1005 and MGR001-1014 is unacceptable. The firm will be asked to repeat the PK BE study at the 250/50 mcg strength.

Comments For Future Submissions

38. *Guidance for Industry - Bioanalytical Method Validation* (posted September 2013) states that incurred sample reanalysis (ISR) sample selection should include “*all study subjects*”. However, the firm's ISR studies did not include all study subjects. For their future studies, the firm will be advised to refer to the aforementioned *Guidance for ISR sample selection*.
39. The firm submitted IND 118769 for the fasting study of the 250/50 mcg strength, but not for the 500/50 µg strength. The firm will be advised for their future study to submit a bio-IND prior to study commencement if the dose given in the PK study exceeds the maximum labeled single dose for the evaluation of safety.

FLOW PROFILING STUDY

Deficiencies Related to the Flow Profiling Study (MGR000-1003)

40. According to p. 40 of 321 of the study report, the reference batch (batch # 547-046) used in this study is Accuhaler™. Therefore, the flow profiling study is unacceptable due to the use of non-US marketed RLD product. The firm will be asked to repeat the flow profiling study using US marketed RLD product.

It is also noted that in the clinical overview (12/29/2015 submission, Module 2.5\Clinical Overview, p. 7 of 21), the firm stated that “[t]he CRC749 device used in this study was identical in terms of the airway geometry (and therefore airflow paths and device resistance) and the drug-containing discs (and therefore the pharmaceutical performance) remained the same the CRC749 Clinical device used in the pivotal clinical endpoint BE study and PK BE studies with the 100/50 and 500/50 product strengths, and the Commercial device which was included in the pivotal PK BE studies with the 250/50 product strength.” Based on this statement, it appears that the firm used test device other than the clinical device (b) (4) and commercial device (b) (4). The firm will be asked to use the commercial device for the test product in their repeat flow profiling study.

Please note that other deficiencies (deficiency #s 41-46) related to the flow profiling study are also identified and listed below. The firm will be asked to take them into consideration when they repeat the flow profiling study.

41. According to the Information for Study Participants and Informed Consent Form (12/29/2015 submission, Module 5.3.4.1\IEC IRB Consent Form List, p. 26-27 of 95), both the test and reference devices were placed in the inhaler connecting box (ICB) in the horizontal orientation. The firm will be asked to specify how patients hold ICB for each device (e.g. which orientation). If same orientation was held between T and R devices, the firm will be asked to justify the impact of device orientation on subject’s flow profile.
42. According to Figure 3 in the aforementioned Information for Study Participants and Informed Consent Form (12/29/2015 submission, Module 5.3.4.1\IEC IRB Consent Form List, p. 26-27 of 95), the firm removed mouthpiece cover of the test device. The firm will also be asked to justify its impact on device resistance.
43. In the study report (12/29/2015 submission, Module 5.3.4.1\Study Report Body\MGR000-1003 Study Report, p. 40 of 321), the firm stated that in order to ensure that the resistance of the dry powder inhaler (DPI) was not affected by enclosing it in the ICB, the resistance of the test and reference DPIs was determined before enclosure in the ICB. This experiment was then repeated after enclosure in the ICB. The resistance of the enclosed DPI had to be $\pm 5\%$ of the resistance before the inhaler was put in the IDB; this was a key step in ensuring suitability of the enclosed

DPI and the results were recorded in the batch records for the ICBs containing the inhalers. The firm will be asked to provide these results. In addition, the firm will be asked to provide details of this study (e.g. study protocol/SOP and study report).

44. It is noted that the concomitant medication SAS .xpt dataset contained drug trade names but not generic names. In addition, route of administration (CM1_ROUT) and frequency was indicated by numbers (e.g. 3, 7, 17 for CM1_ROUT and 1, 5, 9 for CM1_FREQ), and it is unclear what these numbers stand for. Moreover, for start and end time of concomitant medications, the firm stated in their data definition file that their data format is DDMMYY10. However, values (e.g. 19029, 19640, 4565) listed in the SAS .xpt file does not match this format. It is also unclear what those numbers in CM1_STA2, CM1_STO2, CM1_ONGO (e.g. 0, 1, 2) stand for. Therefore, the firm will be asked to clarify so. In addition, the firm will be asked to list out the washout/withhold period between the concomitant medications and study procedures for each subject visit.
45. For pressure drop acceleration rate (kPa/sec), the firm excluded the multiple values from the summary statistics [e.g. Subject (b) (6) (healthy adult subject) / device: Accuhaler™/Diskus® / manoeuver 8; Subject (b) (6) (healthy adult subject) / device: CRC749 / manoeuver 1]. The firm will be asked to provide their pre-specified acceptance criteria (e.g. in an SOP) for pressure drop acceleration rate data at the time of this study.
46. It is noted that although the use of rescue medicine is not mentioned in the study protocol or study report, the firm provided a SAS .xpt dataset “RESCUE”, which, according to the data definition file, is about “*Salbutamol Intake (Rescue Medication)*”. According to this dataset, multiple subjects took rescue medication. For each of these subjects, the firm will be asked to list out the washout period between the rescue medication and study procedures for each visit. The firm will also be asked to justify the impact of rescue medication usage on inhalation profile of these subjects.

DEVICE ORIENTATION STUDY

Deficiency Related to the Device Orientation Study (MGR000-1004)

47. The firm’s proposed Wixela Inhub device has a different device orientation when compared to the reference listed drug (RLD), Advair Diskus. Specifically, the firm’s Wixela Inhub device is intended to be held vertically during administration, while the Advair Diskus device is intended to be held horizontally during administration. The Agency has reviewed the Device Orientation Study submitted to the firm’s application. The study submitted does not provide FDA with sufficient information to conclude that proposed product can be substituted with the full expectation that it will produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling, including whether the proposed product can be substituted for

the RLD without the intervention of a health care provider and/or without additional training prior to use.

In addressing this deficiency, we refer the firm to the general principles in FDA's draft guidance entitled Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA (January 2017) (available at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm536959.pdf>). Although this is draft guidance, it sets forth FDA's current thinking regarding important principles for evaluating proposed generic combination products submitted in ANDAs. As reflected in that draft guidance, FDA recommends that applicants seek to minimize differences in the user interface of a proposed generic combination product and the RLD. The firm may consider modifying the design of the user interface for the Wixela Inhub device to minimize differences from the RLD product, specifically with regard to the orientation of the firm's proposed product. To the extent that differences remain between the user interface of the proposed generic combination product and the user interface of the RLD, the guidance provides recommendations on the identification and assessment of differences in the design of the user interface for a proposed generic combination product when compared to its RLD, including a discussion of when data from a comparative use human factors study may be warranted to address certain identified differences. It would be useful to provide the Agency with the results of the three threshold analyses (e.g., comparative labeling analysis, comparative task analyses, comparison in the design of the delivery device constituent) described in this draft guidance, as well as the firm's overall assessment of the identified differences for their proposed product when compared to the RLD. Please note that the Agency may view the design differences for the firm's proposed presentation as not being minor if these analyses suggest that differences in the user interface of their product as compared to that of the RLD may impact the clinical effect or safety profile of their proposed product as compared to the RLD when the proposed product is substituted for the RLD. In such cases, additional information and/or data, such as data from comparative human factors studies, may be warranted.

The Agency will consider these analyses and any comparative use human factors data or information submitted to evaluate the acceptability of the differences in device and labeling resulting from these differences in user interface, and to evaluate whether the firm's proposed product can be substituted for the RLD with the full expectation that their proposed product will produce the same clinical effect and safety under the conditions specified in labeling when the proposed product is substituted for the RLD. Should the firm have an alternative approach to addressing this deficiency that they believe would be acceptable, they will be asked to contact the regulatory project manager (RPM).

CLINICAL ENDPOINT STUDY

Deficiencies Related to the Office of Study Integrity and Surveillance (OSIS) Inspectional Finding for the Clinical Site

48. FDA's *Guidance for Industry - Handling and Retention of BA and BE Testing Samples* (May 2004) states "if additional supplies of the test article and the reference standard will be used by a testing facility to perform the same study or additional studies, the testing facility should retain a sufficient quantity of reserve samples from the **subsequent shipment**." (Emphasis added.) Based on the Office of Study Integrity and Surveillance (OSIS) review of the inspectional findings from FDA's inspection of several clinical sites for Study MGR001-3001, the following clinical sites did not retain reserve samples of test and reference drug products from all shipments used during the study:

Clinical site#	FEI#	Clinical site
3001010	3012251316	Prestige Clinical Research Center, Inc., Miami, FL
3001058	3011200143	AAPRI Research Institute (FKA Kent Surgical Associates, Inc.)
3001018	3009592813	Timber Lane Allergy & Asthma Associates, South Burlington, VT
3001063	3005906303	Allergy and Asthma Research Group, Eugene, OR
3001067	3007013291	Providence Clinical Research, North Hollywood, CA
3001120	3010729442	Linfriz Research Center, Coral Gables, FL

In the absence of these reserve samples, the authenticity of the test and reference products used at these clinical sites could not be verified and, accordingly, the reliability of the data from these clinical sites could not be determined.

We have concerns that the reserve samples retained by the remaining (91) clinical sites for Study MGR001-3001 are not representative of the test and reference products provided by the study sponsor to each clinical site. Therefore, for each of the clinical sites for Study MGR001-3001 not identified above, the firm will be asked to provide (1) the number of shipments of test and reference product received from the study sponsor during the course of the study and (2) documentation to support that reserve samples were appropriately retained.

49. The FDA investigators inspected several clinical sites for study MGR001-3001. Form FDA 483 was issued at the close of inspection at Prestige Clinical Research Center, Inc. (PCRC), Miami, FL from 6/7/2016 to 6/10/2016 and 6/13/2016 to 6/15/2016. One of the observations was as follows:

"Failure to retain sealed randomization schedule prior to commencement of subject enrollment. Specifically, a sealed randomization scheme, including blinding codes, was not maintained in the possession of the clinical site prior to the dosing of the initial subject (Run-in placebo on [REDACTED] (b) (6) and Randomized dosing on [REDACTED] (b) (6)). The site completed the study and was closed by the IRB on September 2015; however, the randomization

scheme, which was not sealed, was sent to your site from PPD on November 6, 2015.”

It is FDA’s understanding that before the start of study MGR001-3001, (b) (4) (b) (4) did not send the records with subject dosing materials, at the time of the study or before the study started. We believe that this finding applies to all 97 sites. Therefore, to enable tracing the history of actions from the time when blinding codes were assigned to dosing materials until today, the firm will be asked to provide a copy of (b) (4) original blinding-packaging records and any log/event history, for all shipments to all 97 clinical sites.

Deficiency Related to Clinical Endpoint Study (MGR001-3001)

50. The firm’s original protocol (dated 11/25/2013) was amended (dated 1/26/2015) during the study. The reviewer could not locate institutional review board (IRB) approval information of the original protocol and its amendment. Therefore, the firm will be asked to provide such information.

4.11 Comments for Other OGD Disciplines

N/A

4.12 Pending Consults (Clinical, Statistical, Science Staff, Chemistry etc.)

N/A

5 APPENDIX

5.1 Individual Study Reviews

5.1.1 Single-dose Fasting Bioequivalence Study MGR001-1006

Reviewer's note: As detailed in reviewer's comments in Section 4.6, the firm assigned each subject with a subject number and also a randomization number. Please refer to the same comments about how a subject will be referred to (using their subject number and/or randomization number) in this section.

5.1.1.1 Study Design

Table 5 Study Information

Study Number	MGR001-1006
Study Title	AN OPEN-LABEL RANDOMIZED, TWO-WAY CROSSOVER STUDY TO DETERMINE PHARMACOKINETIC BIOEQUIVALENCE OF SINGLE DOSES OF FLUTICASONE PROPIONATE / SALMETEROL FIXED DOSE COMBINATION (100/50 µg) POWDER ADMINISTERED BY ORAL INHALATION FROM MGR001 AND ADVAIR® DISKUS® IN HEALTHY ADULT SUBJECTS.
Clinical Site (Name & Address)	Worldwide Clinical Trials Early Phase Services, LLC 2455 NE Loop 410, Suite 150 San Antonio, Texas 78217
Principal Investigator	Dr Cynthia A. Zamora, MD
Dosing Dates	Group 1 Period 1: 07-April-2015 Group 1 Period 2: 14-April-2015 Group 2 Period 1: 08-April-2015 Group 2 Period 2: 15-April-2015 Group 3 Period 1: 09-April-2015 Group 3 Period 2: 16-April-2015
Analytical Site (Name & Address)	Mylan Pharmaceuticals Inc. Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505
Analysis Dates	21-April-2015 – 30-April-2015
Analytical Director	Patrick T. Vallano, Ph.D.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	Fluticasone Propionate (FP): Longest storage duration and condition: 23 days at -70°C Salmeterol (SA): Longest storage duration and condition: 23 days at -70°C LTSS coverage: FP: 132 days at -70°C SA: 132 days at -70°C

Table 6. Product information

Product	Test	Reference
Treatment ID	Treatment A	Treatment B
Product Name	MGR001	Advair® Diskus®
Manufacturer	Mylan Global Respiratory Group	GlaxoSmithKline
Batch/Lot No.	631-002	4ZP3863
Manufacture Date	25 June 2014	N/A
Expiration Date	N/A	September 2015
Strength	100/50 mcg	100/50 mcg
Dosage Form	Inhalation Powder	Inhalation Powder
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)	Emitted Dose as % of Target: FP 104 %* SA 108 %	Emitted Dose as % of Target: FP 101 % SA 102 %
Content Uniformity (expressed as mean, %CV or per USP)	FP: Mean 101 % of Label Claim CV 3.1 % SA 100 % of Label Claim CV 2.8 %	N/A
Dose Administered	FP 300 mcg SA 150 mcg	FP 300 mcg SA 150 mcg
Route of Administration	Inhalation	Inhalation

* Please see reviewer's comments below.

Table 7. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: Not specified by the firm Dosed: 66 Completed: 64 Samples Analyzed: 66 Data Analyzed: 64
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	3 (Group 1: Randomization (b) (6) Group 2: (b) (6) Group 3: (b) (6)
Washout Period	7 days
Randomization Scheme (Sequence of T and R)	Please see table below
Blood Sampling Times	Pre-dose (0 hour) and 2, 5, 10, 15, 20, 30, 45, 60, and 90 minutes, and 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post-dose.

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Blood Volume Collected/Sample	10 mL
Anticoagulant Used	K2EDTA
Blood Sample Processing & Storage (include storage temperature)	Blood samples for the analysis of FP and SA in plasma and subsequent pharmacokinetic analysis were collected into 1 x 10 mL K2EDTA tubes. The collection tube was inverted 5-10 times immediately after collection, then immediately placed in an ice bath. Blood samples were centrifuged at approximately 1990 g ± 400 g (e.g. 3000 rpm) for 10 minutes under refrigeration (4 °C ± 3 °C). The time interval between sample collection and the start of centrifugation did not exceed 45 minutes. As soon as centrifugation stopped, samples were returned to an ice bath and the plasma transferred into two equal aliquots to labeled polypropylene tubes. Plasma samples were capped and frozen in an upright position in -70 °C ±15 °C freezer or colder, pending shipment to Mylan Pharmaceuticals Inc. Transfer of the samples into the freezer took place no later than 90 minutes after the start of centrifugation. Plasma samples were maintained in an ice bath until transfer to the storage freezer occurred.
IRB Approval (Y/N, Date)	Y Protocol and protocol amendment 1: 3/3/2015 Protocol amendment 2: 3/24/2015
Informed Consent (Y/N, Date)	Y Informed consent: 3/3/2015 Revised informed consent: 3/11/2015 Revised informed consent: 3/24/2015
Length of Fasting	8 hours prior and 4 hours post the start of pharmacokinetic sample collections on Day 1
Length of Confinement	From the day prior to dosing until 24 hours post-dose
Safety Monitoring	The Investigator evaluated safety using the following assessments: medical history, prior/concomitant medication, history of drug, alcohol, and tobacco use, physical examination, 12-lead ECG, supine blood pressure and pulse rate, spirometry (forced expiratory volume in 1 second [FEV ₁] and forced vital capacity [FVC]), safety laboratory/urinalysis, pregnancy tests (all females of childbearing potential), continuous cardiac monitoring; with any clinically significant changes recorded as adverse events (AEs). Subjects were routinely queried (at least every 8 hours during confinement and at each visit) for the presence or absence of AEs using open ended questions. Spontaneously reported AEs were also recorded. Subjects were monitored for any AEs from the signing of the informed consent forms to 30 days after the last dose of study medication.
Was the study design used for the fasting BE study acceptable?	NO (please see comments below)

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Single-Dose Fasting Bioequivalence Study Review

Randomization Scheme

Randomization Number	Subject Number	Treatment received at Period 1	Treatment received at Period 2	Randomization Number	Subject Number	Treatment received at Period 1	Treatment received at Period 2
	(b) (6)	A	B		(b) (6)	A	B
		B	A			A	B
		B	A			A	B
		A	B			B	A
		A	B			A	B
		B	A			A	B
		A	B			A	B
		A	B			B	A
		A	B			B	A
		B	A			A	B
		B	A			B	A
		B	A			B	A
		A	B			A	B
		A	B			B	A
		A	B			A	B
		B	A			A	B
		B	A			B	A
		B	A			A	B
		B	A			B	A
		A	B			B	A
		B	A			A	B

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Single-Dose Fasting Bioequivalence Study Review

Randomization Number	Subject Number	Treatment received at Period 1	Treatment received at Period 2
	(b) (6)	B	A
		A	B
		A	B
		A	B
		B	A
		B	A
		B	A
		A	B
		B	A
		A	B
		B	A
		A	B
		A	B
		B	A
		B	A
		B	A
		A	B
		A	B
		B	A
		B	A
		A	B
		B	A
		A	B
		A	B

A = test
B = RLD

Comments on Study Design:

- The firm stated that the test device used for this fasting study MGR001-1006 (clinical device: (b) (4) is different from the proposed commercial device (b) (4)



Due to the device difference, the firm will be asked to conduct in vitro BE studies (SAC and APSD studies) comparing RLD product and the test product with final commercial device as bridging studies for the

⁵⁵ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.7\Container Closure System, p. 66-67 of 229).

⁵⁶ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 2.3.P\Drug Product Part 2 _ FPSX – Mylan Dublin, p. 58 of 103).

⁵⁷ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 2.5\Clinical Review, p. 12 of 21).

100/50 mcg strength of the product. These in vitro studies should be conducted according to the product specific guidance, and use at least 3 batches each of T and R products with no fewer than 10 units from each batch.

2. According to the firm's product information summary table⁵⁸, emitted dose of FP as % target for test product batch #631-002 is 104%. However, this value is 105.4% according to its Certificate of Analysis (COA)⁵⁹. The firm stated that emitted dose values reported in the COA for batch #631-002 was based on the development specification in place at the time of batch release, which was calculated as a % of the target emitted dose value of 92 mcg for FP, rather than 93 mcg proposed in the commercial specification.⁶⁰ The value of 104% for emitted dose of FP in the product information summary table was calculated against the proposed commercial specification, with a target emitted dose value of 93 mcg for FP, which is in line with the RLD labeling. The reviewer considers the firm's explanation for this discrepancy acceptable.
3. The firm conducted the PK fasting study based on 3 inhalations of the drug product, which was found acceptable in CC 12-0731.⁶¹ In the same CC, the Agency also recommended the firm to submit a Bio-IND to the Agency for the evaluation of the safety if the dose given in the PK study exceeds the maximum labeled single dose. The firm submitted IND 118769 for the 250/50 mcg strength, but not for the 100/50 mcg strength. Since the Division of Clinical Review (DCR) found the proposed study for the higher strength (250/50 mcg) in IND 118769 reasonably safe to proceed from the clinical standpoint,⁶² the reviewer will not pursue this issue further.
4. It is noted that the firm evaluated AUClast (the firm defined AUClast as AUC "from time 0 to the time of the last measurable concentration"⁶³) instead of AUCt. The use of AUClast was not opposed by the agency in CC 12-0731.⁶¹ In addition, the AUCt calculated by the reviewer does not change the study outcome as compared to the firm's outcome for this study (please see details in Section 5.1.1.4).
5. On Day -1 and Day 1 prior to dosing for both study periods, subjects were trained to achieve an appropriate inhalation maneuver for both the CRC749 and Diskus[®] inhalers. Subjects were trained on inhalation technique, per the instruction for use (i.e., standing upright, lips creating a seal around the inhaler mouthpiece, a rapid

⁵⁸ GS Review: ANDA 208891, New/ANDA, 12/29/2015 [Module 2.7.1\Summary of Biopharmaceutic Studies and Associated Analytical Methods (Biosummary Tables 1-6 and 9-17), p. 34 of 47].

⁵⁹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.5.4\Lot 631-002 – Mylan Certificate of Analysis, p. 2 of 3).

⁶⁰ GS Review: ANDA 208891, Response to ECD/Bioequivalence, 1/12/2017 (Module 1.2\Cover Letter..., p. 16 of 21).

⁶¹ [\\cdsnas\OGDS6\CONTROLS\2012-docs\12-0731.pdf](#) p. 26 of 34.

⁶² DARRTS: IND 118769, REV-CLINICAL-21(Primary Review), 9/11/2013.

⁶³ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.1.2. mgr001-1006...\Study Report Body\MGR001-1006 Study Report, p. 12 of 98).

and deep inhalation, holding breath for 10 seconds, and exhaling away from the inhaler). Subjects also needed to show they were capable of achieving an appropriate inhalation maneuver (i.e., a rapid and deep inhalation technique, achieving a maximum inspiratory flow rate 60-100 L/min through CRC749 and 80-120 L/min through Diskus[®]).

6. According to the study report, the research unit staff prepared (as per the instruction for use) each inhaler ready for dosing, before handing to the subject for dosing. The inhaler was re-prepared by the research unit staff following each inhalation and prior to the next inhalation. There was an interval of approximately 30 seconds between each inhalation.
7. Subjects were instructed to rinse their mouths (without swallowing) with approximately 50 mL water after completing the three inhalations, and to spit the water out after rinsing. This is in line with the product-specific guidance, which states that “[s]ubjects should adhere to labeling as follows: ‘Rinse your mouth with water after breathing in the medicine. Spit the water out, do not swallow.’”.

The firm’s study design is **incomplete**.

5.1.1.2 Clinical Results

Table 8A. Demographics Profile of Subjects Completing the Bioequivalence Study

Study Number MGR001-1006			
		Treatment Groups	
		Test Product (MGR001 100/50mcg) N = 65	Reference Product (Advair® Diskus®) N = 65
Age (years)	Mean ± SD Range	33.7 ± 8.8 19 - 53	34.0 ± 8.7 19 - 53
Age Groups	<18 18-40 41-64 65-75 >75	0 (0%) 49 (75.4%) 16 (24.6%) 0 (0%) 0 (0%)	0 (0%) 48 (73.8%) 17 (26.2%) 0 (0%) 0 (0%)
Sex	Male Female	36 (55.4%) 29 (44.6%)	37 (56.9%) 28 (43.1%)
Race	White Black or African American American Indian or Alaska Native White, Black or African American, American Indian or Alaska Native	39 (60.0%) 23 (35.4%) 2 (3.1%) 1 (1.5%)	39 (60.0%) 23 (35.4%) 2 (3.1%) 1 (1.5%)
BMI	Mean ± SD Range	26.3 ± 2.7 20.8 - 30.4	26.3 ± 2.7 20.8 - 30.4
Other Factors		N/A	N/A

Table 8B. Demographics Profile of Individual Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. MGR001-1006				
Subject No (b) (6)	Age	Gender	Race	BMI
	38	M	WHITE	29.7
	49	F	WHITE	27.3
	29	M	WHITE	29.8
	44	F	WHITE	29.9
	36	F	AMERICAN INDIAN OR ALASKA NATIVE	29.6
	48	F	WHITE	27
	23	M	WHITE	23.9
	20	F	WHITE	30.2
	29	F	WHITE	30.4
	47	F	WHITE	21.8
	29	M	WHITE	30.1
	45	M	BLACK OR AFRICAN AMERICAN	26.1
	27	M	WHITE	23.7
	38	M	WHITE	24.7
	48	F	BLACK OR AFRICAN AMERICAN	25
	43	M	BLACK OR AFRICAN AMERICAN	22.7
	48	F	WHITE	25.5
	42	M	WHITE	28.5
	22	F	BLACK OR AFRICAN AMERICAN	20.8
	32	M	BLACK OR AFRICAN AMERICAN	29.6

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(b) (6)	44	M	BLACK OR AFRICAN AMERICAN	29.8
	36	F	AMERICAN INDIAN OR ALASKA NATIVE	23.6
	33	M	BLACK OR AFRICAN AMERICAN	29.5
	39	M	WHITE	24
	32	M	WHITE	23.1
	44	M	WHITE	27.2
	19	F	MULTIPLE	24.4
	33	M	WHITE	22.9
	34	M	WHITE	28.2
	32	M	BLACK OR AFRICAN AMERICAN	23.1
	33	F	WHITE	21.3
	47	M	BLACK OR AFRICAN AMERICAN	27.6
	31	M	BLACK OR AFRICAN AMERICAN	22.6
	32	F	BLACK OR AFRICAN AMERICAN	23.1
	26	M	WHITE	25.6
	36	F	WHITE	28.1
	46	F	BLACK OR AFRICAN AMERICAN	26.7
	28	F	BLACK OR AFRICAN AMERICAN	30.3
	26	M	WHITE	29.2
	21	F	BLACK OR AFRICAN AMERICAN	25.2
	34	F	WHITE	28
	53	M	BLACK OR AFRICAN AMERICAN	26.5
	29	M	WHITE	25.5
	33	M	BLACK OR AFRICAN AMERICAN	28.3
	33	M	BLACK OR AFRICAN AMERICAN	27.2
	25	F	WHITE	22.1
	29	M	BLACK OR AFRICAN AMERICAN	29.4
	27	M	WHITE	24.4
	33	F	BLACK OR AFRICAN AMERICAN	28.5
	22	F	WHITE	24.6
	27	F	WHITE	21.9
	27	M	WHITE	25.8
	28	M	WHITE	26.4
	33	M	WHITE	25.7
	31	M	WHITE	23.3
	43	F	WHITE	28.5
	32	F	BLACK OR AFRICAN AMERICAN	26.1
	32	F	WHITE	26.4
	20	F	WHITE	30.3
	19	M	WHITE	25.7
44	M	WHITE	26.4	
33	M	BLACK OR AFRICAN AMERICAN	27.6	
35	M	WHITE	30.4	
50	F	BLACK OR AFRICAN AMERICAN	27.7	
19	F	WHITE	26.6	
31	M	BLACK OR AFRICAN AMERICAN	21.7	

Table 9. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
(b) (6)	Subject was discontinued prior to Period 2 for an adverse event of upper respiratory tract infection and did not receive Advair® Diskus® 100/50 mcg Date: (b) (6) Treatment: Prior to receiving Reference	1	No
(b) (6)	Subject was withdrawn prior to Period 2 for deviation/noncompliance with the protocol (positive ethanol breath test) and did not receive MGR001 100/50 mcg Date: (b) (6) Treatment: Prior to receiving Test	1	No

Table 10. Study Adverse Events, Fasting Bioequivalence Study

System Organ Class/ Preferred Term	Reported Incidence by Treatment Groups	
	Study Number MGR001-1006*	
	Test Product (MGR001 100/50 mcg) No. of Subjects n (%)	Reference Product (Advair® Diskus® 100/50 mcg) No. of Subjects n (%)
Blood and lymphatic system disorders		
Neutropenia	0 (0.0%)	1 (1.5%)
Gastrointestinal disorders		
Nausea	1 (1.5%)	0 (0.0%)
Vomiting	1 (1.5%)	0 (0.0%)
Infections and infestations		
Upper respiratory tract infection	1 (1.5%)	0 (0.0%)
Nervous system disorders		
Dizziness	0 (0.0%)	1 (1.5%)
Headache	1 (1.5%)	2 (3.1%)
Presyncope	1 (1.5%)	1 (1.5%)
Somnolence	0 (0.0%)	1 (1.5%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	0 (0.0%)	1 (1.5%)
Upper-airway cough syndrome	0 (0.0%)	1 (1.5%)
Skin and subcutaneous tissue disorders		
Dermatitis contact	0 (0.0%)	1 (1.5%)
Total	5 (7.7%)	9 (13.8%)
*3 Inhalations (total dose 300/150 mcg FP/salmeterol)		
Adverse Events were coded using MedDRA version 18.0		

Subjects Experiencing Emesis (Include in eCTD)

Subject Number*	Test/Reference	Period	Time Post-Dose	Duration Between Dosing and Emesis (hrs)
(b) (6)	Test	1	16:35	9.83 hrs

Do any of the adverse events require statistical analysis consideration (e.g. emesis)?

No. One subject (b) (6) experienced emesis outside the two times the T_{max} window (2 x 1 to 2 hrs = 2 to 4 hrs for FP; and 2 x 5 min = 10 min for SA). This subject was not withdrawn from the study. The reviewer agrees with the firm's decision.

If yes, does the time exceed two times the median T_{max} value (immediate release products) or the labeled dosing interval (modified release products) according to the *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products*?

N/A

Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Please comment.

Yes. The frequency of headache and presyncope for the test product is equal to or less than those for the reference product. One incidence each of nausea, vomiting and upper respiratory tract infection was observed for test products. One incidence each of neutropenia, dizziness, somnolence, dyspnea, upper-airway cough syndrome and dermatitis contact was observed only in subjects dosed with reference treatment.

The firm considered all the adverse events to be unrelated/not related to treatment, except somnolence and 1 incidence of headache (RLD treatment group), which was considered possibly related to treatment; 2 incidences of headache (1 from test and 1 from RLD treatment group), which were considered probably related to treatment; and upper-airway cough syndrome, which was considered unlikely related to treatment.

All adverse events were mild in severity, except dyspnea and presyncope, which were moderate in severity. And all symptoms of adverse events reported during the study were resolved.

Are there any safety concerns based on the adverse event profile?

The firm reported one significant AE (upper respiratory tract infection) that led to subject discontinuation and one serious AE (dyspnoea).

Subject (b) (6), who completed Period 1 (test treatment) on (b) (6), experienced an AE (non-serious) of upper respiratory tract infection with an onset date of (b) (6). The AE was considered by the firm to be mild in severity, unrelated to study medication, and was resolved. This subject was discontinued from the study and did not receive treatment in Period 2. It should be noted that the incidence of upper respiratory tract infection (1.5%) in the this study is lower than that reported in the RLD labeling (27%)³⁰.

Subject (b) (6) reported a serious AE of dyspnea 2 days and 7 hrs following RLD treatment (Period 2), and after completion of all study procedures. The principal investigator classified the serious AE as dyspnoea of moderate severity and unrelated/not related to the study treatment. The adverse event was resolved. It is noted that dyspnea is among the adverse reactions that are listed in the RLD labeling under the postmarketing experience section.³⁰

No deaths or other significant AEs were reported during the study.

There is no strong evidence suggesting that the test drug caused substantially more serious adverse events compared to the reference drug.

Table 11. Protocol Deviations, Fasting Bioequivalence Study

Study No. MGR001-1006		
Type	Subject #s (Test)	Subject #s (Ref.)
Study drug administration ¹	(b) (6)	
Blood collection time deviations		
Non-compliance (positive ethanol breath test at Period 2 check-in)		
Missed assessments (blood samples not collected per protocol)		
Inhalation training not completed due to subject arriving late for check-in		
Whole blood sample tube contained piece of plastic observed after centrifugation (manufacturer error)		

¹ Study drug administration deviations included: pausing during an inhalation (Subjects (b) (6), (b) (6)), slow inhalation (Subject (b) (6)) and reports that an inhalation did not sound deep (Subjects (b) (6), (b) (6)).

^ In the firm's summary table in Module 2.7.1, the firm stated that this protocol deviation occurred in the test treatment group. However, according to this individual's CRF and the firm's Documentation of Statistical Methods, this protocol deviation occurred in the RLD treatment group. Thus the reviewer corrected it in this table accordingly.

Did dropouts/adverse events/protocol deviations affect the study outcome?

Please see comments below.

Comments on Dropouts/Adverse Events/Protocol Deviations:

- A total of 66 subjects were randomized into the study. Sixty-four (64) subjects who completed both periods of the study were included in the PK analysis set (i.e. contributed to the statistical analysis of BE). Two (2) dropout subjects (b) (6), (b) (6) that completed 1 period of the study were included in the PK parameter set (i.e. had PK parameters derived), but were not included for in the PK analysis set.

- For Subjects (b) (6) that were dropped out of the study, the reviewer verified from their corresponding case report forms (CRFs) that these subjects were not dosed in Period 2.
- Concomitant medications were given to Subject (b) (6) who experienced dyspnoea in the reference drug treatment group. All these concomitant medications (Sodium Chloride 0.9% for iv route, 1000 mL; Albuterol Sulfate/Ipratropium for inhalation route, 3 mL; Metoprolol Tartrate for oral route, 25 mg; Aspirin for oral route, 81 mg; Pravastatin Sodium for oral route, 10 mg; Famotidine for oral route, 20 mg) were given (at or after 17:59, (b) (6)) after completion of PK blood sampling (6:30, (b) (6)), thus they are not expected to affect the study outcome.
- The use of the following concomitant medications as birth controls was also reported: levonorgestrel/ethinyl estradiol, drospirenone/ethinyl estradiol, levonorgestrel, and medroxyprogesterone acetate. The firm evaluated the specificity of the analytical methods in the presence of levonorgestrel, ethinyl estradiol and drospirenone. Based on representative chromatograms provided, none of the tested compounds significantly interfere with the analysis of FP, SA and the internal standards.



The reviewer verified from Micromedex that there are no known drug-drug interactions between the aforementioned concomitant medications and the study drug FP/SX.⁶⁴

- There were sampling time deviations. Since the firm used the actual sampling time points for the PK analysis, these deviations do not affect the study outcome.
- Five (5) subjects had missing blood sample collections (due to restick or subject not showing up), and the firm included all these 5 subjects into the statistical analysis⁶⁵. However, the reviewer noticed that some of these missing sample blood collection time points are close to Tmax, thus may potentially affect Cmax

⁶⁴ Micromedex:

<http://www.micromedexsolutions.com/micromedex2/librarian/PFDefaultActionId/evidencexpert.ShowDrugInteractionsResults> Last accessed: 9/30/2016.

⁶⁵ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.1.2. mgr001-1006...\Statistical Methods Interim Analysis Plan, p. 44-51 of 64).

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of these subjects (please see table and representative plots of plasma concentration vs time below).

Subject	Randomization Code	Period	Treatment	Time of missing blood collection	Potentially affect C _{max} for FP?	Potentially affect C _{max} for SA?	
(b) (6)		2	R	5 min (0.08 hr)	No	Yes	
		2	T	10 min (0.16 hr)	Might (2 time points prior to current T _{max} of 0.33 hr)	Might (2 time points after current T _{max} of 0.33 hr)	
		1	R	20 min (0.33 hr)	Yes	No	
				90 min (1.5 hrs)	No	No	
		1	T	48 hrs	No	No	
		2	R		10 min (0.16 hr)	Might (3 time points prior to current T _{max} of 0.5 hr)	Might (5 time points prior to current T _{max} of 1 hr, but have a trend of double peak)
					15 min (0.25 hr)	Might (3 time points prior to current T _{max} of 0.5 hr)	Might (please see above)
		2	R		2 min (0.03 hr)	No	Yes

Please note that the subject numbers mentioned in the rest of this bullet point are their corresponding randomization codes as listed in the table above.

The reviewer will **exclude** subjects with missing time point(s) that are **very likely to impact C_{max}**. For subjects with missing time point(s) that **might affect C_{max}**, the reviewer will also exclude them as a conservative approach. However, it should be noted that excluding the latter subjects does not change study outcome (please see tables below).

FP

Excluding Subject ^{(b) (6)} (with missing samples that **might affect C_{max}**) [and excluding Subjects ^{(b) (6)} (with missing sample that is **very likely to impact C_{max}**) and excluding]

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
Group 1					
LAUCT (hr *pg/ml)	567.02	581.56	0.98	91.27	104.16
LAUCI (hr *pg/ml)	592.74	607.71	0.98	91.39	104.10
LCMAX (pg/ml)	99.92	107.96	0.93	86.12	99.47
Group 2					
LAUCT (hr *pg/ml)	611.59	557.84	1.10	102.38	117.40
LAUCI (hr *pg/ml)	637.68	579.28	1.10	102.94	117.72
LCMAX (pg/ml)	104.88	110.89	0.95	87.75	101.96
Group 3					
LAUCT (hr *pg/ml)	702.22	657.49	1.07	100.47	113.53
LAUCI (hr *pg/ml)	733.11	685.59	1.07	100.78	113.46
LCMAX (pg/ml)	111.69	122.54	0.91	83.36	99.66

Note: The subjects were dosed in 3 groups, and the treatment*group interaction was statistically significant (p<0.1) for LAUC_{0-t} and LAUC_{0-∞}, and was not statistically significant (p>0.1) for LC_{max}.

Not excluding Subject ^{(b) (6)} (with missing samples that **might affect C_{max}**) [but excluding Subjects ^{(b) (6)} (with missing sample that is **very likely to impact C_{max}**)]

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
Group 1					
LAUCT (hr *pg/ml)	567.02	581.56	0.98	91.27	104.16
LAUCI (hr *pg/ml)	592.74	607.71	0.98	91.39	104.10
LCMAX (pg/ml)	99.92	107.96	0.93	86.12	99.47
Group 2					
LAUCT (hr *pg/ml)	581.55	524.69	1.11	103.47	118.73
LAUCI (hr *pg/ml)	606.88	545.76	1.11	103.99	118.91
LCMAX (pg/ml)	100.23	105.23	0.95	88.56	102.43
Group 3					
LAUCT (hr *pg/ml)	702.22	657.49	1.07	100.47	113.53
LAUCI (hr *pg/ml)	733.11	685.59	1.07	100.78	113.46
LCMAX (pg/ml)	111.69	122.54	0.91	83.36	99.66

Note: The subjects were dosed in 3 groups, and the treatment*group interaction was statistically significant (p<0.1) for LAUC_{0-t} and LAUC_{0-∞}, and was not statistically significant (p>0.1) for LC_{max}.

SA

Excluding Subjects ^{(b) (6)} (with missing samples that **might affect C_{max}**) [and excluding Subjects ^{(b) (6)} (with missing samples that are **very likely to impact C_{max}**)]

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Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
Group 1, 2 and 3 (trt*troup = 2)					
LAUCT (hr *pg/ml)	712.40	659.12	1.08	104.81	111.46
LAUCI (hr *pg/ml)	745.82	692.05	1.08	104.65	110.98
LCMAX (pg/ml)	347.94	349.15	1.00	94.35	105.26

Note: The subjects were dosed in 3 groups, and the treatment*group interaction was not statistically significant (p>0.1) for LAUC_{0-t}, LAUC_{0-∞} and LCmax.

Not excluding Subjects (b) (6) (with missing samples that might affect Cmax)
[but excluding Subjects (b) (6) (with missing samples that are very likely to impact Cmax)]

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
Group 1, 2 and 3 (trt*troup = 2)					
LAUCT (hr *pg/ml)	710.62	658.65	1.08	104.59	111.29
LAUCI (hr *pg/ml)	743.66	691.35	1.08	104.42	110.81
LCMAX (pg/ml)	344.07	346.41	0.99	93.99	104.96

Note: The subjects were dosed in 3 groups, and the treatment*group interaction was not statistically significant (p>0.1) for LAUC_{0-t}, LAUC_{0-∞} and LCmax.

- Six (6) subjects had study drug administration deviation as detailed in table below.

Subject	Randomization Code	Period	Treatment	Study Drug Administration Deviation
(b) (6)		2	R	Subject paused during the first inhalation.
		1	T	An observation from the clinic staff stated that the subject still performed a rapid and deep inhalation.
		1	R	Subject paused during the start of the third inhalation. An observation from the clinic staff stated that the subject still performed a rapid and deep inhalation.
		2	T	Subject inhaled slowly during the first inhalation.
		1	R	Subject did not inhale deeply during the second inhalation.
		2	R	Subject did not inhale deeply during the first inhalation.

According to the firm's Documentation of Statistical Methods⁶⁶, the firm checked the concentration vs. time plots of these subjects, and considered that the PK profile of these subjects did not appear to be affected. Subsequently, the firm included all these 6 subjects in the PK analysis.

Based on internal discussion with ORS, it is acceptable to include these subjects in the statistical analysis.

⁶⁶ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.1.2. mgr001-1006...\Statistical Methods Interim Analysis Plan, p. 38-43 of 64).

- For Subject [REDACTED] ^{(b) (6)} a large piece of plastic was reported to be in the blood collection tube for the 1 hr sample in Period 1 (RLD treatment). According to the firm's Documentation of Statistical Methods, the firm treated this Period 1, 1 hr sample time concentration as missing, and the concentration was excluded from the PK analysis for both analytes. The reviewer agrees with the firm's exclusion of this sample.

In the SAS .xpt file submitted by the firm, the reviewer noticed that the concentration of this sample is still listed, and this point does not appear to affect C_{max} for both FP and SA. Therefore, the reviewer will exclude this sample from the firm's SAS .xpt file during recalculation.

- Other protocol deviations mentioned above do not affect study outcome.

5.1.1.3 Bioanalytical Results

Table 12. Sample Analysis Calibration and Quality Control – Within the Fasting Bioequivalence Study

Bioequivalence Study MGR001-1006										
ANALYTE FP										
Parameter	Standard Curve Samples									
Concentration (pg/mL)	1.000	2.000	3.000	10.00	30.00	100.0	300.0	400.0	500.0	600.0
Inter day Precision (% CV)	2.73	4.36	4.62	2.60	2.19	1.62	1.83	1.70	1.98	2.01
Inter day Accuracy (% Actual)	98.85	101.15	101.10	101.60	101.47	100.40	99.73	99.37	97.68	98.62
Linearity	0.9951 - 0.9998									
Linearity Range (pg/mL)	1.000 - 600.0									
Sensitivity/LOQ (pg/mL)	1.000									

Bioequivalence Study MGR001-1006						
ANALYTE FP						
Parameter	Quality Control Samples					
Concentration (pg/mL)	3.000	15.00	90.00	240.0	450.0	450.0 Dilution=2
Inter day Precision (% CV)	6.64	4.24	3.95	3.75	3.94	0.74
Inter day Accuracy (% Actual)	93.43	93.60	96.02	95.17	96.04	94.82

Bioequivalence Study MGR001-1006										
ANALYTE SA										
Parameter	Standard Curve Samples									
Concentration (pg/mL)	1.000	2.000	3.000	10.00	30.00	100.0	300.0	400.0	500.0	600.0
Inter day Precision (% CV)	1.90	3.06	2.80	2.26	1.75	1.48	1.50	1.57	1.62	1.71
Inter day Accuracy (% Actual)	99.67	100.90	99.30	100.60	101.23	100.90	100.53	100.05	98.06	98.73
Linearity	0.9975 - 0.9998									
Linearity Range (pg/mL)	1.000 - 600.0									
Sensitivity/LOQ (pg/mL)	1.000									

Bioequivalence Study MGR001-1006						
ANALYTE SA						
Parameter	Quality Control Samples					
Concentration (pg/mL)	3.000	15.00	90.00	240.0	450.0	450.0 Dilution=2
Inter day Precision (% CV)	5.26	4.09	3.63	3.47	3.54	1.59
Inter day Accuracy (% Actual)	93.53	94.13	98.00	98.29	99.07	101.47

Number of Acceptable Runs	FP: 69 SA: 72
Number of Rejected Runs (Run ID, volume/page location)	FP: 5 rejected runs (Runs 38, 40, 41, 56 and 68) and 1 “N/A” run (Run 63. Please see reviewer’s comments in Section 4.6.1 for more details.) SA: 2 rejected runs (Runs 38 and 41) and 1 “N/A” run (Run 63. Please see reviewer’s comments in Section 4.6.1 for more details.) (1/29/2015 submission, Module 5.3.1.4. mgr001-1006...MGR001-1006 Bioanalytical Report Appendix 1... p. 7-12 of 1838)

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If sample and QC diluted during study, specify all dilution factors	2-fold
Was 100% of raw numerical data submitted?	Yes

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes (maximum sample concentration: 224.1 pg/mL for FP, and 894 pg/mL for SA)
Do you agree with the firm's accepted and rejected runs?	Yes (please see comments in Section 4.6.1)

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes [Run IDs 2-15, which includes subjects with randomization numbers (b) (6) Both of these subjects only completed 1 period of the study)]
Were chromatograms serially or randomly selected?	Serially
Were the chromatograms submitted by the firm acceptable?	Yes

Table 13. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
MGWBIO-SOP-BIO-GEN-0018 (v. 3.0)	9/3/2013	Evaluation and Acceptance Criteria for Analytical Runs
MPI-SOP-BIO-GEN-0019 (v. 2.0)	2/4/2015	Chromatography Acceptance Criteria
MGWBIO-SOP-BIO-GEN-0020 (v. 3.0)	9/3/2013	Re-assay or Re-injection of Clinical Samples

Table 14. Additional Comments on Repeat Assays

Were all SOPs followed?	No, but is justifiable (please see comments below)
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Were Calibration and Quality Control for the Sample Analysis acceptable?

Yes (maximum sample concentration: 224.1 pg/mL for FP, and 894 pg/mL for SA).

Summary/Conclusions, Study Assays:

General Comments

- Prior to biosample analysis, the firm conducted 1 run of QC pool qualification (Run 1). The firm also conducted 2 runs of qualification experiment accuracy and precision (Runs 18 and 64) in the middle of the study sample analysis. According to raw data provided, no biosamples were pre-analyzed in these runs.
- The firm stated that one deviation from SOP MGWBIO-SOP-BIO-GEN-0018 (v. 3.0) “Evaluation and Acceptance Criteria for Analytical Runs” occurred during the study for Run 72.

According to this SOP, “[a]t least 67% (typically 2 of 3, or 3 of 4) QC samples run before, between (if applicable), and after each set of subject samples must calculate within 15% of the theoretical values.” However, for Run 72 [a whole subject re-assay for randomization code (b) (6) (Subject (b) (6) for FP and also several miscellaneous re-assays for both FP and SA], 60% (3 of 5) of the QC samples that ran before the subjects samples were within 15% of the theoretical values for FP (LQC and HQC were -15.30% and -16.53%, respectively, of their theoretical value). The firm stated that since the concentration of HQC (450 pg/mL) is not relevant to the subject samples for FP, and there was limited volume remaining for Subject (b) (6) for additional re-assay, this Run 72 was considered acceptable by the firm for FP based on the following:

- i) The overall acceptance rate for FP QCs in this run was 80%, which exceeds the 67% SOP requirement.
- ii) The overall acceptance rate for FP QCs other than HQCs was 87.5%. It should be noted that none of the subject sample concentration in Run 72 exceeded the next highest QC level of 240 pg/mL for FP.
- iii) The principal reason for the SOP requirement of at least 67% acceptance applied individually to the front and back bracketing QC sets is to control potential assay drift across the run. The front and back bracketing FP QCs showed no evidence of significant assay drift.

The reviewer verified from the raw data that study sample concentrations of this run were all below 240 pg/mL for FP, which was the concentration of the next highest acceptable QC. In addition, this run met the QC acceptance criteria as recommended by the *Guidance for Industry – Bioanalytical Method Validation* (draft recommended on September 2013) (at least 67% of the QCs concentration result should be within 15% of their respective theoretical values. At least 50% of QCs at each level should be within 15% of their theoretical concentrations.). Therefore, the reviewer will not pursue this SOP deviation issue further.

Comments for FP

- The incurred sample reanalysis (ISR) was performed on 8.12% of the samples (200 out of 2462 total samples). It is noted that the firm conducted ISR on 25

subjects (samples from 66 subjects were analyzed). Based on the data provided, it appeared that for each subject period of these 25 subjects, the firm selected 4 samples with at least one sample near C_{max} and at least one sample in the elimination phase. This ISR sample selection is in accordance with SOP MGWBIO-SOP-BIO-GEN-0023 (version 2.0) “Within-Study Incurred Sample Re-Analysis (ISR)”, which states that “[t]he ISR samples must be from a minimum of 8 subjects (this requirement does not apply for re-dosed BE studies with fewer than 8 subjects... Typically, ISR samples will be chosen such that at least 1 time point is selected from the high concentration portion of the profiles (i.e., near the C_{max}) and at least 1 time point from the elimination phase.” However, the number of subject to be selected for ISR in this SOP is not in line with the Bioanalytical Method Validation Guidance, which states that ISR sample selection should be include all study subjects. Therefore, for their future studies, the firm will be advised that the Bioanalytical Method Validation Guidance states that ISR sample selection should include “all study subjects”. 100.00% of the ISR were within 20% of the mean of original and ISR concentration.

Comments for SA

- For reassay of samples above ULOQ, the firm used 2-fold dilution, which was covered by the dilution integrity study in pre-study method validation. It is noted that the firm did not include dilution QCs (DQCs) in the analytical run. Instead, they diluted high QCs (450 pg/mL) 2-fold with K2EDTA human plasma according to SOP MGWBIO-SOP-BIO-GEN-0020. However, since the method validation guidance did not require DQC in the reassay run, the reviewer will not pursue this issue further.
- ISR was performed on 8.12% of the samples (200 out of 2462 total samples). It is noted that the firm conducted ISR on 25 subjects (samples from 66 subjects were analyzed). Please refer to the FP section above for the firm’s ISR sample selection. 99.5% of the ISR were within 20% of the mean of original and ISR concentration. As mentioned above, the firm will be advised about the ISR recommendation in the bioanalytical guidance for their future study.

The bioanalytical results are **acceptable**.

5.1.1.4 Pharmacokinetic Results

Table 15. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 9 and Figure 1

Fasting Bioequivalence Study, Study No. MGR001-1006									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	%CV	Min	Max	
FP									
AUC _{0-t} (hr *pg/ml)	662.527	30.26	153.85	1155.64	629.129	27.95	183.57	1119.27	1.05
AUC _∞ (hr *pg/ml)	690.927	30.17	164.72	1217.76	655.372	27.94	191.30	1176.07	1.05
C _{max} (pg/ml)	110.760	32.27	53.16	224.10	118.870	28.43	60.78	220.20	0.93
T _{max} * (hr)	0.750	.	0.08	1.50	0.750	.	0.08	1.50	1.00
Kel (hr ⁻¹)	0.067	34.90	0.04	0.20	0.072	41.86	0.04	0.25	0.93
T _{1/2} (hr)	11.100	23.90	3.40	17.51	10.651	28.80	2.81	18.31	1.04
SA									
AUC _{0-t} (hr *pg/ml)	742.957	31.15	406.22	1825.26	694.939	36.52	398.97	1875.02	1.07
AUC _∞ (hr *pg/ml)	777.117	30.88	455.96	1893.22	728.838	36.23	435.26	1954.29	1.07
C _{max} (pg/ml)	381.518	42.01	143.80	894.00	377.317	35.59	115.80	744.60	1.01
T _{max} * (hr)	0.083	.	0.03	1.50	0.083	.	0.03	2.00	1.00
Kel (hr ⁻¹)	0.057	15.08	0.04	0.08	0.057	16.00	0.03	0.09	1.01
T _{1/2} (hr)	12.382	15.50	8.40	19.58	12.568	16.82	7.96	21.70	0.99

* T_{max} values are presented as median, range.

Table 16. Geometric Means and 90% Confidence Intervals - Firm Calculated

MGR001 100/50 MCG AND ADVAIR® DISKUS® 100/50 MCG						
Dose: 3 Inhalations; Total Dose 300/150 mcg FP/SA						
Number of Subjects Completed = 64						
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study Number MGR001-1006): FP						
Parameter	Test	N	Reference	N	Ratio*	90% C.I.**
AUC _{clast} (pg.h/mL)	600.3	64	576.4	64	104.15	100.27% - 108.18%
AUC _{inf} (pg.h/mL)	614.1	64	597.3	64	102.82	98.69% - 107.12%
C _{max} (pg/mL)	103.7	64	112.9	64	91.91	87.88% - 96.12%
Fasting Bioequivalence Study (Study Number MGR001-1006): SA						
Parameter	Test	N	Reference	N	Ratio*	90% C.I.**
AUC _{clast} (pg.h/mL)	696.4	64	644.9	64	107.99	104.60% - 111.47%
AUC _{inf} (pg.h/mL)	730.3	64	676.8	64	107.90	104.62% - 111.28%
C _{max} (pg/mL)	347.7	64	348.3	64	99.84	94.57% - 105.41%

*Ratio (A/B) = e^(LSMEAN of LNA - LSMEAN of LNB); **Used Natural Log Transformed Parameter

Table 17. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder 3 x 100/50 mcg Fasting Bioequivalence Study, Study No. MGR001-1006, N=64 (Male=36 and Female=28) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
FP							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
Group 1							
LAUCT (hr *pg/ml)	567.02	20	581.56	20	0.98	91.27	104.16
LAUCI (hr *pg/ml)	592.74	20	607.71	20	0.98	91.39	104.10
LCMAX (pg/ml)	99.92	20	107.96	20	0.93	86.12	99.47
Group 2							
LAUCT (hr *pg/ml)	611.59	20*	557.84	20*	1.10	102.38	117.40
LAUCI (hr *pg/ml)	637.68	20*	579.28	20*	1.10	102.94	117.72
LCMAX (pg/ml)	104.88	20*	110.89	20*	0.95	87.75	101.96
Group 3							
LAUCT (hr *pg/ml)	702.22	22	657.49	22	1.07	100.47	113.53
LAUCI (hr *pg/ml)	733.11	22	685.59	22	1.07	100.78	113.46
LCMAX (pg/ml)	111.69	22	122.54	22	0.91	83.36	99.66
SA							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
Group 1, 2 and 3 (trt*troup = 2)							
LAUCT (hr *pg/ml)	712.40	60^	659.12	60^	1.08	104.81	111.46
LAUCI (hr *pg/ml)	745.82	60^	692.05	60^	1.08	104.65	110.98
LCMAX (pg/ml)	347.94	60^	349.15	60^	1.00	94.35	105.26

* Subjects (b) (6) were excluded by the reviewer due to missing samples that potentially affect Cmax.
^ Subjects (b) (6) were excluded by the reviewer due to missing samples that potentially affect Cmax.

Table 18. Additional Study Information, Fasting Study No. MGR001-1006

FP

DB SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALKE	
Reason(s) for Selecting Above SAS Program Macro	Please provide comment below the table	
Root mean square error, AUC _{0-t}	Group 1: 0.1198 Group 2: 0.1242 Group 3: 0.1175	
Root mean square error, AUC _∞	Group 1: 0.1181 Group 2: 0.1217 Group 3: 0.1139	
Root mean square error, C _{max}	0.1461	
	Test	Reference
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC _∞	62	62
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC _∞	Mostly agree*	Mostly agree^
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C _{max}	0	0
C _{max} at the first time point	0	0
Were the subjects dosed as more than one group?	Yes	

* Mostly agree, except for 3 subjects (subjects (b) (6)) that don't agree. The firm excluded these subjects from Kel and AUC_i determination, whereas the reviewer thinks that these parameters could be determined for these subjects.

^ Mostly agree, except for 5 subjects (subjects (b) (6)) that don't agree with the same reason mentioned above.

SA

DB SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALKE	
Reason(s) for Selecting Above SAS Program Macro	Please provide comment below the table	
Root mean square error, AUC _{0-t}	0.1003	
Root mean square error, AUC _∞	0.0960	
Root mean square error, C _{max}	0.1787	
	Test	Reference
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC _∞	60	60
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC _∞	Mostly agree*	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0

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first measurable drug concentration as C _{max}	7	12
C _{max} at the first time point	7	12
Were the subjects dosed as more than one group?	Yes	

* Mostly agree, except for 1 subject (subject (b) (6)) that don't agree. The firm excluded this subject from Kel and AUC_i determination, whereas the reviewer thinks that these parameters could be determined for this subject.

Group Analysis Consideration (FP)

If more than one group were dosed, did you use the statistical model with group effect included?	Yes
Was the group*treatment interaction term statistically significant at alpha=0.1 (i.e., p< 0.1)?	Yes for AUC _t (0.0828) and AUC _i (0.0655) No for C _{max} (0.8496)
If yes, specify which PK parameter(s)	AUC _t and AUC _i
If yes (group*treatment term is significant), was each group analyzed separately?	Yes for AUC _t and AUC _i No for C _{max}
If each group was analyzed, did any individual group meet BE criteria?	All 3 groups
If none of individual group meets the BE criteria, did you have other justifications for accepting the data? If yes, please provide justifications. Additional justification comments may be provided under the Comments section below.	N/A

Group Analysis Consideration (SA)

If more than one group were dosed, did you use the statistical model with group effect included?	Yes
Was the group*treatment interaction term statistically significant at alpha=0.1 (i.e., p< 0.1)?	No
If yes, specify which PK parameter(s)	N/A
If yes (group*treatment term is significant), was each group analyzed separately?	N/A
If each group was analyzed, did any individual group meet BE criteria?	N/A
If none of individual group meets the BE criteria, did you have other justifications for accepting the data? If yes, please provide justifications. Additional justification comments may be provided under the Comments section below.	N/A

Ratio of AUC _{0-t} /AUC _∞				
FP				
Treatment	n	Mean	Minimum	Maximum
Test	62	0.96	0.91	0.98
Reference	62	0.96	0.92	0.98
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.				N/A
SA				
Treatment	n	Mean	Minimum	Maximum
Test	60	0.96	0.88	0.98
Reference	60	0.95	0.84	0.98
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.				N/A

Was the fasting bioequivalence study acceptable?

Yes

Comments on SAS Program selected, Subject variability, any Tmax differences (if applicable), Pharmacokinetic and Statistical Analysis:

- The reviewer specified linear range used to calculate Kel; therefore, SAS code CALKE was used for statistical analysis.
- The subjects were dosed in 3 groups; therefore, analysis of variance was performed with the group effect incorporated in the model.

For FP, there was no significant group*treatment effect for LnCmax (p=0.8496). However, the group*treatment effect for LnAUCt (p= 0.0828), LnAUCi (p= 0.0655) is significant. Therefore, the reviewer calculated 90% CIs of PK parameters for each group separately as per current DB practice.

For SA, there was no statistically significant difference (p> 0.1) in terms of group*treatment for LnAUCt (p= 0.1014), LnAUCi (p= 0.1055), LnCmax (p= 0.4294). All of the subjects in this study were recruited from the same geographic region and were dosed at the same clinical facility within 3 days. Accordingly, the reviewer combined three groups for statistical analysis as per current DB practice⁶⁷.

- There are differences between the firm and the reviewer calculated geometric means and 90% confidence intervals for AUC_{0-t}, AUC_∞ and Cmax (Tables 16 and 17). It should be noted that the reviewer excluded subjects that had missing samples that could potentially affect Cmax. In addition, according to the study report, the firm's AUC was calculated by the linear-log trapezoidal method,

⁶⁷ V:\FIRMSNZ\^{(b)(4)}\CONTROLS\98-392A.doc

whereas the Agency’s SAS code used the linear trapezoidal method. Also, as mentioned in the study design section, the firm calculated AUClast (the firm defined AUClast as AUC “from time 0 to the time of the last measurable concentration”⁶⁸) instead of AUC_{0-t}. Moreover, the reviewer also suspects that the firm did not incorporate group effect in their calculation, as leaving out the group effect (let trtgroup=“ ” instead of “2” in SAS code) using the firm’s dataset leads to exactly the same results as firm-calculated Cmax (verified by the reviewer, results not shown).

- The study still meet BE acceptance criteria after statistical analysis was completed under the assumption that all groups are homogenous and can therefore be treated as a single group for statistical analysis purposes⁶⁹ (please see table below).

trtgroup=null

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
FP					
LAUCT (hr *pg/ml)	627.20	602.00	1.04	100.30	108.22
LAUCI (hr *pg/ml)	654.77	627.34	1.04	100.54	108.36
LCMAX (pg/ml)	105.53	114.31	0.92	88.29	96.54
SA					
LAUCT (hr *pg/ml)	712.65	661.75	1.08	104.19	111.32
LAUCI (hr *pg/ml)	746.19	694.97	1.07	103.99	110.86
LCMAX (pg/ml)	348.99	351.52	0.99	93.93	104.94

- For SA, 7 subjects for the test product and 12 for the RLD had the first measurable drug concentration as Cmax as well as first post-dose time point as Cmax. However, it should be noted that the firm included sufficient PK sampling times to cover the expected Tmax range per the RLD label (i.e. about 5 min for SA and 1 to 2 hrs for FP). The firm included early time points (2, 5, 10, 15 min) in addition to 4 more time points within the first hour. This time point selection is in line with *Draft Guidance for Industry – Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted under an ANDA* (posted Dec 2013).

It is noted that subjects treated with reference product had more first time point Cmax as compared to subjects treated with test product (12 subjects for the reference product vs. 7 subjects for the test product). However, it should be noted that Tmax values for the test and reference product are considered comparable (please see details in the bullet point below).

⁶⁸ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.1.2. mgr001-1006...\Study Report Body\MGR001-1006 Study Report, p. 12 of 98).

⁶⁹ Because the study met the following criteria, it is not necessary to include group*treatment interaction in the statistical model: 1) the clinical study took place at once site; 2) all subjects were recruited from the same enrollment pool; 3) all of the subjects had similar demographics and; 4) all enrolled subjects were randomly assigned to treatment groups at study outset. Therefore, statistical analysis was performed with the group*treatment interaction set to null.

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- Tmax (hr) for the test and reference product are provided below:

FP

	Test	Reference	Ratio
Median	0.75	0.75	1.00
Min	0.08	0.08	1.00
Max	1.50	1.50	1.00

SA

	Test	Reference	Ratio
Median	0.083	0.083	1.00
Min	0.03	0.03	1.00
Max	1.500	2.00	0.75

The Tmax values for the test and reference products are considered comparable for FP and SA.

- The 90% confidence intervals for FP and SA are within the acceptable limits of 80%-125%.

The *in vivo* fasting BE study MGR001-1006 is **incomplete** due to deficiencies related to method validation.

Table 19A. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

FP

Time (hr)	Test (n=62)		Reference (n=62)		Ratio (T/R)
	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	
0.00	0.00	.	0.00	.	.
0.03	22.32	101.32	27.48	68.35	0.81
0.08	40.02	66.54	55.21	58.59	0.72
0.17	57.50	45.43	70.27	39.79	0.82
0.25	77.80	42.64	86.96	35.46	0.89
0.33	87.46	41.71	99.29	35.21	0.88
0.50	98.57	34.14	109.26	29.17	0.90
0.75	103.57	32.80	108.82	27.50	0.95
1.00	101.31	30.69	104.29	26.70	0.97
1.50	88.59	27.78	89.63	26.07	0.99
2.00	78.73	30.22	76.99	25.31	1.02
3.00	60.19	30.08	57.55	26.57	1.05
4.00	49.44	31.36	46.40	26.35	1.07
6.00	29.80	33.21	27.36	31.50	1.09
8.00	22.35	33.50	20.08	32.71	1.11
12.00	12.34	33.67	11.04	33.23	1.12
24.00	4.75	35.18	4.26	38.18	1.12
36.00	2.23	45.71	1.93	52.04	1.16
48.00	1.32	67.41	1.06	85.75	1.25

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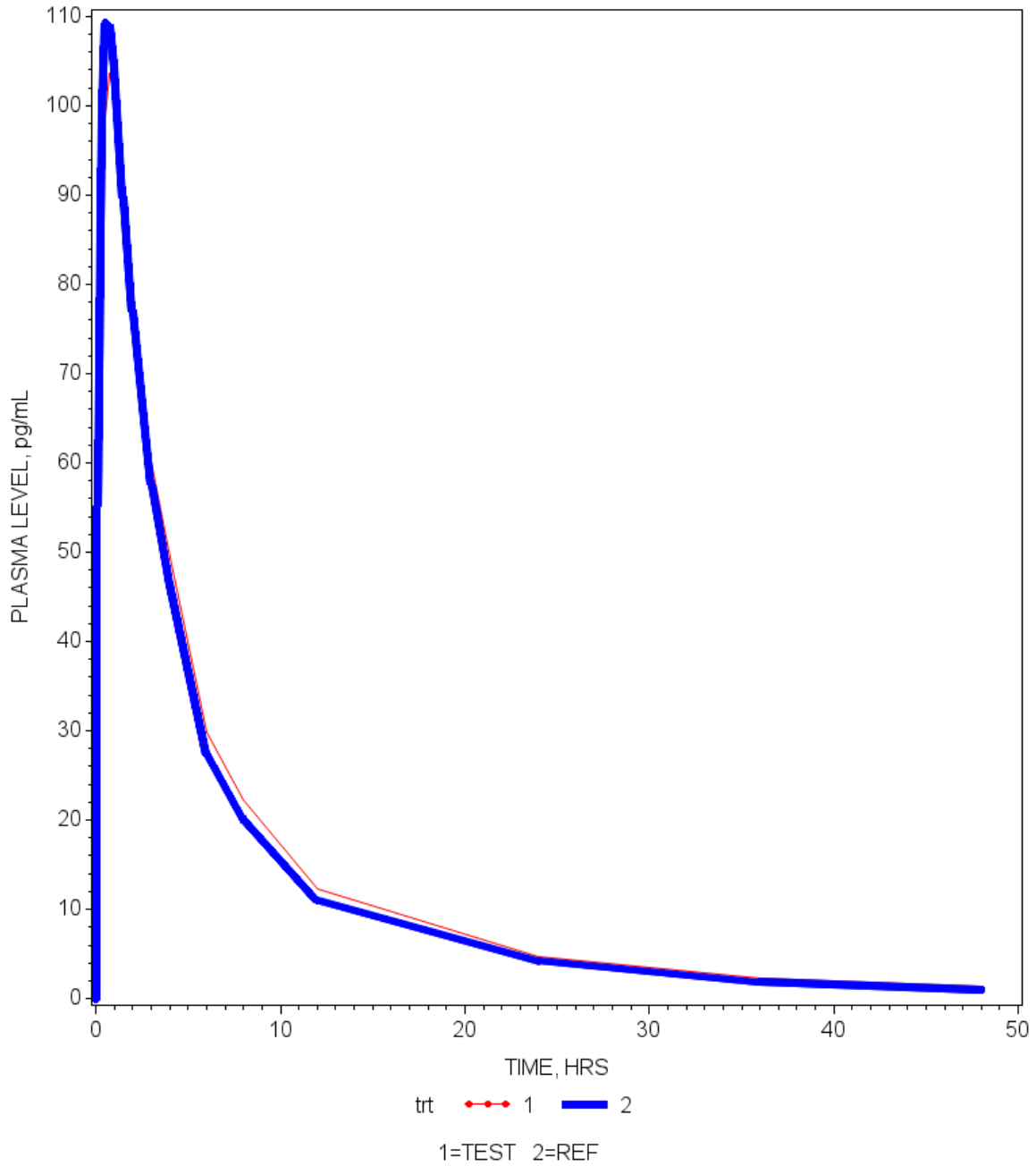
SA

Time (hr)	Test (n=60)		Reference (n=60)		Ratio (T/R)
	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	
0.00	0.00	.	0.00	.	.
0.03	274.31	60.29	303.29	47.47	0.90
0.08	369.45	39.68	369.07	34.74	1.00
0.17	244.35	31.60	232.77	30.49	1.05
0.25	178.56	29.31	164.23	24.93	1.09
0.33	147.58	26.67	133.73	24.00	1.10
0.50	122.17	28.57	108.13	26.53	1.13
0.75	109.76	35.78	94.99	28.54	1.16
1.00	98.89	37.00	88.03	28.19	1.12
1.50	84.82	38.84	75.54	33.34	1.12
2.00	72.72	39.88	67.34	45.87	1.08
3.00	52.63	39.69	48.38	52.58	1.09
4.00	39.81	38.79	37.72	53.32	1.06
6.00	27.85	39.01	27.02	53.36	1.03
8.00	20.60	34.29	19.48	46.93	1.06
12.00	13.38	32.29	12.52	45.06	1.07
24.00	6.73	36.80	6.45	42.68	1.04
36.00	3.12	37.10	2.99	44.17	1.04
48.00	1.81	42.93	1.69	55.34	1.08

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

FP

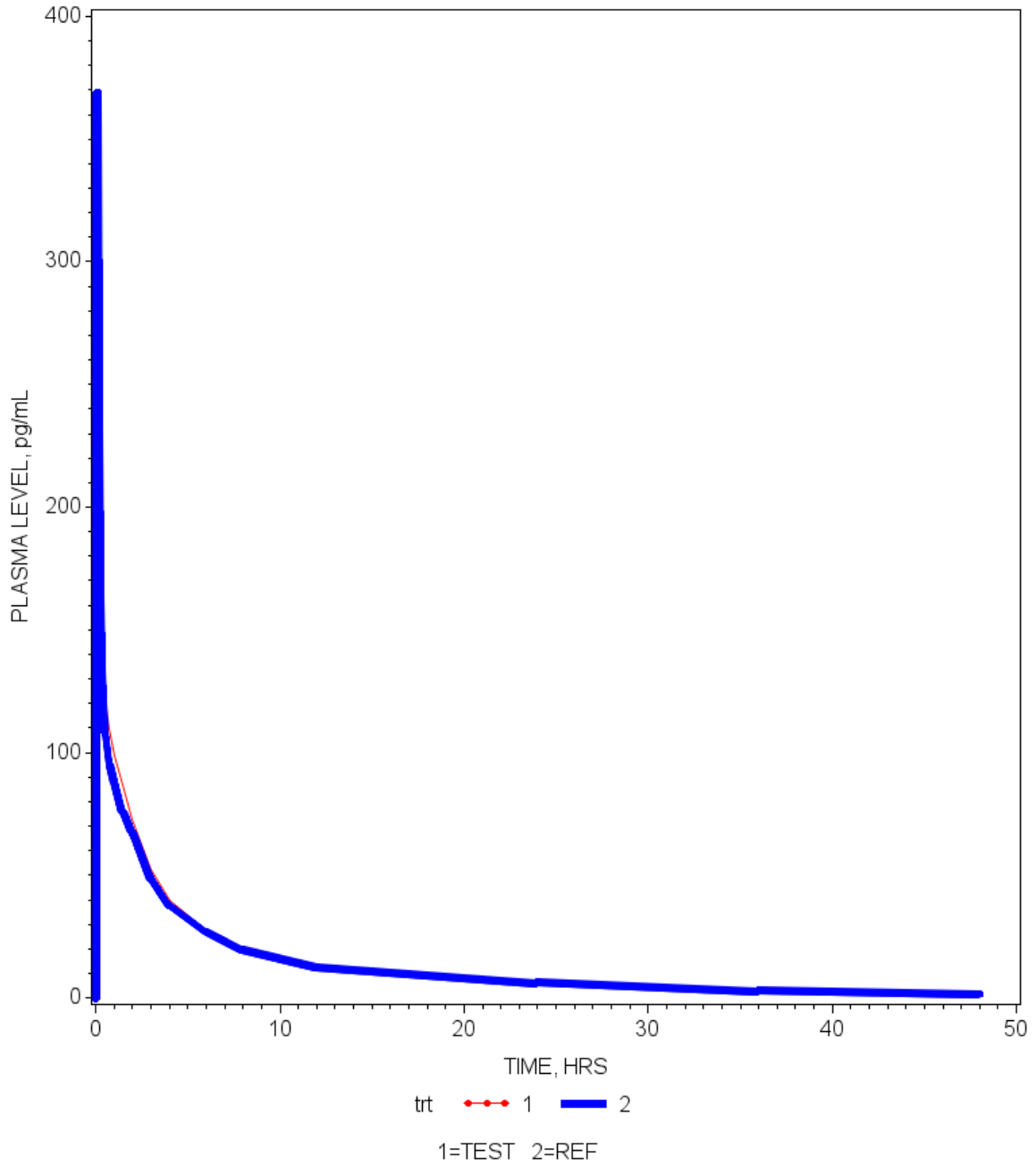
PLASMA Fluticasone Propionate LEVELS
Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder, ANDA 208891
UNDER Fasting CONDITIONS
DOSE= 3 x 100/50 MCG



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Study Number

SA

PLASMA Salmeterol LEVELS
Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder, ANDA 208891
UNDER Fasting CONDITIONS
DOSE= 3 x 100/50 MCG



5.1.2 Single-dose Fasting Bioequivalence Study MGR001-1007

Reviewer's note: As detailed in reviewer's comments in Section 4.6, the firm assigned each subject with a subject number and also a randomization number. Please refer to the same comments about how a subject will be referred to (using their subject number and/or randomization number) in this section.

5.1.2.1 Study Design

Table 20 Study Information

Study Number	MGR001-1007
Study Title	AN OPEN-LABEL RANDOMIZED, TWO-WAY CROSSOVER STUDY TO DETERMINE PHARMACOKINETIC BIOEQUIVALENCE OF SINGLE DOSES OF FLUTICASONE PROPIONATE / SALMETEROL FIXED DOSE COMBINATION (500/50 µg) POWDER ADMINISTERED BY ORAL INHALATION FROM MGR001 AND ADVAIR® DISKUS® IN HEALTHY ADULT SUBJECTS.
Clinical Site (Name & Address)	Worldwide Clinical Trials Early Phase Services, LLC 2455 NE Loop 410, Suite 150 San Antonio, Texas 78217
Principal Investigator	Dr Cynthia A. Zamora, MD
Dosing Dates	Group 1 Period 1: 14-July-2015 Group 1 Period 2: 21-July-2015 Group 2 Period 1: 15-July-2015 Group 2 Period 2: 22-July-2015 Group 3 Period 1: 16-July-2015 Group 3 Period 2: 23-July-2015
Analytical Site (Name & Address)	Mylan Pharmaceuticals Inc. Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505
Analysis Dates	04-August-2015 – 20-August-2015
Analytical Director	Patrick T. Vallano, Ph.D.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	FP: Longest storage duration and condition: 37 days at -70°C SA: Longest storage duration and condition: 37 days at -70°C LTSS coverage: FP: 132 days at -70°C SA: 132 days at -70°C

Table 21. Product information

Product	Test	Reference
Treatment ID	Treatment A	Treatment B
Product Name	MGR001	Advair® Diskus®
Manufacturer	Mylan Global Respiratory Group	GlaxoSmithKline
Batch/Lot No.	631-006	4ZP5917
Manufacture Date	09 Jan 2015	N/A
Expiration Date	N/A	February 2016
Strength	500/50 mcg	500/50 mcg
Dosage Form	Inhalation Powder	Inhalation Powder
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)	Emitted Dose (% of Target): FP 100 %* SA 103 %*	Emitted Dose (% of Target): FP 103 % SA 105 %
Content Uniformity (expressed as mean, %CV or per USP)	FP: Mean 100 % of Label Claim CV 4.3 % SA 99 % of Label Claim CV 4.1 %	N/A
Dose Administered	FP 1500 mcg SA 150 mcg	FP 1500 mcg SA 150 mcg
Route of Administration	Inhalation	Inhalation

* Please see reviewer's comments below.

Table 22. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: Not specified by the firm Dosed: 66 Completed: 65 Samples Analyzed: 66 Data Analyzed: 65
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	3 (Group 1: Randomization # (b) (6); Group 2: (b) (6); Group 3: (b) (6))
Washout Period	7 days
Randomization Scheme (Sequence of T and R)	Please see table below
Blood Sampling Times	Pre-dose (0 hour) and 2, 5, 10, 15, 20, 30, 45, 60, and 90 minutes, and 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post dose.

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Blood Volume Collected/Sample	10 mL
Anticoagulant Used	K2EDTA
Blood Sample Processing & Storage (include storage temperature)	Blood samples for the analysis of FP and SA in plasma and subsequent pharmacokinetic analysis were collected into 1 x 10 mL K2-EDTA tubes. The collection tube was inverted 5-10 times immediately after collection, then immediately placed in an ice bath. Blood samples were centrifuged at approximately 1990 g ± 400 g (e.g. 3000 rpm) for 10 minutes under refrigeration (4 °C ± 3 °C). The time interval between sample collection and the start of centrifugation did not exceed 45 minutes. As soon as centrifugation stopped, samples were returned to an ice bath and the plasma transferred into two equal aliquots to labeled polypropylene tubes. Plasma samples were capped and frozen in an upright position in -70 °C ±15 °C freezer or colder, pending shipment to Mylan Pharmaceuticals Inc. Transfer of the samples into the freezer took place no later than 90 minutes after the start of centrifugation. Plasma samples were maintained in an ice bath until transfer to the storage freezer occurred.
IRB Approval (Y/N, Date)	Y Protocol: 5/27/2015 Protocol amendment 1: 6/10/2015
Informed Consent (Y/N, Date)	Y Informed consent: 5/27/2015 Revised informed consent: 6/10/2015
Length of Fasting	8 hours prior and 4 hours post the start of pharmacokinetic sample collections on Day 1
Length of Confinement	From the day prior to dosing until 24 hours post-dose
Safety Monitoring	The Investigator evaluated safety using the following assessments: medical history, prior/concomitant medication, history of drug, alcohol, and tobacco use, physical examination, 12-lead ECG, supine blood pressure and pulse rate, spirometry (forced expiratory volume in 1 second [FEV1] and forced vital capacity [FVC]), safety laboratory/urinalysis, pregnancy tests (all females of childbearing potential), continuous cardiac monitoring; with any clinically significant changes recorded as adverse events (AEs). Subjects were routinely queried (at least every 8 hours during confinement and at each visit) for the presence or absence of AEs using open ended questions. Spontaneously reported AEs were also recorded. Subjects were monitored for any AEs from the signing of the informed consent forms to 30 days after the last dose of study medication.
Was the study design used for the fasting BE study acceptable?	NO (please see comments below)

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Randomization Scheme

Randomization Number	Subject Number	Treatment received at Period 1	Treatment received at Period 2	Randomization Number	Subject Number	Treatment received at Period 1	Treatment received at Period 2
	(b) (6)	B	A		(b) (6)	B	A
		B	A			B	A
		A	B			B	A
		A	B			A	B
		B	A			A	B
		A	B			A	B
		B	A			B	A
		B	A			B	A
		A	B			A	B
		A	B			A	B
		A	B			B	A
		B	A			A	B
		A	B			B	A
		B	A			B	A
		A	B			A	B
		A	B			B	A
		A	B			B	A

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Randomization Number	Subject Number	Treatment received at Period 1	Treatment received at Period 2
	(b) (6)	A	B
		A	B
		B	A
		A	B
		B	A
		B	A
		B	A
		A	B
		B	A
		A	B
		A	B
		B	A
		B	A
		A	B
		A	B
		B	A
		B	A
		B	A
		A	B

A = test
B = RLD

Comments on Study Design:

1. Same as in the fasting study MGR001-1006, the firm stated that the test device used for the fasting study MGR001-1007 (clinical device: (b) (4)) is different from the proposed commercial device (b) (4)

(b) (4)

Due to the device difference, the firm will be asked to conduct in vitro BE studies (SAC and APSD studies) comparing RLD product and the test product with final commercial device as bridging studies. These studies should be conducted for the 500/50 mcg strength of the product, and these in vitro studies should be conducted according to the product specific guidance, and use at least 3 batches each of T and R products with no fewer than 10 units from each batch.

⁷⁰ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.7\Container Closure System, p. 66-67 of 229).

2. According to the firm's product information summary table⁷¹, emitted dose as % target for test product batch #631-006 is 100% for FP and 103% for SA. However, this value is (b) (4) according to its COA^{72,73}. The firm stated that emitted dose values reported in the COA for batch #631-006 was based on the development specification in place at the time of batch release, which was calculated as a % of the target emitted dose value of (b) (4) mcg for FP and (b) (4) mcg for SA, rather than 465 mcg and 45 mcg set in the proposed commercial specification.⁷⁴ The value of 100% for emitted dose of FP and 103% for SA in the product information summary table was calculated against the proposed commercial specification, with a target emitted dose value of 465 mcg for FP and 45 mcg for SA, which is in line with the RLD labeling. The reviewer considers the firm's explanation for this discrepancy acceptable.
3. The firm conducted the PK fasting study based on 3 inhalations of the drug product, which was found acceptable in CC 12-0731.⁷⁵ In the same CC, the Agency also recommended the firm to submit a Bio-IND to the Agency for the evaluation of the safety if the dose given in the PK study exceeds the maximum labeled single dose. The firm submitted IND 118769 for the lower strength (250/50 mcg), but not for the 500/50 mcg strength. The firm will be advised for their future study to submit a bio-IND prior to study commencement if the dose given in the PK study exceeds the maximum labeled single dose for the evaluation of safety.
4. As noted for the fasting study MGR001-1006, the agency did not oppose the firm's use of AUClast in place of AUCt.⁶¹ In addition, the AUCt calculated by the reviewer does not change the study outcome as compared to the firm's outcome for this study (please see details in Section 5.1.2.4).
5. Same as the fasting study MGR001-1006, on Day -1 and Day 1 prior to dosing for both study periods, subjects were trained to achieve an appropriate inhalation maneuver for both the CRC749 and Diskus[®] inhalers.
6. Same as the fasting study MGR001-1006, the research unit staff prepared (as per the instruction for use) each inhaler ready for dosing, before handing to the subject for dosing. The inhaler was re-prepared by the research unit staff

⁷¹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 [Module 2.7.1\Summary of Biopharmaceutic Studies and Associated Analytical Methods (Biosummary Tables 1-6 and 9-17), p. 35 of 47].

⁷² GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.5.4\Lot 631-006 – Mylan Certificate of Analysis, p. 2 of 3).

⁷³ According to the firm's 1/12/2017 ECD response [GS Review: ANDA 208891, Response to ECD/Bioequivalence, 1/12/2017 (Module 1.2\Cover Letter..., p. 17 of 21)], the emitted dose values reported in the COA of 101.0% for FP and 100.0% for SA contained a minor rounding error. The correct values are 101.4% for FP and 100.4% for SA.

⁷⁴ GS Review: ANDA 208891, Response to ECD/Bioequivalence, 1/12/2017 (Module 1.2\Cover Letter..., p. 16 of 21).

⁷⁵ [\\cdsnas\OGDS6\CONTROLS\2012-docs\12-0731.pdf](#) p. 26 of 34.

following each inhalation and prior to the next inhalation. There was an interval of approximately 30 seconds between each inhalation.

7. Same as in the fasting study MGR001-1006, subjects were instructed to rinse their mouths (without swallowing) with approximately 50 mL water after completing the three inhalations, and to spit the water out after rinsing. This is in line with the product-specific guidance, which states that “[s]ubjects should adhere to labeling as follows: ‘Rinse your mouth with water after breathing in the medicine. Spit the water out, do not swallow.’”

The firm’s study design is **incomplete**.

5.1.2.2 Clinical Results

Table 23A. Demographics Profile of Subjects Completing the Bioequivalence Study

Study Number MGR001-1007			
		Treatment Groups	
		Test Product (MGR001 500/50mcg) N = 65	Reference Product (Advair® Diskus®) N = 66
Age (years)	Mean ± SD Range	35.7 ± 10.3 19 – 53	35.7 ± 10.2 19 – 53
Age Groups	<18 18-40 41-64 65-75 >75	0 (0%) 42 (64.6%) 23 (35.4%) 0 (0%) 0 (0%)	0 (0%) 43 (65.2%) 23 (35.4%) 0 (0%) 0 (0%)
Sex	Male Female	24 41	24 42
Race	White Black or African American Native Hawaiian or Other Pacific Islander White, Black or African American	46 (70.8%) 17 (26.2%) 1 (1.5%) 1 (1.5%)	47 (71.2%) 17 (26.2%) 1 (1.5%) 1 (1.5%)
BMI	Mean ± SD Range	25.8 19.5 – 30.5	25.8 19.5 – 30.5
Other Factors		N/A	N/A

Table 23B. Demographics Profile of Individual Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. MGR001-1007				
Subject No	Age	Gender	Race	BMI
(b) (6)	24	F	WHITE	23.7
	29	F	WHITE	24.9
	50	F	BLACK OR AFRICAN AMERICAN	27.6
	52	M	WHITE	25.2
	33	F	BLACK OR AFRICAN AMERICAN	26.5
	39	F	WHITE	29.2
	31	F	WHITE	23
	40	F	WHITE	27.4
	48	F	WHITE	26.1
	53	F	WHITE	28
	42	F	WHITE	26.4
	33	F	WHITE	23.2
	35	F	WHITE	26.1
	28	M	WHITE	27.4
	31	M	WHITE	23.7
	33	F	WHITE	20.1
	45	F	WHITE	25.1
	34	M	BLACK OR AFRICAN AMERICAN	24.7
	45	M	BLACK OR AFRICAN AMERICAN	26.1
	37	F	WHITE	25.6
	26	F	MULTIPLE	22.2
	52	F	WHITE	30.2

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(b) (6)	27	M	WHITE	28
	48	F	WHITE	26.4
	46	M	WHITE	26.8
	31	M	BLACK OR AFRICAN AMERICAN	23.5
	37	M	WHITE	25.3
	20	F	WHITE	25.1
	22	M	BLACK OR AFRICAN AMERICAN	30.5
	35	M	WHITE	28.7
	53	M	BLACK OR AFRICAN AMERICAN	26.6
	40	F	WHITE	22.8
	27	M	WHITE	25.6
	22	F	WHITE	23.6
	23	F	WHITE	25.9
	22	F	WHITE	24.1
	46	M	WHITE	28.9
	47	M	WHITE	22.9
	19	F	WHITE	25.9
	21	F	WHITE	26.2
	31	F	BLACK OR AFRICAN AMERICAN	25.7
	35	F	WHITE	23
	44	M	BLACK OR AFRICAN AMERICAN	29.7
	43	F	BLACK OR AFRICAN AMERICAN	19.5
	24	F	WHITE	26.9
	37	F	BLACK OR AFRICAN AMERICAN	21
	47	F	BLACK OR AFRICAN AMERICAN	26
	41	F	WHITE	27.9
	46	M	WHITE	29.2
	38	F	WHITE	29.8
	50	M	BLACK OR AFRICAN AMERICAN	26.2
	25	M	WHITE	23.4
	49	F	BLACK OR AFRICAN AMERICAN	22.1
	26	M	BLACK OR AFRICAN AMERICAN	27.9
	20	F	WHITE	26.4
	50	F	WHITE	30.2
	32	F	WHITE	29.6
	25	M	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	27
30	F	BLACK OR AFRICAN AMERICAN	26.4	
22	F	BLACK OR AFRICAN AMERICAN	23.1	
33	M	WHITE	26.1	
46	F	WHITE	22.9	
34	M	WHITE	28.6	
25	F	WHITE	25.1	
26	M	WHITE	23.3	
51	F	WHITE	29.1	

Table 24. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
(b) (6)	Subject was withdrawn prior to Period 2 for deviation/noncompliance with the protocol (positive drug screen) and did not receive MGR001 500/50 mcg Date: (b) (6) Treatment: Prior to receiving Test	1	No

Table 25. Study Adverse Events, Fasting Bioequivalence Study

System Organ Class/ Preferred Term	Reported Incidence by Treatment Groups	
	Study Number MGR001-1007*	
	Test Product (MGR001 500/50 mcg) No. of Subjects n (%)	Reference Product (Advair® Diskus 500/50 mcg) No. of Subjects n (%)
General disorders and administration site conditions		
Asthenia	1 (1.5%)	0 (0.0%)
Injury, poisoning and procedural complications		
Contusion	1 (1.5%)	0 (0.0%)
Musculoskeletal and connective tissue disorders		
Back pain	1 (1.5%)	0 (0.0%)
Neck pain	1 (1.5%)	0 (0.0%)
Total	4 (6.2%)	0 (0.0%)
*3 Inhalations (total dose 1500/150 mcg FP/salmeterol)		
Adverse Events were coded using MedDRA version 18.0		

Do any of the adverse events require statistical analysis consideration (e.g. emesis)?
No

If yes, does the time exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products) according to the Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products?

N/A

Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Please comment.

Yes. One incidence each of asthenia, contusion, back pain and neck pain was observed for test products, but the firm considered it unrelated/not related (contusion and back pain) or unlikely related to treatment (asthenia and neck pain).

All adverse events were mild in severity, and all symptoms of adverse events reported during the study were resolved. From such a small sample size, there is insufficient

evidence of safety concern regarding the test product when compared to reference product.

Are there any safety concerns based on the adverse event profile?

No. The firm reported that there were no deaths or other serious adverse events reported during the study.

Table 26. Protocol Deviations, Fasting Bioequivalence Study

Study No. MGR001-1007		
Type	Subject #s (Test)	Subject #s (Ref.)
Blood collection time deviations	(b) (6)	
Non-compliance (positive amphetamine screen at Period 2 admission, Subject withdrawn)		
Missed assessments (blood samples not collected per protocol)		
Period 2, 8 and 12h plasma and whole blood samples contained white debris (possible manufacturers error)		

Did dropouts/adverse events/protocol deviations affect the study outcome?

Please see comments below.

Comments on Dropouts/Adverse Events/Protocol Deviations:

- A total of 66 subjects were randomized into the study. Sixty-four (65) subjects who completed both periods of the study were included in the PK analysis set (i.e. contributed to the statistical analysis of BE). One (1) dropout subject (b) (6) that completed 1 period of the study were included in the PK parameter set (i.e. had PK parameters derived), but were not included for in the PK analysis set.
- For Subject (b) (6) that were dropped out of the study, the reviewer verified from the corresponding CRF that this subject was not dosed in Period 2.
- The use of the following concomitant medications as birth controls was reported: desogestrel (prodrug to etonogestrel)/ethinyl estradiol, drospirenone/ethinyl estradiol, levonorgestrel, norethinrone/ethinyl estradiol, and etonogestrel. The firm evaluated the specificity of the analytical methods in the presence of the above drug compounds⁷⁶. Based on representative chromatograms provided, none of the tested compounds significantly interfere with the analysis of FP, SA and the internal standards.

⁷⁶ For the inactive prodrug desogestrel, the firm evaluated the specificity of the analytical methods in the presence of its active metabolite etonogestrel.

The reviewer also verified from Micromedex that there are no known drug-drug interactions between the aforementioned concomitant medications and the study drug FP/SX⁷⁷.

- There were sampling time deviations. Since the firm used the actual sampling time points for the PK analysis, these deviations do not affect the study outcome.
- Five (5) subjects had missing blood sample collections [due to restick(s)], and the firm included all these 5 subjects into the statistical analysis⁷⁸. However, the reviewer noticed that some of these missing sample blood collection time points are close to Tmax, thus may potentially affect Cmax of these subjects (please see table below. For representative plots of plasma concentration vs time of subjects with missing samples that potentially affect Cmax, please see reviewer's comments in Section 5.1.1.2.).

Subject	Randomization Code	Period	Treatment	Time of missing blood collection	Potentially affect Cmax for FP?	Potentially affect Cmax for SA?
(b) (6)		2	R	5 min (0.08 hr)	No	Yes
		2	T	2 min (0.03 hr)	No	Yes
		1	R	10 min (0.16 hr)	No	No
		1	T	30 min (0.5 hr)	Yes	No
				45 min (0.75 hr)	Yes	No
				60 min (1 hr)	Yes	No
		2	R	15 min (0.25 hr)	No	No
		2	T	10 min (0.16 hr)	No	Yes
		1	T	10 min (0.16 hr)	No	Yes
				15 min (0.25 hr)	No	Yes
2	R	2 min (0.03 hr)	No	Yes		

The reviewer will **exclude** subjects with missing time point(s) that are **very likely to impact Cmax**.

⁷⁷ Micromedex:

<http://www.micromedexsolutions.com/micromedex2/librarian/PFDefaultActionId/evidencexpert.ShowDrugInteractionsResults> Last accessed: 9/30/2016.

⁷⁸ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.1.2. mgr001-1007...\Statistical Methods Interim Analysis Plan, p. 46-54 of 75).

- One (1) subject (b) (6) had their Period 2, 8 and 12 hrs plasma and whole blood samples containing “white debris”, and the firm considered it as a possible manufacturer’s error. The firm also stated that the samples were able to be processed per protocol specifications. According to the firm’s Documentation of Statistical Methods⁷⁹, the firm excluded these samples from PK analysis for both analytes. The reviewer agrees with the firm’s exclusion of this sample.

In the SAS .xpt file submitted by the firm, the reviewer noticed that the concentration of this sample is still listed, and this point does not appear to affect Cmax for both FP and SA. Therefore, the reviewer will exclude these samples from the firm’s SAS .xpt file during recalculation.

- According to the firm’s Documentation of Statistical Methods⁸⁰, 3 subjects had a slight pause on one of the inhalations and 1 subject made a light snoring noise while dosing (please see details in table below). The firm did not report these in protocol deviations. They checked the concentration vs. time plots of these subjects, and considered that the PK profile of these subjects did not appear to be affected. Subsequently, the firm included all these 4 subjects in the PK analysis.

Subject	Randomization Code	Period	Treatment	Study Drug Administration Deviation
(b) (6)	(b) (6)	1	T	Subject had a pause during the second inhalation. Observation from clinic staff stated that subject still performed a rapid and deep inhalation.
(b) (6)	(b) (6)	1	R	Subject had a slight pause on the third inhalation. Observation from clinic staff stated that subject still performed a rapid and deep inhalation.
(b) (6)	(b) (6)	1	R	Subject had a slight pause on the first inhalation. Observation from clinic staff stated that subject still performed a rapid and deep inhalation.
(b) (6)	(b) (6)	2	T	Subject made a light snoring noise while dosing 1st inhalation. Nose clips were used during the 2nd and 3rd inhalations. Observation from clinic staff stated that subject still performed a rapid and deep inhalation.

Based on internal discussion with ORS, it is acceptable to include these subjects in the statistical analysis.

- Other protocol deviations mentioned above do not affect study outcome.

⁷⁹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.1.2. mgr001-1007... \Statistical Methods Interim Analysis Plan, p. 40 of 75).

⁸⁰ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.1.2. mgr001-1007... \Statistical Methods Interim Analysis Plan, p. 41-44 of 75).

5.1.2.3 Bioanalytical Results

Table 27. Sample Analysis Calibration and Quality Control – Within the Fasting Bioequivalence Study

Bioequivalence Study MGR001-1007										
ANALYTE FP										
Parameter	Standard Curve Samples									
Concentration (pg/mL)	1.000	2.000	3.000	10.00	30.00	100.0	300.0	400.0	500.0	600.0
Inter day Precision (% CV)	2.83	5.19	3.68	2.84	1.82	1.83	1.56	1.99	1.57	1.56
Inter day Accuracy (% Actual)	98.69	100.80	101.63	103.20	102.17	100.50	99.07	98.82	97.40	97.67
Linearity	0.9948 - 0.9997									
Linearity Range (pg/mL)	1.000 - 600.0									
Sensitivity/LOQ (pg/mL)	1.000									

Bioequivalence Study MGR001-1007						
ANALYTE FP						
Parameter	Quality Control Samples					
Concentration (pg/mL)	3.000	15.00	90.00	240.0	450.0	450.0 Dilution=2
Inter day Precision (% CV)	6.34	3.72	3.45	3.85	3.63	1.89
Inter day Accuracy (% Actual)	93.20	96.67	97.26	96.79	97.02	98.58

Bioequivalence Study MGR001-1007										
ANALYTE SA										
Parameter	Standard Curve Samples									
Concentration (pg/mL)	1.000	2.000	3.000	10.00	30.00	100.0	300.0	400.0	500.0	600.0
Inter day Precision (% CV)	2.36	4.07	2.77	2.26	2.16	1.84	1.54	1.33	1.60	1.91
Inter day Accuracy (% Actual)	99.24	101.25	99.83	101.30	101.60	100.70	99.93	99.70	98.16	98.20
Linearity	0.9970 - 0.9998									
Linearity Range (pg/mL)	1.000 - 600.0									
Sensitivity/LOQ (pg/mL)	1.000									

Bioequivalence Study MGR001-1007						
ANALYTE SA						
Parameter	Quality Control Samples					
Concentration (pg/mL)	3.000	15.00	90.00	240.0	450.0	450.0 Dilution=2
Inter day Precision (% CV)	4.99	3.13	2.79	3.04	3.12	2.31
Inter day Accuracy (% Actual)	91.27	94.80	96.23	96.38	96.69	99.22

Number of Acceptable Runs	FP: 76 SA: 73
Number of Rejected Runs (Run ID, volume/page location)	FP: no rejected runs SA: 3 rejected runs (Runs 23, 47 and 58) (1/29/2015 submission, Module 5.3.1.4. mgr001-1007... \MGR001-1007 Bioanalytical Report Appendix 1... p. 7-11 of 1948)
If sample and QC diluted during study, specify all	2-fold

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dilution factors	
Was 100% of raw numerical data submitted?	Yes

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes (maximum sample concentration: 533.8 pg/mL for FP, and 972.5 pg/mL for SA)
Do you agree with the firm's accepted and rejected runs?	To be determined (please see comments in Section 4.6.2)

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes (Run IDs 2-16, which includes subjects with randomization numbers (b) (6))
Were chromatograms serially or randomly selected?	Serially
Were the chromatograms submitted by the firm acceptable?	Yes

Table 28. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
MGWBIO-SOP-BIO-GEN-0018 (v. 3.0)	9/3/2013	Evaluation and Acceptance Criteria for Analytical Runs
MPI-SOP-BIO-GEN-0019 (v. 2.0)	2/4/2015	Chromatography Acceptance Criteria
MGWBIO-SOP-BIO-GEN-0020 (v. 3.0)	9/3/2013	Re-assay or Re-injection of Clinical Samples

Table 29. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes (please see comments in Section 4.6.1)
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Were Calibration and Quality Control for the Sample Analysis acceptable?

Yes (maximum sample concentration: 533.8 pg/mL for FP, and 972.5 pg/mL for SA)

Summary/Conclusions, Study Assays:

General Comments

- Prior to biosample analysis, the firm conducted 1 run of QC pool qualification (Run 1). According to raw data provided, no biosamples were pre-analyzed in this run.

Comments for FP

- ISR was performed on 9.69% of the samples (240 out of 2478 total samples). It is noted that the firm conducted ISR on 30 subjects (samples from 66 subjects were analyzed). Based on the data provided, it appeared that for each subject period of these 30 subjects, the firm selected 4 samples with at least one sample near C_{max} and at least one sample in the elimination phase. Similar to fasting study MGR001-1006, this ISR sample selection is in accordance with SOP MGWBIO-SOP-BIO-GEN-0023 (version 3.0) “*Within-Study Incurred Sample Re-Analysis (ISR)*”, which states that “[t]he ISR samples must be from a minimum of 8 subjects (this requirement does not apply for re-dosed BE studies with fewer than 8 subjects... Typically, ISR samples will be chosen such that at least 1 time point is selected from the high concentration portion of the profiles (i.e., near the C_{max}) and at least 1 time point from the elimination phase.” However, the number of subject to be selected for ISR in this SOP is not in line with the Bioanalytical Method Validation Guidance, which states that ISR sample selection should be include all study subjects. Therefore, the firm will be advised about the ISR recommendation in the bioanalytical guidance for their future study.

There were 3 samples excluded by the firm from ISR calculation. Two of these samples were excluded due to “documented sample processing error – broken vial”, and one sample was excluded due to abnormal IS response. The reviewer verified from the numerical raw data that all these 3 samples were correctly identified. Based on raw data provided, these 3 samples were not repeated, and the firm excluded these samples for ISR calculation. However, regardless of whether these samples are included for ISR calculation or not, the results of ISR meets the acceptance criteria (including these 3 samples 98.75% of ISR samples were within $\pm 20\%$ of the mean of original and repeat values compared to 100% excluding these samples).

Comments for SA

- For reassay of samples above ULOQ, the firm used 2-fold dilution, which was covered by the dilution integrity study in pre-study method validation. Similar to the fasting study MGR001-1006, the firm did not include DQCs (the firm diluted HQC instead as per SOP) in the analytical run. However, since the method validation guidance did not require DQC in the reassay run, the reviewer will not pursue this issue further.
- ISR was performed on 9.69% of the samples (240 out of 2478 total samples). It is noted that the firm conducted ISR on 30 subjects (samples from 66 subjects were analyzed). Please refer to the FP section above for the firm’s ISR sample selection. As mentioned above, the firm will be advised about the ISR recommendation in the bioanalytical guidance for their future study.

There were 7 samples excluded by the firm from ISR calculation. Two of these samples were excluded due to “documented sample processing error – broken vial”, and five samples were excluded due to abnormal IS response. The reviewer verified from the numerical raw data that all these 7 samples were correctly identified. Based on raw data provided, these 7 samples were not repeated, and the firm excluded these samples for ISR calculation. However, regardless of whether these samples are included for ISR calculation or not, the results of ISR meets the acceptance criteria (including these 7 samples 97.08% of ISR samples were within $\pm 20\%$ of the mean of original and repeat values compared to 100% excluding these samples).

The bioanalytical results are **acceptable**.

5.1.2.4 Pharmacokinetic Results

Table 30. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in [Table 34](#) and [Figure 2](#)

Fasting Bioequivalence Study, Study No. MGR001-1007									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
FP									
AUC _{0-t} (hr *pg/ml)	2922.064	34.81	1040.35	5678.24	2991.859	28.95	822.87	5333.85	0.98
AUC _∞ (hr *pg/ml)	3117.305	34.63	1119.39	5816.19	3138.442	29.07	842.56	5636.64	0.99
C _{max} (pg/ml)	262.288	26.48	150.40	437.60	291.798	25.68	124.10	533.80	0.90
T _{max} * (hr)	1.500	.	0.33	4.00	1.500	.	0.33	4.00	1.00
Kel (hr ⁻¹)	0.054	15.88	0.03	0.08	0.061	15.68	0.04	0.08	0.89
T _{1/2} (hr)	13.069	16.93	8.80	21.87	11.655	16.77	8.59	18.12	1.12
SA									
AUC _{0-t} (hr *pg/ml)	743.660	41.82	206.64	1877.61	721.105	34.02	284.93	1544.38	1.03
AUC _∞ (hr *pg/ml)	774.982	41.11	231.21	1947.50	754.419	33.26	306.60	1605.00	1.03
C _{max} (pg/ml)	376.470	48.07	108.30	972.50	416.183	35.75	81.59	796.50	0.90
T _{max} * (hr)	0.083	.	0.03	1.00	0.083	.	0.03	1.50	1.00
Kel (hr ⁻¹)	0.062	17.85	0.04	0.09	0.059	18.01	0.03	0.08	1.04
T _{1/2} (hr)	11.609	18.09	7.84	18.37	12.131	23.15	8.35	26.76	0.96

Table 31. Geometric Means and 90% Confidence Intervals - Firm Calculated

MGR001 500/50 MCG AND ADVAIR® DISKUS®						
Dose: 3 Inhalations; Total Dose 1500/150 mcg FP/salmeterol						
Number of Subjects Completed = 65						
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study Number MGR001-1007): FP						
Parameter	Test	N	Reference	N	Ratio*	90% C.I.**
AUC _{last} (pg h/mL)	2689	65	2783	65	96.63	92.75% - 100.67%
AUC _{inf} (pg.h/mL)	2853	65	2906	65	98.18	94.21% - 102.32%
C _{max} (pg/mL)	252.8	65	281.8	65	89.70	86.27% - 93.27%
Fasting Bioequivalence Study (Study Number MGR001-1007): SA						
Parameter	Test	N	Reference	N	Ratio*	90% C.I.**
AUC _{last} (pg h/mL)	672.3	65	670.8	65	100.21	96.18% - 104.42%
AUC _{inf} (pg.h/mL)	701.7	65	704.0	65	99.67	95.76% - 103.74%
C _{max} (pg/mL)	334.9	65	388.6	65	86.18	81.41% - 91.22%

*Ratio (A/B) = e^[LSMEAN of LNA - LSMEAN of LNB] **Used Natural Log Transformed Parameter

Table 32. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder 3 x 500/50 mcg Fasting Bioequivalence Study, Study No. MGR001-1007, N=65 (Male=24 and Female=41) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
FP							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
Group 1, 2 and 3 (trt*troupe = 2)							
LAUCT (hr *pg/ml)	2763.22	64*	2865.93	64*	0.96	92.43	100.58
LAUCI (hr *pg/ml)	2947.30	64*	3004.17	64*	0.98	94.09	102.30
LCMAX (pg/ml)	253.89	64*	283.06	64*	0.90	86.15	93.38
SA							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
Group 1, 2 and 3 (trt*troupe = 2)							
LAUCT (hr *pg/ml)	686.10	61^	684.20	61^	1.00	96.13	104.61
LAUCI (hr *pg/ml)	716.94	61^	717.53	61^	1.00	95.95	104.05
LCMAX (pg/ml)	335.10	61^	387.72	61^	0.86	81.57	91.58

* Subject (b) (6) was excluded by the reviewer due to missing samples that potentially affect Cmax.

^ Subject #s (b) (6) were excluded by the reviewer due to missing samples that potentially affect Cmax.

Table 33. Additional Study Information, Fasting Study No. MGR001-1007

FP

DB SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALKE	
Reason(s) for Selecting Above SAS Program Macro	Please provide comment below the table	
Root mean square error, AUC0-t	0.1423	
Root mean square error, AUC∞	0.1410	
Root mean square error, Cmax	0.1357	
	Test	Reference
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC∞	64	64
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC∞	Mostly agree*	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	2 (Subject (b) (6) Period 1 and Subject (b) (6) Period 2, not excluded. Please see comment below)	2 (Subject (b) (6) Period 2 and Subject (b) (6) Period 2, not excluded. Please see comment below)
first measurable drug concentration as Cmax	0	0
Cmax at the first time point	0	0

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Were the subjects dosed as more than one group?	Yes

* Mostly agree, except for 1 subject (subject (b) (6)) that don't agree. The firm excluded this subject from Kel and AUC_i determination, whereas the reviewer thinks that these parameters could be determined for this subject.

SA

DB SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALKE	
Reason(s) for Selecting Above SAS Program Macro	Please provide comment below the table	
Root mean square error, AUC_{0-t}	0.1391	
Root mean square error, AUC_∞	0.1334	
Root mean square error, C_{max}	0.1905	
	Test	Reference
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC_∞	61	61
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC_∞	Agree	Mostly agree*
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C_{max}	2	5
C_{max} at the first time point	2	5
Were the subjects dosed as more than one group?	Yes	

* Mostly agree, except for 1 subject (subject (b) (6)) that don't agree. The firm excluded this subject from Kel and AUC_i determination, whereas the reviewer thinks that these parameters could be determined for this subject.

Group Analysis Consideration (FP)

If more than one group were dosed, did you use the statistical model with group effect included?	Yes
Was the group*treatment interaction term statistically significant at alpha=0.1 (i.e., p< 0.1)?	No
If yes, specify which PK parameter(s)	N/A
If yes (group*treatment term is significant), was each group analyzed separately?	N/A
If each group was analyzed, did any individual group meet BE criteria?	N/A
If none of individual group meets the BE criteria, did you have other justifications for accepting the data? If yes, please provide justifications. Additional justification comments may be provided under the Comments section below.	N/A

Group Analysis Consideration (SA)

If more than one group were dosed, did you use the statistical model with group effect included?	Yes
Was the group*treatment interaction term statistically significant at alpha=0.1 (i.e., p< 0.1)?	No
If yes, specify which PK parameter(s)	N/A
If yes (group*treatment term is significant), was each group analyzed separately?	N/A

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If each group was analyzed, did any individual group meet BE criteria?	N/A
If none of individual group meets the BE criteria, did you have other justifications for accepting the data? If yes, please provide justifications. Additional justification comments may be provided under the Comments section below.	N/A

Ratio of AUC _{0-t} /AUC _∞				
FP				
Treatment	n	Mean	Minimum	Maximum
Test	64	0.94	0.89	0.99
Reference	64	0.95	0.90	0.98
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.				N/A
SA				
Treatment	n	Mean	Minimum	Maximum
Test	61	0.96	0.88	0.99
Reference	61	0.95	0.80	0.98
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.				N/A

Was the fasting bioequivalence study acceptable?

Yes

Comments on SAS Program selected, Subject variability, any Tmax differences (if applicable), Pharmacokinetic and Statistical Analysis:

- For FP, 4 subjects (please see table below) have measurable drug concentration at 0 hr. Repeat analysis confirmed that their pre-dose concentration are all <5% C_{max} of the corresponding period. The firm did not exclude these subjects from statistical analysis, and the reviewer agrees with the firm's inclusion of these subjects (please see additional comment for Subject ^{(b) (6)}, Period 1 below).

Subject	Period	Time (hr)	Treatment	Original Concentration (pg/mL)	Repeated Concentration (pg/mL)	Final Reported Concentration* (pg/mL)	<5% of C _{max} of the Corresponding Period?
(b) (6)	2	0	R	1.435	1.499	1.467	Yes (C _{max} =241.1 pg/mL)
	2	0	R	1.307	1.180	1.244	Yes (C _{max} =508.7 pg/mL)
	1	0	T	1.552	1.518	1.535	Yes (C _{max} =207 pg/mL)
	2	0	T	1.015	1.092	1.054	Yes (C _{max} =313.8 pg/mL)

* According to the firm's SOP, if all re-assay replicates are $\geq$ LLOQ, and "if the CV of all the results (including the original) is $\leq$ 25%, then the mean of all determinations will be reported."

As highlighted in table above, it is noted that Subject ^{(b) (6)} had measurable drug concentration at 0 hr in *Period 1*, which may raise concern on subject screening procedure. However, since 1) only 1 subject had measurable drug concentration at 0 hr in Period 1, 2) the measurable drug concentration (1.535 pg/mL) is slightly above LLOQ (1 pg/mL) and is remarkably smaller than C_{max} of the corresponding period (207 pg/mL), and 3) excluding this subject from statistical analysis does not change study outcome (please see table below), the reviewer will not pursue this issue further.

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
LAUCT (hr *pg/ml)	2773.84	2865.94	0.97	92.93	100.81
LAUCI (hr *pg/ml)	2942.67	2990.00	0.98	94.49	102.51
LCMAX (pg/ml)	253.88	281.55	0.90	86.81	93.66

- The reviewer specified linear range used to calculate Kel; therefore, SAS code CALKE was used for statistical analysis.
- The subjects were dosed in 3 groups; therefore, analysis of variance was performed with the group effect incorporated in the model.

For both FP and SA, there was no statistically significant difference ($p > 0.1$) in terms of treatment*group for LnAUC_t ($p = 0.1423$ for FP; $p = 0.1391$ for SA), LnAUC_i ($p = 0.1410$ for FP; $p = 0.1334$ for SA), LnC_{max} ($p = 0.1357$ for FP; $p = 0.1905$ for SA). All of the subjects in this study were recruited from the same geographic region and were dosed at the same clinical facility within 3 days. Accordingly, the reviewer combined three groups for statistical analysis as per current DB practice⁸¹.

- There are differences between the firm and the reviewer calculated geometric means and 90% confidence intervals for AUC_{0-t}, AUC_∞ and C_{max} (Tables 31 and 32). It should be noted that the reviewer excluded subjects that had missing samples that could potentially affect C_{max}. In addition, according to the study report, the firm's AUC was calculated by the linear-log trapezoidal method, whereas the Agency's SAS code used the linear trapezoidal method. Also, as mentioned in the study design section, the firm calculated AUC_{last} (the firm defined AUC_{last} as AUC "from time 0 to the time of the last measurable concentration"⁸²) instead of AUC_{0-t}. Moreover, the reviewer also suspects that the firm did not incorporate group effect in their calculation, as leaving out the group effect (let trtgroup=" " instead of "2" in SAS code) using the firm's dataset leads

⁸¹ V:\FIRMSNZ ^{(b) (4)}\CONTROLS\98-392A.doc

⁸² GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.1.2. mgr001-1006...\Study Report Body\MGR001-1006 Study Report, p. 12 of 98).

to exactly the same results as firm-calculated Cmax (verified by the reviewer, results not shown).

- The study still meet BE acceptance criteria after statistical analysis was completed under the assumption that all groups are homogenous and can therefore be treated as a single group for statistical analysis purposes⁸³ (please see table below).

trtgroup=null

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
FP					
LAUCT (hr *pg/ml)	2750.79	2848.81	0.97	92.60	100.69
LAUCI (hr *pg/ml)	2933.98	2986.65	0.98	94.23	102.41
LCMAX (pg/ml)	253.50	282.27	0.90	86.32	93.44
SA					
LAUCT (hr *pg/ml)	688.38	683.91	1.01	96.46	105.03
LAUCI (hr *pg/ml)	719.28	717.05	1.00	96.28	104.51
LCMAX (pg/ml)	334.77	386.06	0.87	81.87	91.84

- For SA, 2 subjects for the test product and 5 for the RLD had the first measurable drug concentration as Cmax as well as first post-dose time point as Cmax. However, it should be noted that the firm included sufficient PK sampling times to cover the expected Tmax range per the RLD label (i.e. about 5 min for SA and 1 to 2 hrs for FP). The firm included early time points (2, 5, 10, 15 min) in addition to 4 more time points within the first hour. This time point selection is in line with *Guidance for Industry – Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted under an ANDA* (draft guidance recommended Dec 2013).

It is noted that subjects treated with reference product had more first time point Cmax as compared to subjects treated with test product (2 subjects for the reference product vs. 5 subjects for the test product). However, it should be noted that Tmax values for the test and reference product are considered comparable (please see details in the bullet point below).

- Tmax (hr) for the test and reference product are provided below:

	Test	Reference	Ratio
Median	1.50	1.50	1.00
Min	0.33	0.33	1.00
Max	4.00	4.00	1.00

⁸³ Because the study met the following criteria, it is not necessary to include group*treatment interaction in the statistical model: 1) the clinical study took place at once site; 2) all subjects were recruited from the same enrollment pool; 3) all of the subjects had similar demographics and; 4) all enrolled subjects were randomly assigned to treatment groups at study outset. Therefore, statistical analysis was performed with the group*treatment interaction set to null.

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SA

	Test	Reference	Ratio
Median	0.083	0.083	1.00
Min	0.03	0.03	1.00
Max	1.00	1.50	0.67

The T_{max} values for the test and reference products are considered comparable for FP and SA.

- The 90% confidence intervals for FP and SA are within the acceptable limits of 80%-125%.

The *in vivo* fasting BE study MGR001-1007 is **incomplete** due to deficiencies related to method validation.

Table 34. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

FP

Time (hr)	Test (n=64)		Reference (n=64)		Ratio (T/R)
	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	
0.00	0.04	571.09	0.04	563.13	0.95
0.03	20.35	74.19	26.65	86.59	0.76
0.08	52.49	62.95	60.01	72.73	0.87
0.17	82.13	43.31	93.61	54.58	0.88
0.25	119.31	35.99	131.74	43.16	0.91
0.33	150.69	32.91	166.37	41.41	0.91
0.50	184.12	31.82	208.67	36.40	0.88
0.75	221.63	29.87	242.59	33.60	0.91
1.00	235.25	28.75	261.18	30.37	0.90
1.50	240.27	28.42	276.59	27.34	0.87
2.00	242.93	29.37	270.32	26.47	0.90
3.00	229.33	31.39	253.95	27.88	0.90
4.00	212.58	33.39	230.13	28.58	0.92
6.00	144.78	37.84	154.55	32.61	0.94
8.00	114.83	39.75	119.90	31.54	0.96
12.00	70.97	41.35	73.15	34.83	0.97
24.00	31.71	37.34	28.02	36.53	1.13
36.00	15.65	41.86	13.65	41.49	1.15
48.00	10.12	45.28	8.39	42.14	1.21

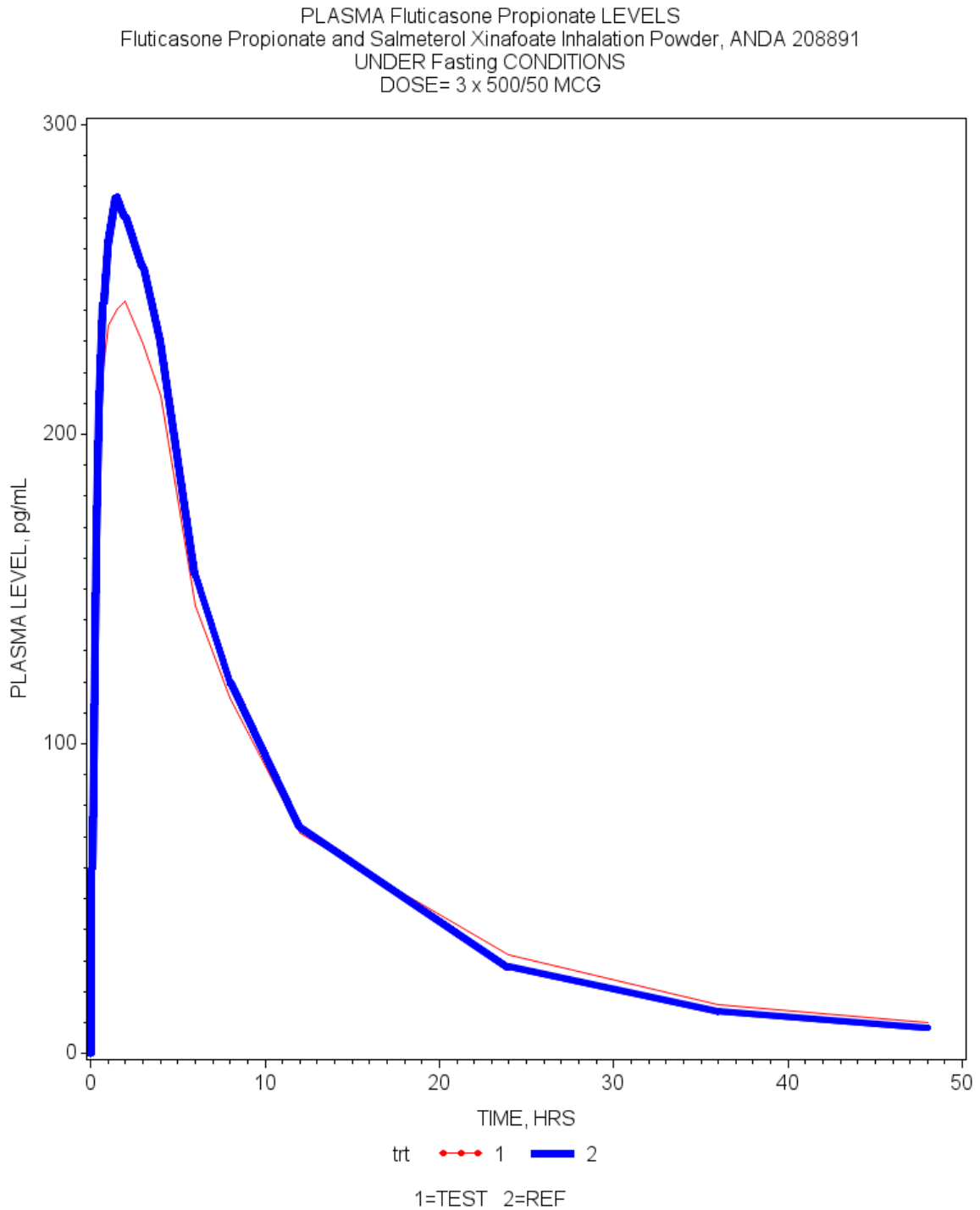
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SA

Time (hr)	Test (n=61)		Reference (n=61)		Ratio (T/R)
	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	
0.00	0.00	.	0.00	.	.
0.03	208.56	57.18	316.71	48.00	0.66
0.08	374.09	48.64	410.14	35.55	0.91
0.17	260.71	43.52	265.95	33.67	0.98
0.25	188.23	39.95	189.95	31.90	0.99
0.33	155.55	38.38	152.00	30.27	1.02
0.50	126.37	36.85	119.78	30.12	1.05
0.75	111.18	38.19	100.25	31.48	1.11
1.00	101.92	40.55	88.94	33.93	1.15
1.50	87.89	41.65	80.34	38.52	1.09
2.00	76.63	42.71	68.30	40.42	1.12
3.00	52.35	44.61	49.91	47.30	1.05
4.00	40.68	48.81	38.28	43.04	1.06
6.00	28.67	53.58	27.54	44.86	1.04
8.00	21.10	52.31	20.39	40.09	1.03
12.00	13.13	48.38	12.96	38.80	1.01
24.00	6.62	45.73	6.57	35.93	1.01
36.00	2.75	42.94	2.78	37.71	0.99
48.00	1.45	71.82	1.62	57.05	0.90

Figure 2. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

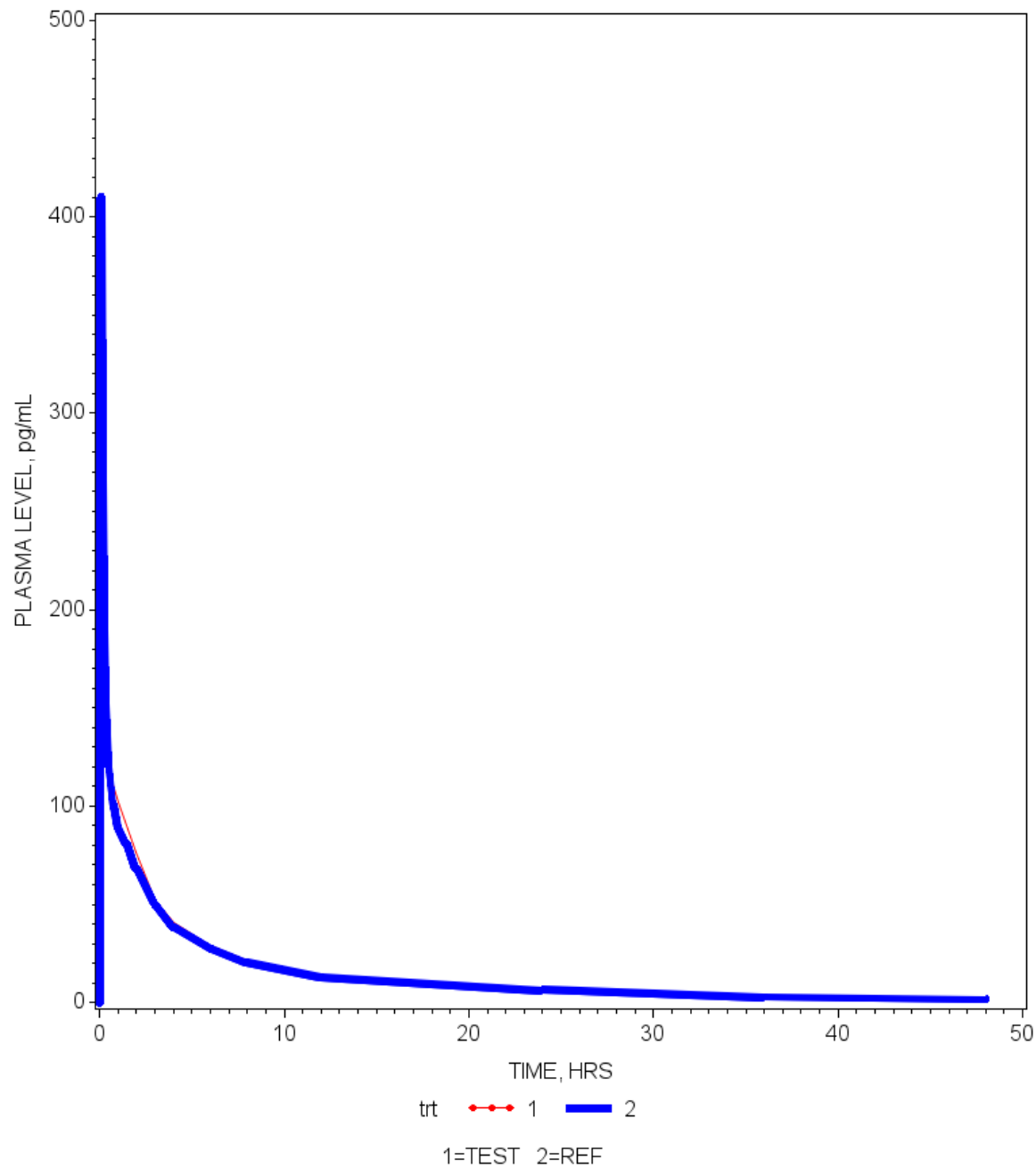
EP



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SA

PLASMA Salmeterol LEVELS
Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder, ANDA 208891
UNDER Fasting CONDITIONS
DOSE= 3 x 500/50 MCG



5.1.3 Single-dose Fasting Bioequivalence Study MGR001-1005

Reviewer's note: Please note that the firm's results for this individual study did not meet the acceptance criteria of 80%-125%. However, the firm conducted a pooled analysis of this study and Study MGR001-1014 (also a failed study as detailed in Section 5.1.4) and stated that the pooled analysis meet the BE criteria.

In addition, as detailed in reviewer's comments in Section 4.6, the firm assigned each subject with a subject number and also a randomization number. Please refer to the same comments about how a subject will be referred to (using their subject number and/or randomization number) in this section.

5.1.3.1 Study Design

Table 35 Study Information

Study Number	MGR001-1005
Study Title	AN OPEN-LABEL RANDOMIZED, TWO-WAY CROSSOVER STUDY TO DETERMINE PHARMACOKINETIC BIOEQUIVALENCE OF SINGLE DOSES OF FLUTICASONE PROPIONATE / SALMETEROL FIXED DOSE COMBINATION (250/50 µg) POWDER ADMINISTERED BY ORAL INHALATION FROM MGR001 AND ADVAIR® DISKUS® IN HEALTHY ADULT SUBJECTS.
Clinical Site (Name & Address)	Worldwide Clinical Trials Early Phase Services, LLC 2455 NE Loop 410, Suite 150 San Antonio, Texas 78217
Principal Investigator	Dr Cynthia A. Zamora, MD
Dosing Dates	Group 1 Period 1: 09-Sept-2015 Group 1 Period 2: 16-Sept-2015 Group 2 Period 1: 10-Sept-2015 Group 2 Period 2: 17-Sept-2015 Group 3 Period 1: 11-Sept-2015 Group 3 Period 2: 18-Sept-2015
Analytical Site (Name & Address)	Mylan Pharmaceuticals Inc. Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505
Analysis Dates	21-September-2015 – 05-October-2015
Analytical Director	Patrick T. Vallano, Ph.D.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	FP: Longest storage duration and condition: 26 days at -70°C SA: Longest storage duration and condition: 26 days at -70°C LTSS coverage:

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	FP: 132 days at -70°C SA: 132 days at -70°C

Table 36. Product information

Product	Test	Reference
Treatment ID	Treatment A	Treatment B
Product Name	MGR001	Advair® Diskus®
Manufacturer	Mylan Global Respiratory Group	GlaxoSmithKline
Batch/Lot No.	631-009	5ZP9304
Manufacture Date	02 April 2015	N/A
Expiration Date	N/A	September 2016
Strength	250/50 mcg	250/50 mcg
Dosage Form	Inhalation Powder	Inhalation Powder
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)	Emitted Dose (% of Target): FP 101 % SA 105 %	Emitted Dose (% of Target): FP 104 % ⁸⁴ SA 106 %
Content Uniformity (expressed as mean, %CV or per USP)	FP: Mean 100 % of Label Claim CV 4.3 % SA 100 % of Label Claim CV 3.8 %	N/A
Dose Administered	FP 750 mcg SA 150 mcg	FP 750 mcg SA 150 mcg
Route of Administration	Inhalation	Inhalation

Table 37. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: Not specified by the firm Dosed: 66 Completed: 66 Samples Analyzed: 66 Data Analyzed: 66
No. of Sequences	2
No. of Periods	2
No. of Treatments	2

⁸⁴ According to the firm's 1/12/2017 ECD response [GS Review: ANDA 208891, Response to ECD/Bioequivalence, 1/12/2017 (Module 1.2\Cover Letter..., p. 17 of 21)], the original value (103%) provided in the firm's summary table in Module 2.7.1 was transcribed incorrectly from the COA. The correct value should be 104%.

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No. of Groups	3 (Group 1: Randomization #301-322; Group 2: 323-344; Group 3: 345-366)
Washout Period	7 days
Randomization Scheme (Sequence of T and R)	Please see table below
Blood Sampling Times	Pre-dose (0 hour) and 2, 5, 10, 15, 20, 30, 45, 60, and 90 minutes, and 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post dose.
Blood Volume Collected/Sample	10 mL
Anticoagulant Used	K2EDTA
Blood Sample Processing & Storage (include storage temperature)	Blood samples for the analysis of FP and SA in plasma and subsequent pharmacokinetic analysis were collected into 1 x 10 mL K2-EDTA tubes. The collection tube was inverted 5-10 times immediately after collection, then immediately placed in an ice bath. Blood samples were centrifuged at approximately 1990 g ± 400 g (e.g. 3000 rpm) for 10 minutes under refrigeration (4 °C ± 3 °C). The time interval between sample collection and the start of centrifugation did not exceed 45 minutes. As soon as centrifugation stopped, samples were returned to an ice bath and the plasma transferred into two equal aliquots to labeled polypropylene tubes. Plasma samples were capped and frozen in an upright position in -70 °C ±15 °C freezer or colder, pending shipment to Mylan Pharmaceuticals Inc. Transfer of the samples into the freezer took place no later than 90 minutes after the start of centrifugation. Plasma samples were maintained in an ice bath until transfer to the storage freezer occurred.
IRB Approval (Y/N, Date)	Y Protocol: 5/27/2015 Protocol amendment 1: 6/10/2015
Informed Consent (Y/N, Date)	Y Informed consent: 5/27/2015 Revised informed consent: 6/10/2015
Length of Fasting	8 hours prior and 4 hours post the start of pharmacokinetic sample collections on Day 1
Length of Confinement	From the day prior to dosing until 24 hours post-dose
Safety Monitoring	The Investigator evaluated safety using the following assessments: medical history, prior/concomitant medication, history of drug, alcohol, and tobacco use, physical examination, 12-lead ECG, supine blood pressure and pulse rate, spirometry (forced expiratory volume in 1 second [FEV1] and forced vital capacity [FVC]), safety laboratory/urinalysis, pregnancy tests (all females of childbearing potential), continuous cardiac monitoring; with any clinically significant changes recorded as adverse events (AEs). Subjects were routinely queried (at least every 8 hours during confinement and at each visit) for the presence or absence of AEs using open ended questions. Spontaneously reported AEs were also recorded. Subjects were monitored for any AEs from the signing of the informed consent forms to 30 days after the last dose of study medication.

Was the study design used for the fasting BE study acceptable?	NO (please see comments below)

Randomization Scheme

Randomization Number	Subject Number	Treatment received at Period 1	Treatment received at Period 2	Randomization Number	Subject Number	Treatment received at Period 1	Treatment received at Period 2
	(b) (6)	B	A		(b) (6)	B	A
		A	B			B	A
		B	A			B	A
		A	B			B	A
		B	A			A	B
		A	B			A	B
		A	B			B	A
		A	B			A	B
		A	B			A	B
		B	A			A	B
		B	A			A	B
		B	A			A	B
		B	A			B	A
		A	B			B	A
		A	B			B	A
		A	B			B	A
		A	B			B	A
		A	B			B	A
		A	B			B	A
		B	A			A	B

Randomization Number	Subject Number (b) (6)	Treatment received at Period 1	Treatment received at Period 2
		A	B
		B	A
		B	A
		A	B
		B	A
		A	B
		B	A
		A	B
		A	B
		B	A
		B	A
		A	B
		A	B
		A	B
		B	A
		B	A
		A	B
		A	B
		B	A
		B	A
		A	B
		B	A

A = test
B = RLD

Comments on Study Design:

1. The firm stated that the test device used for the fasting study MGR001-1005 is the proposed commercial device (b) (4)⁸⁵.
2. The firm conducted the PK fasting study based on 3 inhalations of the drug product, which was found acceptable in CC 12-0731.⁸⁶ The firm also submitted IND 118769 for this 250/50 µg strength, and was found reasonably safe to proceed from the clinical standpoint by DCR.⁶²
3. As noted for the fasting study MGR001-1006, the agency did not oppose the firm’s use of AUClast in place of AUCt.⁶¹ In addition, the AUCt calculated by the reviewer does not change the study outcome as compared to the firm’s outcome for this study (please see details in Section 5.1.3.4).

⁸⁵ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.7\Container Closure System, p. 66 of 229).

⁸⁶ [\cdsnas\OGDS6\CONTROLS\2012-docs\12-0731.pdf](#) p. 26 of 34.

4. Same as the fasting study MGR001-1006, on Day -1 and Day 1 prior to dosing for both study periods, subjects were trained to achieve an appropriate inhalation maneuver for both the CRC749 and Diskus[®] inhalers.
5. Same as the fasting study MGR001-1006, the research unit staff prepared (as per the instruction for use) each inhaler ready for dosing, before handing to the subject for dosing. The inhaler was re-prepared by the research unit staff following each inhalation and prior to the next inhalation. There was an interval of approximately 30 seconds between each inhalation.
6. Same as in the fasting study MGR001-1006, subjects were instructed to rinse their mouths (without swallowing) with approximately 50 mL water after completing the three inhalations, and to spit the water out after rinsing. This is in line with the product-specific guidance, which states that “[s]ubjects should adhere to labeling as follows: ‘Rinse your mouth with water after breathing in the medicine. Spit the water out, do not swallow.’”

The firm’s study design is **acceptable**.

5.1.3.2 Clinical Results

Table 38A. Demographics Profile of Subjects Completing the Bioequivalence Study

Study Number MGR001-1005			
		Treatment Groups	
		Test Product (MGR001 250/50mcg) N = 66	Reference Product (Advair® Diskus®) N = 66
Age (years)	Mean ± SD Range	33.5 ± 9.6 19 - 53	33.5 ± 9.6 19 - 53
Age Groups	<18 18-40 41-64 65-75 >75	0 (0.0%) 47 (71.2%) 19 (28.8%) 0 (0.0%) 0 (0.0%)	0 (0.0%) 47 (71.2%) 19 (28.8%) 0 (0.0%) 0 (0.0%)
Sex	Male Female	35 (53.0%) 31 (47.0%)	35 (53.0%) 31 (47.0%)
Race	White Black or African American American Indian or Alaska Native White, Black or African American	41 (62.1%) 22 (33.3%) 2 (3.0%) 1 (1.5%)	41 (62.1%) 22 (33.3%) 2 (3.0%) 1 (1.5%)
BMI	Mean ± SD Range	26.2 ± 2.7 (19.5 – 30.5)	26.2 ± 2.7 (19.5 – 30.5)
Other Factors		N/A	N/A

Table 38B. Demographics Profile of Individual Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. MGR001-1005				
Subject No	Age	Gender	Race	BMI
(b) (6)	38	F	WHITE	28.9
	22	M	BLACK OR AFRICAN AMERICAN	22.3
	49	F	WHITE	28.2
	31	M	WHITE	21.3
	26	M	WHITE	25.3
	24	F	BLACK OR AFRICAN AMERICAN	24.6
	37	M	WHITE	25
	28	M	WHITE	29.1
	27	M	WHITE	26.3
	19	F	WHITE	30.5
	50	M	WHITE	28.6
	41	M	MULTIPLE	27.5
	52	M	WHITE	22.8
	43	M	BLACK OR AFRICAN AMERICAN	27.6
	29	F	WHITE	28.7
	25	M	WHITE	25.6
	33	F	WHITE	28.5
	53	M	BLACK OR AFRICAN AMERICAN	26.7
	39	M	WHITE	30.5
	19	M	WHITE	24.5
	34	F	BLACK OR AFRICAN AMERICAN	27.8
	35	F	WHITE	29

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(b) (6)	43	F	BLACK OR AFRICAN AMERICAN	19.5
	41	F	BLACK OR AFRICAN AMERICAN	22.1
	27	M	BLACK OR AFRICAN AMERICAN	24
	43	M	AMERICAN INDIAN OR ALASKA NATIVE	27.1
	24	F	WHITE	28
	23	F	WHITE	25.3
	42	M	BLACK OR AFRICAN AMERICAN	29.5
	26	F	WHITE	22.5
	26	M	BLACK OR AFRICAN AMERICAN	26.9
	38	F	WHITE	29.5
	45	M	WHITE	29.4
	24	M	WHITE	23.1
	47	M	WHITE	27.1
	29	F	WHITE	24.6
	28	F	BLACK OR AFRICAN AMERICAN	28.2
	23	M	BLACK OR AFRICAN AMERICAN	23.2
	45	M	BLACK OR AFRICAN AMERICAN	26.9
	23	M	WHITE	27.9
	45	F	WHITE	24.8
	30	F	WHITE	26.9
	19	M	WHITE	24.1
	42	F	BLACK OR AFRICAN AMERICAN	29
	27	F	WHITE	25.8
	28	F	BLACK OR AFRICAN AMERICAN	27.8
	38	F	WHITE	22.9
	43	M	BLACK OR AFRICAN AMERICAN	28
	26	M	BLACK OR AFRICAN AMERICAN	20.5
	35	M	AMERICAN INDIAN OR ALASKA NATIVE	22.5
	53	F	WHITE	24.3
	34	F	WHITE	28.6
	48	M	WHITE	26.3
	22	M	WHITE	24.7
	34	F	WHITE	26.6
	33	M	BLACK OR AFRICAN AMERICAN	25.5
	38	M	WHITE	30
	31	F	BLACK OR AFRICAN AMERICAN	30
	26	M	BLACK OR AFRICAN AMERICAN	24.3
	27	M	BLACK OR AFRICAN AMERICAN	24.4
	23	F	WHITE	23.6
	20	F	WHITE	25
30	M	WHITE	21.8	
31	F	WHITE	28.3	
51	F	WHITE	29	
26	F	BLACK OR AFRICAN AMERICAN	29.6	

Table 39. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
N/A			

Table 40. Study Adverse Events, Fasting Bioequivalence Study

System Organ Class/ Preferred Term	Reported Incidence by Treatment Groups	
	Study Number MGR001-1005*	
	Test Product (MGR001 250/50 mcg) No. of Subjects n (%)	Reference Product (Advair® Diskus® 250/50 mcg) No. of Subjects n (%)
Gastrointestinal disorders		
Abdominal pain	0 (0.0%)	1 (1.5%)
Toothache	1 (1.5%)	0 (0.0%)
General disorders and administration site conditions		
Asthenia	0 (0.0%)	1 (1.5%)
Fatigue	1 (1.5%)	0 (0.0%)
Vessel Puncture site pain	2 (3.0%)	1 (1.5%)
Infections and Infestations		
Carbuncle	0 (0.0%)	1 (1.5%)
Nervous system disorders		
Dizziness	1 (1.5%)	3 (4.5%)
Headache	0 (0.0%)	3 (4.5%)
Myoclonus	0 (0.0%)	1 (1.5%)
Paraesthesia	0 (0.0%)	1 (1.5%)
Presyncope	2 (3.0%)	1 (1.5%)
Tremor	0 (0.0%)	2 (3.0%)
Psychiatric Disorders		
Anxiety	1 (1.5%)	1 (1.5%)
Respiratory, thoracic and mediastinal disorders		
Dysphonia	0 (0.0%)	1 (1.5%)
Epistaxis	1 (1.5%)	0 (0.0%)
Skin and subcutaneous tissue disorders		
Acne	0 (0.0%)	1 (1.5%)
Hyperhidrosis	0 (0.0%)	1 (1.5%)
Pruritus generalised	0 (0.0%)	1 (1.5%)
Vascular disorders		
Flushing	0 (0.0%)	1 (1.5%)
Total	9 (13.6%)	21 (31.8%)
*3 Inhalations (total dose 750/150 mcg FP/salmeterol)		
Adverse Events were coded using MedDRA version 18.0		

Do any of the adverse events require statistical analysis consideration (e.g. emesis)?

No

If yes, does the time exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products) according to the *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products*?

N/A

Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Please comment.

Yes. The frequency of anxiety was same for both test and reference treatments, while the frequency of dizziness was lower in test treatment. Two and one incidence each of vessel puncture site pain and presyncope was observed for test and reference product, respectively. One incidence each of toothache, fatigue and epistaxis was observed for test products. One incidence each of abdominal pain, asthenia, carbuncle, myoclonus, paraesthesia, dysphonia, acne, hyperhidrosis, pruritus generalized, and flushing; two incidences of tremor; and three incidences of headache were observed for RLD treatment.

The firm considered 1 incidence of anxiety (test treatment group), 2 incidences of dizziness (1 from test and 1 from RLD treatment group), dysphonia, 2 incidences of headache (2 RLD treatment group) and tremor to be possibly related to treatment; anxiety to be probable related to treatment; asthenia, 1 incidence of dizziness (RLD treatment group), epistaxis, fatigue, flushing, myoclonus, 2 incidences of presyncope (1 from test and 1 from RLD treatment group), and pruritus generalized to be unlikely related to treatment; and all the rest AE incidences to be unrelated/not related to treatment.

All adverse events were mild in severity, except carbuncle and 1 incidence of presyncope (RLD treatment), which were considered moderate in severity. All symptoms of adverse events reported during the study were resolved, except for myoclonus and skin abrasion with unknown outcome.

There is no strong evidence suggesting that the test drug caused substantially more serious adverse events compared to the reference drug.

Are there any safety concerns based on the adverse event profile?

No. The firm reported that there were no deaths or other serious adverse events reported during the study.

Table 41. Protocol Deviations, Fasting Bioequivalence Study

Study No. MGR001-1005		
Type	Subject #s (Test)	Subject #s (Ref.)
Blood collection time deviations		(b) (6)
Missed assessments (blood samples not collected per protocol)		
Unable to verify period 2 day 3 spirometry was performed after a 5-10 minute rest		
End of study spirometry testing and end of study physical exam performed late due to subject late		
4h confirmation time of centrifugation settings was not documented prior to start of centrifugation		
8h confirmation time of		

centrifugation settings was not documented prior to start of centrifugation	 (b) (6)
36h confirmation time of centrifugation settings was not documented prior to start of centrifugation	

Did dropouts/adverse events/protocol deviations affect the study outcome?

Please see comments below.

Comments on Dropouts/Adverse Events/Protocol Deviations:

- A total of 66 subjects were randomized into the study. All of them completed both periods of the study were included in both PK parameter set (i.e. had PK parameters derived) and the PK analysis set (i.e. contributed to the statistical analysis of BE).
- The use of the following concomitant medications as birth controls was reported: norgestimate/ethinyl estradiol, etonogestrel, medroxyprogesterone acetate, and levonorgestrel/ethinyl estradiol. The firm evaluated the specificity of the analytical methods in the presence of ethinyl estradiol, etonogestrel, and levonorgestrel. Based on representative chromatograms provided, none of the tested compounds significantly interfere with the analysis of FP, SA and the internal standards.



The reviewer verified from Micromedex that there are no known drug-drug interactions between the aforementioned concomitant medications and the study drug FP/SX.⁸⁷

- There were sampling time deviations. Since the firm used the actual sampling time points for the PK analysis, these deviations do not affect the study outcome.
- Six (6) subjects had missing blood sample collections [due to restick(s), technical difficulty , adverse event , or subject not showing up , and

⁸⁷ Micromedex:
<http://www.micromedexsolutions.com/micromedex2/librarian/PFDefaultActionId/evidencexpert.ShowDrugInteractionsResults> Last accessed: 9/30/2016.

the firm included all these 6 subjects into the statistical analysis⁸⁹. However, the reviewer noticed that some of these missing sample blood collection time points are close to Tmax, thus may potentially affect Cmax of these subjects (please see table below. For representative plots of plasma concentration vs time of subjects with missing samples that potentially affect Cmax, please see reviewer’s comments in Section 5.1.1.2.).

Subject	Randomization Code	Period	Treatment	Time of missing blood collection	Potentially affect Cmax for FP?	Potentially affect Cmax for SA?
(b) (6)		1	R	30 min (0.5 hr)	Might (2 time points prior to current Cmax at 1 hr)	No
		2	R	2 min (0.03 hr)	No	Yes
		2	T	36 hrs	No	No
		1	T	10 min (0.16 hr)	Yes	Yes
				15 min (0.25 hr)	Yes	Yes
				20 min (0.33 hr)	Yes	Yes
				30 min (0.5 hr)	Yes	Yes
				45 min (0.75 hr)	Yes	Yes
		2	R	15 min (0.25 hr)	No	No
		2	R	10 min (0.16 hr)	No	Yes
				45 min (0.75 hr)	Yes	No
		2	R	2 min (0.03 hr)	No	Yes
				10 min (0.16 hr)	No	Yes

The reviewer will **exclude** subjects with missing time point(s) that are **very likely to impact Cmax**. For subjects with missing time point(s) that **might affect Cmax**, the reviewer will also exclude them as a conservative approach. However, it should be noted that excluding the latter subjects does not change study outcome

⁸⁸ The firm did not specify which adverse event was the cause of this missing sample collection. However, based on the reviewer’s comparison of timing between adverse events and blood collection time in CRF, it is possible that presyncope (vasovagal episode) was the adverse event that caused this missing sample collection.

⁸⁹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.1.2. mgr001-1005...\Statistical Methods Interim Analysis Plan, p. 41-47 of 59).

(please see tables below). Please note that the subject numbers mentioned in the rest of this bullet point are their corresponding randomization codes as listed in the table above.

FP

Excluding Subject ^{(b) (6)} (with missing samples that might affect C_{max}) [and excluding Subjects ^{(b) (6)} (with missing sample that is very likely to impact C_{max})]

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
Group 1					
LAUCT (hr *pg/ml)	1882.22	1493.75	1.26	115.59	137.36
LAUCI (hr *pg/ml)	1966.71	1548.13	1.27	116.35	138.70
LCMAX (pg/ml)	242.69	201.03	1.21	110.85	131.47
Group 2					
LAUCT (hr *pg/ml)	1901.97	1460.99	1.30	123.85	136.85
LAUCI (hr *pg/ml)	2007.77	1516.38	1.32	126.20	138.91
LCMAX (pg/ml)	253.74	209.02	1.21	114.12	129.13
Group 3					
LAUCT (hr *pg/ml)	1963.37	1628.03	1.21	113.35	128.31
LAUCI (hr *pg/ml)	2079.71	1689.37	1.23	115.82	130.85
LCMAX (pg/ml)	263.01	242.29	1.09	103.34	114.02

Note: The subjects were dosed in 3 groups, and the treatment*group interaction was statistically significant (p<0.1) for LC_{max}, and was not statistically significant (p>0.1) for LAUC_{0-t} and LAUC_{0-∞}.

Not excluding Subject ^{(b) (6)} (with missing samples that might affect C_{max}) [but excluding Subjects ^{(b) (6)} (with missing sample that is very likely to impact C_{max})]

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
Group 1					
LAUCT (hr *pg/ml)	1882.22	1493.75	1.26	115.59	137.36
LAUCI (hr *pg/ml)	1966.71	1548.13	1.27	116.35	138.70
LCMAX (pg/ml)	242.69	201.03	1.21	110.85	131.47
Group 2					
LAUCT (hr *pg/ml)	1891.94	1445.69	1.31	124.71	137.33
LAUCI (hr *pg/ml)	1997.31	1499.84	1.33	127.11	139.52
LCMAX (pg/ml)	251.41	207.23	1.21	114.41	128.64
Group 3					
LAUCT (hr *pg/ml)	1963.37	1628.03	1.21	113.35	128.31
LAUCI (hr *pg/ml)	2079.71	1689.37	1.23	115.82	130.85
LCMAX (pg/ml)	263.01	242.29	1.09	103.34	114.02

Note: The subjects were dosed in 3 groups, and the treatment*group interaction was statistically significant (p<0.1) for LC_{max}, and was not statistically significant (p>0.1) for LAUC_{0-t} and LAUC_{0-∞}.

- Other protocol deviations mentioned above do not affect study outcome.

5.1.3.3 Bioanalytical Results

Table 42. Sample Analysis Calibration and Quality Control – Within the Fasting Bioequivalence Study

Bioequivalence Study MGR001-1005										
ANALYTE FP										
Parameter	Standard Curve Samples									
Concentration (pg/mL)	1.000	2.000	3.000	10.00	30.00	100.0	300.0	400.0	500.0	600.0
Inter day Precision (% CV)	2.55	4.93	3.75	2.54	1.70	1.48	1.39	1.86	1.40	1.78
Inter day Accuracy (% Actual)	101.30	98.50	98.87	98.64	100.20	100.10	100.93	100.85	100.06	100.58
Linearity	0.9952 - 0.9999									
Linearity Range (pg/mL)	1.000 - 600.0									
Sensitivity/LOQ (pg/mL)	1.000									

Bioequivalence Study MGR001-1005							
ANALYTE FP							
Parameter	Quality Control Samples						
Concentration (pg/mL)	3.000	15.00	90.00	240.0	450.0	450.0 Dilution=2	450.0 Dilution=4
Inter day Precision (% CV)	5.52	3.42	2.73	2.96	2.96	3.71	2.53
Inter day Accuracy (% Actual)	96.80	98.20	99.81	99.58	100.40	97.51	96.84

Bioequivalence Study MGR001-1005										
ANALYTE SA										
Parameter	Standard Curve Samples									
Concentration (pg/mL)	1.000	2.000	3.000	10.00	30.00	100.0	300.0	400.0	500.0	600.0
Inter day Precision (% CV)	2.03	3.84	3.13	2.02	2.50	1.88	1.67	2.07	1.55	2.03
Inter day Accuracy (% Actual)	102.10	97.90	97.63	97.41	98.73	101.00	101.67	101.63	100.64	101.33
Linearity	0.9962 - 0.9999									
Linearity Range (pg/mL)	1.000 - 600.0									
Sensitivity/LOQ (pg/mL)	1.000									

Bioequivalence Study MGR001-1005							
ANALYTE SA							
Parameter	Quality Control Samples						
Concentration (pg/mL)	3.000	15.00	90.00	240.0	450.0	450.0 Dilution=2	450.0 Dilution=4
Inter day Precision (% CV)	4.27	3.05	2.15	2.43	2.80	3.16	1.13
Inter day Accuracy (% Actual)	97.63	98.07	101.44	101.38	101.89	100.13	102.76

Number of Acceptable Runs	FP: 70 SA: 71
Number of Rejected Runs (Run ID, volume/page location)	FP: 2 rejected runs (Runs 26 and 49) and 2 “N/A” runs (Runs 23 and 34. Please see reviewer’s comments in Section 4.6.3 for more details.) SA: 1 rejected run (Run 49) and 2 “N/A” runs (Runs 23 and 34. Please see reviewer’s comments in Section 4.6.1 for more details.) (1/29/2015 submission, Module 5.3.1.4. mgr001-1005...MGR001-1005 Bioanalytical Report Appendix 1... p. 5-11 of 165)

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If sample and QC diluted during study, specify all dilution factors	2-fold and 4-fold
Was 100% of raw numerical data submitted?	Yes

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes (maximum sample concentration: 460.6 pg/mL for FP, and 1033 pg/mL for SA)
Do you agree with the firm's accepted and rejected runs?	Yes (please see comments in Section 4.6.3)

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes (Run IDs 5-18, which includes subjects with randomization numbers (b) (6))
Were chromatograms serially or randomly selected?	Serially
Were the chromatograms submitted by the firm acceptable?	Yes

Table 43. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
MPI-SOP-BIO-GEN-0018 (v. 4.0)	8/27/2015	Evaluation and Acceptance Criteria for Analytical Runs
MPI-SOP-BIO-GEN-0019 (v. 2.0)	2/4/2015	Chromatography Acceptance Criteria
MPI-SOP-BIO-GEN-0020 (v. 4.0)	8/27/2015	Re-assay or Re-injection of Clinical Samples

Table 44. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Were Calibration and Quality Control for the Sample Analysis acceptable?

Yes (maximum sample concentration: 460.6 pg/mL for FP, and 1033 pg/mL for SA)

Summary/Conclusions, Study Assays:

General Comments

- The firm referenced 3 SOPs that dealt with bioanalytical repeats of study samples. One SOP (MPI-SOP-BIO-GEN-0019) was the same as the one used in the fasting studies MGR001-1006 and MGR001-1007. The rest 2 SOPs (MPI-SOP-BIO-GEN-0018 and MPI-SOP-BIO-GEN-0020) were the updated version of those used in the aforementioned fasting studies. These updates included typographical

correction, format update and reference updates, and did not affect the actual procedure for sample reassay.

- Prior to biosample analysis, the firm conducted 1 run of QC pool qualification (Run 1) and 3 runs of qualification experiment accuracy and precision (Runs 2-4). The firm also conducted 2 runs of qualification experiment accuracy and precision (Runs 20 and 30) in the middle of biosample analysis. According to raw data provided, no biosamples were pre-analyzed in these runs.

Comments for FP

- ISR was performed on 8.66% of the samples (216 out of 2495 total samples). It is noted that the firm conducted ISR on 27 subjects (samples from 66 subjects were analyzed). Based on the data provided, it appeared that for each subject period of these 30 subjects, the firm selected 4 samples with at least one sample near C_{max} and at least one sample in the elimination phase. As mentioned in fasting study MGR001-1007, the firm will be advised about the ISR recommendation in the bioanalytical guidance for their future study. 99.5% of the ISR were within 20% of the mean of original and ISR concentration.

Comments for SA

- For reassay of samples above ULOQ, the firm used 2- and 4-fold dilution, which was covered by the dilution integrity study in pre-study method validation. Similar to the fasting study MGR001-1006, the firm did not include DQCs (the firm diluted HQC instead as per SOP) in the analytical run. However, since the method validation guidance did not require DQC in the reassay run, the reviewer will not pursue this issue further.
- ISR was performed on 8.66% of the samples (216 out of 2495 total samples). It is noted that the firm conducted ISR on 27 subjects (samples from 66 subjects were analyzed). Please refer to the FP section above for the firm's ISR sample selection. As mentioned above, the firm will be advised about the ISR recommendation in the bioanalytical guidance for their future study. 100% of the ISR were within 20% of the mean of original and ISR concentration.

The bioanalytical results are **acceptable**.

5.1.3.4 Pharmacokinetic Results

Table 45. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in [Table 49](#) and [Figure 3](#)

Fasting Bioequivalence Study, Study No. MGR001-1005									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
FP									
AUC _{0-t} (hr *pg/ml)	1984.517	24.98	1090.92	3162.49	1600.819	26.68	544.60	2639.36	1.24
AUC _∞ (hr *pg/ml)	2090.987	25.01	1155.89	3276.02	1661.022	26.75	557.97	2727.11	1.26
C _{max} (pg/ml)	260.571	25.71	146.30	460.60	224.461	26.87	83.04	393.80	1.16
T _{max} * (hr)	1.000	.	0.33	2.00	1.000	.	0.50	3.00	1.00
Kel (hr ⁻¹)	0.056	15.37	0.04	0.08	0.063	17.36	0.04	0.10	0.89
T _{1/2} (hr)	12.727	15.00	8.46	16.99	11.391	16.36	7.25	16.31	1.12
SA									
AUC _{0-t} (hr *pg/ml)	896.844	30.30	366.02	1635.72	760.015	34.67	235.91	1479.01	1.18
AUC _∞ (hr *pg/ml)	940.935	30.39	386.01	1720.39	798.300	35.20	259.62	1564.66	1.18
C _{max} (pg/ml)	514.727	33.79	192.40	1033.00	436.458	38.14	75.92	954.50	1.18
T _{max} * (hr)	0.083	.	0.03	0.10	0.083	.	0.03	0.12	1.00
Kel (hr ⁻¹)	0.057	14.52	0.04	0.08	0.059	18.38	0.04	0.10	0.97
T _{1/2} (hr)	12.459	15.28	8.73	18.32	12.155	17.66	7.27	17.93	1.03

Table 46. Geometric Means and 90% Confidence Intervals - Firm Calculated
Individual analysis of Study MGR001-1005

MGR001 250/50 MCG AND ADVAIR® DISKUS®						
Dose: 3 Inhalations; Total Dose 750/150 mcg FP/salmeterol						
Number of Subjects Completed = 66						
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study Number MGR001-1005) : FP						
Parameter	Test	N	Reference	N	Ratio*	90% C.I.**
AUC _{last} (pg.h/mL)	1876	66	1502	66	124.89	120.12% - 129.85%
AUC _{inf} (pg h/mL)	1975	62	1562	63	126.48	121.84% - 131.30%
C _{max} (pg/mL)	250.2	66	216.0	66	115.86	111.31% - 120.59%
Fasting Bioequivalence Study (Study Number MGR001-1005): SA						
Parameter	Test	N	Reference	N	Ratio*	90% C.I.**
AUC _{last} (pg.h/mL)	838.1	66	704.1	66	119.03	114.71% - 123.52%
AUC _{inf} (pg h/mL)	879.1	66	739.8	66	118.82	114.61% - 123.19%
C _{max} (pg/mL)	483.8	66	398.1	66	121.51	114.81% - 128.61%

*Ratio (A/B) = e^[LSMEAN OF LNA - LSMEAN OF LNB] **Used Natural Log Transformed Parameter

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Pooled analysis⁹⁰ of Studies MGR001-1005 and MGR001-1014

MGR001 250/50 MCG AND ADVAIR® DISKUS®						
Dose: 3 Inhalations; Total Dose 705/150 mcg FP/salmeterol						
Number of Subjects Completed = 131						
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Studies (Study Numbers MGR001-1005 and MGR001-1014): FP						
Parameter	Test	N	Reference	N	Ratio*	90% C.I.**
AUC _{last} (pg.h/mL)	1620	131	1477	131	109.71	106.57% - 112.95%
AUC _{inf} (pg h/mL)	1720	124	1534	124	112.10	108.90% - 115.40%
C _{max} (pg/mL)	215.5	131	219.2	131	98.32	95.45% - 101.28%
Fasting Bioequivalence Studies (Study Numbers MGR001-1005 and MGR001-1014): SA						
Parameter	Test	N	Reference	N	Ratio*	90% C.I.**
AUC _{last} (pg.h/mL)	782.0	131	727.5	131	107.50	104.87% - 110.18%
AUC _{inf} (pg h/mL)	819.1	131	762.8	131	107.38	104.82% - 110.00%
C _{max} (pg/mL)	399.3	131	400.5	131	99.69	95.61% - 103.95%

*Ratio (A/B) = e^[LSMEAN of LNA - LSMEAN of LNB] **Used Natural Log Transformed Parameter

⁹⁰ Please see reviewer's comments in Section 5.1.4.1 for details.

Table 47. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder 3 x 250/50 mcg Fasting Bioequivalence Study, Study No. MGR001-1005, N=66 (Male=35 and Female=31) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
FP							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
Group 1							
LAUCT (hr *pg/ml)	1882.22	22	1493.75	22	1.26	115.59	137.36
LAUCI (hr *pg/ml)	1966.71	22	1548.13	22	1.27	116.35	138.70
LCMAX (pg/ml)	242.69	22	201.03	22	1.21	110.85	131.47
Group 2							
LAUCT (hr *pg/ml)	1901.97	21*	1460.99	21*	1.30	123.85	136.85
LAUCI (hr *pg/ml)	2007.77	21*	1516.38	21*	1.32	126.20	138.91
LCMAX (pg/ml)	253.74	21*	209.02	21*	1.21	114.12	129.13
Group 3							
LAUCT (hr *pg/ml)	1963.37	20^	1628.03	20^	1.21	113.35	128.31
LAUCI (hr *pg/ml)	2079.71	20^	1689.37	20^	1.23	115.82	130.85
LCMAX (pg/ml)	263.01	20^	242.29	20^	1.09	103.34	114.02
SA							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
Group 1, 2 and 3 (trt*troup = 2)							
LAUCT (hr *pg/ml)	851.86	62#	708.72	62#	1.20	115.51	125.07
LAUCI (hr *pg/ml)	893.17	62#	744.37	62#	1.20	115.44	124.72
LCMAX (pg/ml)	485.94	62#	401.57	62#	1.21	114.44	127.96

* Subject (b) (6) was excluded by the reviewer due to missing samples that potentially affect Cmax.
 ^ Subjects (b) (6) were excluded by the reviewer due to missing samples that potentially affect Cmax.
 # Subjects (b) (6) were excluded by the reviewer due to missing samples that potentially affect Cmax.

Table 48. Additional Study Information, Fasting Study No. MGR001-1005

FP

DB SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALKE	
Reason(s) for Selecting Above SAS Program Macro	Please provide comment below the table	
Root mean square error, AUC _{0-t}	0.1277	
Root mean square error, AUC _∞	0.1276	
Root mean square error, C _{max}	Group 1: 0.1633 Group 2: 0.1156 Group 3: 0.0879	
	Test	Reference
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC _∞	63	63
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC _∞	Mostly agree*	Mostly agree^
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C _{max}	0	0
C _{max} at the first time point	0	0
Were the subjects dosed as more than one group?	Yes	

* Mostly agree, except for 4 subjects (subjects (b) (6) that don't agree. The firm excluded these subjects from Kel and AUC_i determination, whereas the reviewer thinks that these parameters could be determined for these subjects.

^ Mostly agree, except for 3 subjects (subjects (b) (6) that don't agree with the same reason mentioned above.

SA

DB SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALKE	
Reason(s) for Selecting Above SAS Program Macro	Please provide comment below the table	
Root mean square error, AUC _{0-t}	0.1308	
Root mean square error, AUC _∞	0.1272	
Root mean square error, C _{max}	0.1836	
	Test	Reference
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC _∞	62	62
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC _∞	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C _{max}	8	17
C _{max} at the first time point	8	17

Were the subjects dosed as more than one group?	Yes

Group Analysis Consideration (FP)

If more than one group were dosed, did you use the statistical model with group effect included?	Yes
Was the group*treatment interaction term statistically significant at alpha=0.1 (i.e., p< 0.1)?	Yes for Cmax (0.0974) No for AUCt (0.4129) and AUCi (0.4453)
If yes, specify which PK parameter(s)	Cmax
If yes (group*treatment term is significant), was each group analyzed separately?	Yes for Cmax No for AUCt and AUCi
If each group was analyzed, did any individual group meet BE criteria?	Yes for Cmax
If none of individual group meets the BE criteria, did you have other justifications for accepting the data? If yes, please provide justifications. Additional justification comments may be provided under the Comments section below.	N/A (please note that AUCt and AUCi did not meet BE criteria)

Group Analysis Consideration (SA)

If more than one group were dosed, did you use the statistical model with group effect included?	Yes
Was the group*treatment interaction term statistically significant at alpha=0.1 (i.e., p< 0.1)?	No
If yes, specify which PK parameter(s)	N/A
If yes (group*treatment term is significant), was each group analyzed separately?	N/A
If each group was analyzed, did any individual group meet BE criteria?	N/A
If none of individual group meets the BE criteria, did you have other justifications for accepting the data? If yes, please provide justifications. Additional justification comments may be provided under the Comments section below.	N/A

Ratio of AUC _{0-t} /AUC _∞				
FP				
Treatment	n	Mean	Minimum	Maximum
Test	63	0.95	0.90	0.99
Reference	63	0.96	0.92	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.				N/A
SA				
Treatment	n	Mean	Minimum	Maximum
Test	62	0.95	0.88	0.98
Reference	62	0.95	0.88	0.98
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.				N/A

Was the fasting bioequivalence study acceptable?

No

Comments on SAS Program selected, Subject variability, any Tmax differences (if applicable), Pharmacokinetic and Statistical Analysis:

- The reviewer specified linear range used to calculate Kel; therefore, SAS code CALKE was used for statistical analysis.
- The subjects were dosed in 3 groups; therefore, analysis of variance was performed with the group effect incorporated in the model.

For FP, there was no significant group*treat effect for LnAUC_t (p= 0.4129), LnAUC_i (p= 0.4453). However, the group*treatment effect for LnC_{max} (p=0.0974) is significant. Therefore, the reviewer calculated 90% CIs of PK parameters for each group separately as per current DB practice.

For SA, there was no statistically significant difference (p> 0.1) in terms of treatment*group for LnAUC_t (p= 0.7188), LnAUC_i (p= 0.7631), LnC_{max} (p= 0.5733). All of the subjects in this study were recruited from the same geographic region and were dosed at the same clinical facility within 3 days. Accordingly, the reviewer combined three groups for statistical analysis as per current DB practice⁹¹.

- There are differences between the firm and the reviewer calculated geometric means and 90% confidence intervals for AUC_{0-t}, AUC_∞ and C_{max} (Tables 46 and 47). It should be noted that the reviewer excluded subjects that had missing samples that could potentially affect C_{max}. In addition, according to the study

⁹¹ V:\FIRMSNZ\^{(b) (4)}\CONTROLS\98-392A.doc

report, the firm’s AUC was calculated by the linear-log trapezoidal method, whereas the Agency’s SAS code used the linear trapezoidal method. Also, as mentioned in the study design section, the firm calculated AUClast (the firm defined AUClast as AUC “from time 0 to the time of the last measurable concentration”⁹²) instead of AUC_{0-t}. Moreover, the reviewer also suspects that the firm did not incorporate group effect in their calculation, as leaving out the group effect (let trtgroup=“ ” instead of “2” in SAS code) using the firm’s dataset leads to exactly the same results as firm-calculated Cmax (verified by the reviewer, results not shown).

- The study still fail to meet BE acceptance criteria after statistical analysis was completed under the assumption that all groups are homogenous and can therefore be treated as a single group for statistical analysis purposes⁹³ (please see table below).

trtgroup=null

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
		FP			
LAUCT (hr *pg/ml)	1922.53	1537.46	1.25	120.17	130.12
LAUCI (hr *pg/ml)	2024.81	1594.83	1.27	122.03	132.09
LCMAX (pg/ml)	252.11	216.25	1.17	112.04	121.30
		SA			
LAUCT (hr *pg/ml)	857.91	716.57	1.20	115.10	124.54
LAUCI (hr *pg/ml)	899.84	752.62	1.20	115.07	124.23
LCMAX (pg/ml)	484.68	405.07	1.20	113.00	126.70

- For SA, 8 subjects for the test product and 17 for the reference product had the first measurable drug concentration as Cmax as well as first post-dose time point as Cmax. However, it should be noted that the firm included sufficient PK sampling times to cover the expected Tmax range per the RLD label (i.e. about 5 min for SA and 1 to 2 hrs for FP). The firm included early time points (2, 5, 10, 15 min) in addition to 4 more time points within the first hour. This time point selection is in line with *Draft Guidance for Industry – Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted under an ANDA* (posted Dec 2013).

It is noted that subjects treated with reference product had remarkably more first time point Cmax as compared to subjects treated with test product (17 subjects for the reference product vs. 8 subjects for the test product). However, it should be

⁹² GS Review: ANDA 208891, New/ANANDA, 12/29/2015 (Module 5.3.1.2. mgr001-1006...\Study Report Body\MGR001-1006 Study Report, p. 12 of 98).

⁹³ Because the study met the following criteria, it is not necessary to include group*treatment interaction in the statistical model: 1) the clinical study took place at once site; 2) all subjects were recruited from the same enrollment pool; 3) all of the subjects had similar demographics and; 4) all enrolled subjects were randomly assigned to treatment groups at study outset. Therefore, statistical analysis was performed with the group*treatment interaction set to null.

noted that Tmax values for the test and reference product are considered comparable (please see details in the bullet point below).

- Tmax (hr) for the test and reference product are provided below:

FP

	Test	Reference	Ratio
Median	1.00	1.00	1.00
Min	0.33	0.50	0.66
Max	2.00	3.00	0.67

SA

	Test	Reference	Ratio
Median	0.083	0.083	1.00
Min	0.03	0.03	1.00
Max	0.10	0.12	0.83

The Tmax values for the test and reference products are considered comparable for FP and SA.

- The overall results indicate that the FP and SA results for fasting BE study MGR001-1005 do not meet the acceptance criteria of 80%-125%.
- The firm conducted additional statistical analyses to examine the effect of outliers on the determination of BE. However, excluding subjects identified as outliers still did not establish BE. The firm then repeated the study (MGR001-1014), which failed to meet BE criteria again. It is noted that the firm conducted pooled analysis on these 2 failed PK studies (MGR001-1005 and MGR001-1014) for the 250/50 mcg strength. As detailed in Section 5.1.4.4.1, it should be noted that this pooled analysis is not acceptable by the Agency.

The *in vivo* fasting BE study MGR001-1005 is **unacceptable**.

Table 49. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

FP

Time (hr)	Test (n=63)		Reference (n=63)		Ratio (T/R)
	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	
0.00	0.00	.	0.00	.	.
0.03	33.79	92.32	26.96	80.57	1.25
0.08	81.16	60.49	64.79	57.00	1.25
0.17	115.10	42.77	93.95	42.53	1.23
0.25	154.17	42.63	130.59	38.67	1.18
0.33	182.70	39.14	155.32	36.85	1.18
0.50	217.39	34.73	186.94	34.49	1.16
0.75	238.48	28.45	208.22	29.43	1.15
1.00	243.54	26.43	211.68	28.09	1.15
1.50	232.04	24.09	199.79	26.16	1.16
2.00	214.32	24.83	185.91	26.34	1.15
3.00	177.39	25.69	151.05	26.59	1.17
4.00	150.81	27.61	127.02	27.81	1.19
6.00	91.68	28.22	75.68	29.42	1.21
8.00	68.82	29.21	56.07	29.84	1.23
12.00	40.69	30.49	31.85	31.81	1.28
24.00	16.81	33.64	11.83	36.21	1.42
36.00	8.57	37.09	5.71	38.46	1.50
48.00	5.62	36.28	3.50	41.20	1.60

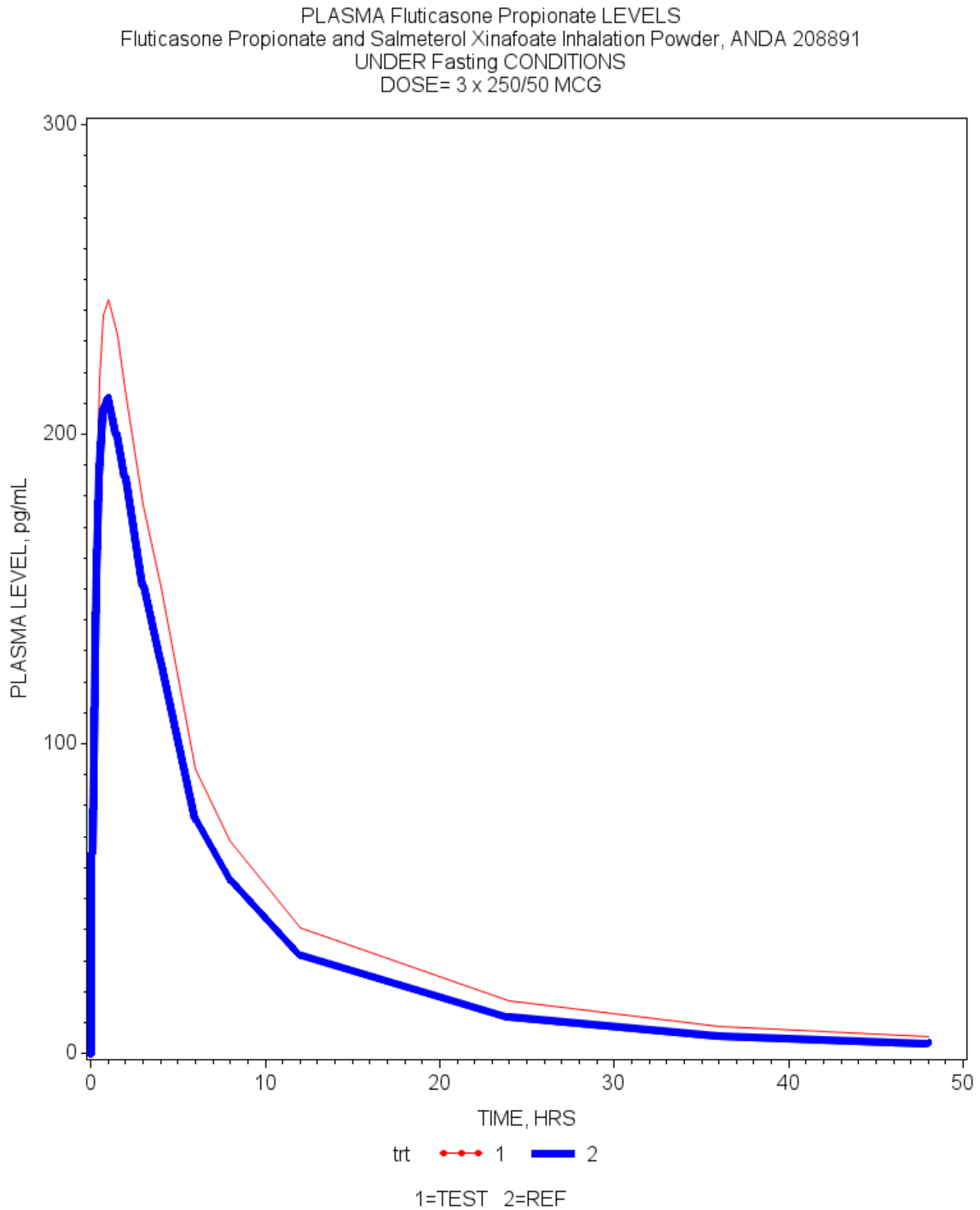
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SA

Time (hr)	Test (n=62)		Reference (n=62)		Ratio (T/R)
	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	
0.00	0.00	.	0.00	.	.
0.03	390.84	48.83	360.75	50.39	1.08
0.08	505.45	32.04	421.76	35.26	1.20
0.17	330.82	30.20	261.53	32.04	1.26
0.25	234.42	30.08	188.58	31.90	1.24
0.33	187.16	29.48	152.10	32.61	1.23
0.50	147.81	30.69	121.03	33.45	1.22
0.75	123.58	32.77	105.28	40.40	1.17
1.00	111.34	37.55	96.49	43.50	1.15
1.50	93.16	36.14	82.68	43.52	1.13
2.00	81.18	36.45	71.43	42.28	1.14
3.00	58.37	36.52	51.12	42.06	1.14
4.00	46.73	35.47	39.36	39.88	1.19
6.00	34.28	33.17	28.87	37.17	1.19
8.00	24.89	34.01	21.44	37.12	1.16
12.00	16.73	35.69	13.91	36.83	1.20
24.00	8.19	37.71	7.15	46.18	1.15
36.00	3.92	48.16	3.17	52.33	1.24
48.00	2.28	51.58	1.86	69.21	1.23

Figure 3. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

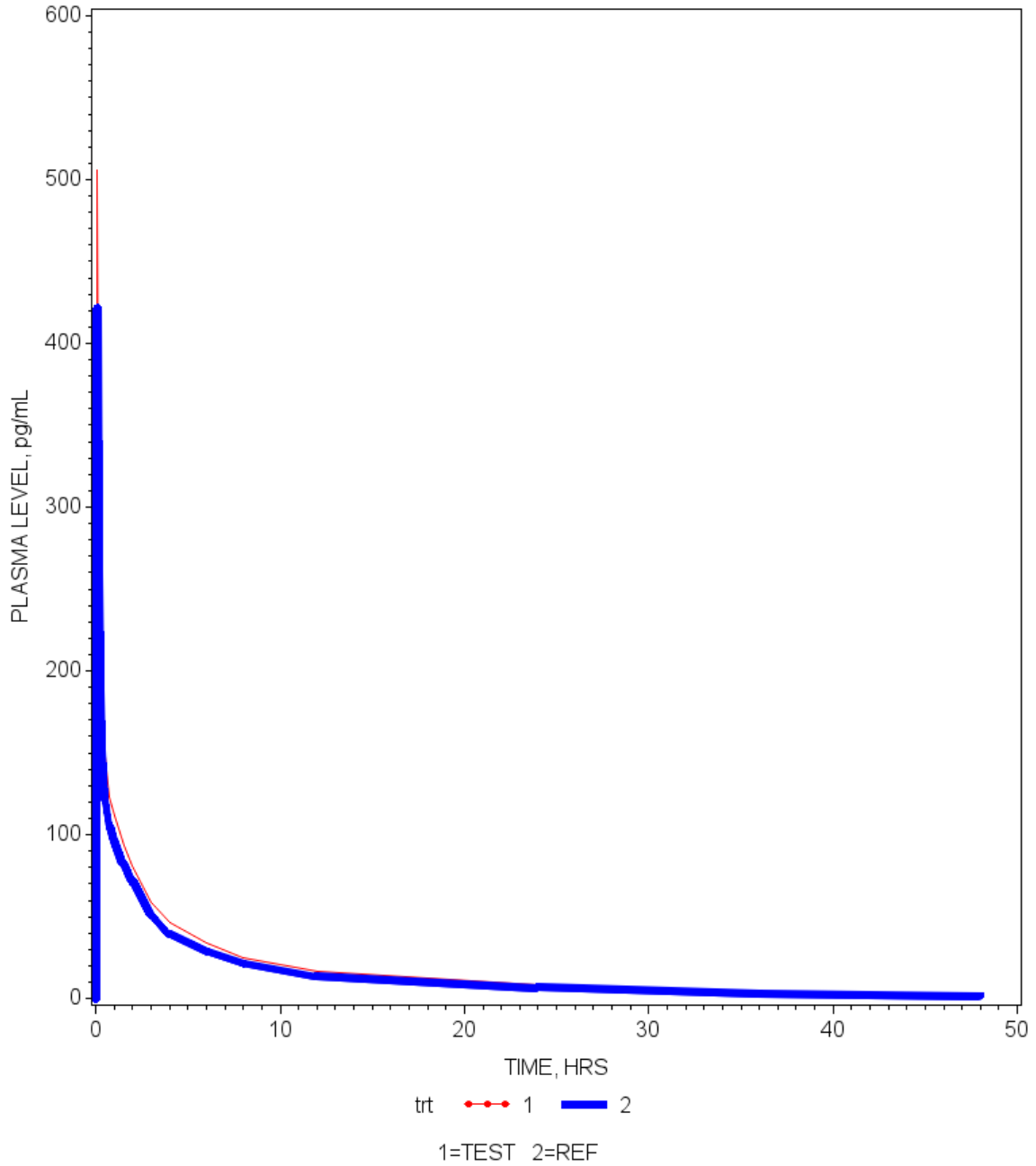
FP



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SA

PLASMA Fluticasone Propionate LEVELS
Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder, ANDA 208891
UNDER Fasting CONDITIONS
DOSE= 3 x 250/50 MCG



5.1.4 Single-dose Fasting Bioequivalence Study MGR001-1014

Reviewer's note: Please note that the firm's results for this individual study did not meet the acceptance criteria of 80%-125%. However, the firm conducted a pooled analysis of this study and Study MGR001-1005 (also a failed study as detailed in Section 5.1.3) and stated that the pooled analysis meet the BE criteria.

As detailed in reviewer's comments in Section 4.6, the firm assigned each subject with a subject number and also a randomization number. Please refer to the same comments about how a subject will be referred to (using their subject number and/or randomization number) in this section.

5.1.4.1 Study Design

Table 50 Study Information

Study Number	MGR001-1014
Study Title	AN OPEN-LABEL RANDOMIZED, TWO-WAY CROSSOVER STUDY TO DETERMINE PHARMACOKINETIC BIOEQUIVALENCE OF SINGLE DOSES OF FLUTICASONE PROPIONATE / SALMETEROL FIXED DOSE COMBINATION (250/50 mcg) POWDER ADMINISTERED BY ORAL INHALATION FROM MGR001 AND ADVAIR® DISKUS® IN HEALTHY ADULT SUBJECTS.
Clinical Site (Name & Address)	Worldwide Clinical Trials Early Phase Services, LLC 2455 NE Loop 410, Suite 150 San Antonio, Texas 78217
Principal Investigator	Dr Cynthia A. Zamora, MD
Dosing Dates	Group 1 Period 1: 11-Nov-2015 Group 1 Period 2: 18-Nov-2015 Group 2 Period 1: 12-Nov-2015 Group 2 Period 2: 19-Nov-2015 Group 3 Period 1: 13-Nov-2015 Group 3 Period 2: 20-Nov-2015
Analytical Site (Name & Address)	Mylan Pharmaceuticals Inc. Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505
Analysis Dates	21-Nov-2015 – 30-Nov-2015
Analytical Director	Patrick T. Vallano, Ph.D.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	FP: Longest storage duration and condition: 19 days at -70°C SA: Longest storage duration and condition: 19 days at -70°C LTSS coverage:

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	FP: 132 days at -70°C SA: 132 days at -70°C

Table 51. Product information

Product	Test	Reference
Treatment ID	Treatment A	Treatment B
Product Name	MGR001	Advair® Diskus®
Manufacturer	Mylan Global Respiratory Group	GlaxoSmithKline
Batch/Lot No.	631-009	5ZP9882
Manufacture Date	02 April 2015	N/A
Expiration Date	N/A	October 2016
Strength	250/50 mcg	250/50 mcg
Dosage Form	Inhalation Powder	Inhalation Powder
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)	Emitted Dose (% of Target): FP 101 % SA 105 %	Emitted Dose (% of Target): FP 103 % ⁹⁴ SA 106 %
Content Uniformity (expressed as mean, %CV or per USP)	FP: Mean 100 % of Label Claim CV 4.3 % SA 100 % of Label Claim CV 3.8 %	N/A
Dose Administered	FP 750 mcg SA 150 mcg	FP 750 mcg SA 150 mcg
Route of Administration	Inhalation	Inhalation

Table 52. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: Not specified by the firm Dosed: 66 Completed: 65 Samples Analyzed: 66 Data Analyzed: 65
No. of Sequences	2
No. of Periods	2
No. of Treatments	2

⁹⁴ According to the firm's 1/12/2017 ECD response [GS Review: ANDA 208891, Response to ECD/Bioequivalence, 1/12/2017 (Module 1.2\Cover Letter..., p. 18 of 21)], the original value (104%) provided in the firm's summary table in Module 2.7.1 was transcribed incorrectly from the COA. The correct value should be 103%.

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No. of Groups	3 (Group 1: Randomization #401-422; Group 2: 423-442 and 444 ⁹⁵ ; Group 3: 445-466)
Washout Period	7 days
Randomization Scheme (Sequence of T and R)	Please see table below
Blood Sampling Times	Pre-dose (0 hour) and 2, 5, 10, 15, 20, 30, 45, 60, and 90 minutes, and 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post dose. The collection tube was inverted 5-10 times immediately after collection, then immediately placed in an ice bath. Blood samples were centrifuged at approximately 1990 g ± 400 g (e.g. 3000 rpm) for 10 minutes under refrigeration (4 °C ± 3 °C). The time interval between sample collection and the start of centrifugation did not exceed 45 minutes. As soon as centrifugation stopped, samples were returned to an ice bath and the plasma transferred into two equal aliquots to labeled polypropylene tubes. Plasma samples were capped and frozen in an upright position in -70 °C ±15 °C freezer or colder, pending shipment to Mylan Pharmaceuticals Inc. Transfer of the samples into the freezer took place no later than 90 minutes after the start of centrifugation. Plasma samples were maintained in an ice bath until transfer to the storage freezer occurred.
Blood Volume Collected/Sample	10 mL
Anticoagulant Used	K2EDTA
Blood Sample Processing & Storage (include storage temperature)	Blood samples for the analysis of FP and S in plasma and subsequent pharmacokinetic analysis were collected into 1 x 10 mL K2-EDTA tubes.
IRB Approval (Y/N, Date)	Y, 10/14/2015
Informed Consent (Y/N, Date)	Y, 10/14/2015
Length of Fasting	8 hours prior and 4 hours post the start of pharmacokinetic sample collections on Day 1
Length of Confinement	From the day prior to dosing until 24 hours post-dose
Safety Monitoring	The Investigator evaluated safety using the following assessments: medical history, prior/concomitant medication, history of drug, alcohol, and tobacco use, physical examination, 12-lead ECG, supine blood pressure and pulse rate, spirometry (forced expiratory volume in 1 second [FEV1] and forced vital capacity [FVC]), safety laboratory/urinalysis, pregnancy tests (all females of childbearing potential), continuous cardiac monitoring; with any clinically significant changes recorded as adverse events (AEs). Subjects were routinely queried (at least every 8 hours during confinement and at each visit) for the presence or absence of AEs using open ended questions. Spontaneously reported AEs were also recorded. Subjects were monitored for any AEs from the signing of the informed consent forms to 30 days after the last dose of study medication.

Was the study design used for the fasting BE study acceptable?	NO (please see

⁹⁵ According to CRF of [REDACTED] ^{(b) (6)} this subject was checked in with Group 1 and dosed with Group 2 in Period 1.

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	comments below)

Randomization Scheme

Randomization Number	Subject Number	Treatment received at Period 1	Treatment received at Period 2
	(b) (6)	B	A
	(b) (6)	A	B
	(b) (6)	B	A
	(b) (6)	A	B
	(b) (6)	A	B
	(b) (6)	B	A
	(b) (6)	A	B
	(b) (6)	A	B
	(b) (6)	B	A
	(b) (6)	B	A
	(b) (6)	B	A
	(b) (6)	B	A
	(b) (6)	A	B
	(b) (6)	A	B
	(b) (6)	B	A
	(b) (6)	A	B
	(b) (6)	B	A
	(b) (6)	A	B

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Randomization Number	Subject Number	Treatment received at Period 1	Treatment received at Period 2
	(b) (6)	B	A
		B	A
		A	B
		B	A
		A	B
		A	B
		B	
		A	B
		A	B
		B	A
		B	A
		B	A
		A	B
		B	A
		B	A
		A	B
		A	B
		B	A
		A	B
		B	A
		B	A

Randomization Number	Subject Number	Treatment received at Period 1	Treatment received at Period 2
	(b) (6)	A	B
		A	B
		B	A
		A	B
		B	A
		B	A
		A	B
		A	B
		B	A
		A	B
		A	B
		B	A
		A	B
		B	A
		B	A
		A	B
		B	A
		A	B
		A	B

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Randomization Number	Subject Number	Treatment received at Period 1	Treatment received at Period 2
	(b) (6)	B	A
		A	B
		B	A
		B	A
		B	A
		A	B
		A	B

A = test
B = RLD

Comments on Study Design:

1. The firm stated that this fasting study MGR001-1014 was conducted as a repeat pivotal PK BE study with the 250/50 product strength (as indicated in Section 5.1.3.1, the previous fasting study MGR001-1005 did not meet BE criteria, and the upper bound of 90% CI for FP AUClast, AUCi and SA Cmax were above the 125.00% acceptance criteria).

This MGR001-1014 study used the same batch of the test product as in MGR001-1005 and a different batch of the RLD product. The firm stated that this RLD batch was selected to “represent the RLD population and the Test versus RLD FPM ratio for FP and salmeterol for batches measured during the MGR001-1014 study was approximately 10% lower than those for (the same test and different RLD) batches measured during the MGR001-1005 study, creating the expectation that lower Test versus RLD Geometric Mean Ratios (GMRs) would be observed in MGR001-1014”.

In this study, the T vs. R geometric mean was slightly lower across all endpoints compared to those observed in MGR001-1005, as expected based on the in vitro data. However, as mentioned in Section 5.1.4.4, this MGR001-1014 study still did not meet BE criteria (the lower bound of 90% CI for FP Cmax and SA Cmax were below the 80% acceptance criteria).

The firm conducted a pooled analysis of these 2 studies. The firm stated that both studies were conducted at the same site, in healthy adult volunteers fulfilling the same inclusion/exclusion criteria, within 2 months of each other and had exactly the same design. The 2 studies used the same test batch, but different batches of RLD. As detailed in Section 5.1.1.4, the Agency does not accept the firm’s pooled analysis of these 2 PK studies.

2. The firm used the same batch of the test product for this study as compared to MGR001-1005, which used the commercial device (b) (4)

3. The firm conducted the PK fasting study based on 3 inhalations of the drug product, which was found acceptable in CC 12-0731.⁹⁶ The firm also submitted IND 118769 for this 250/50 µg strength, and was found reasonably safe to proceed from the clinical standpoint by DCR.⁶²
4. As noted for the fasting study MGR001-1006, the agency did not oppose the firm's use of AUClast in place of AUCt.⁶¹ In addition, the AUCt calculated by the reviewer does not change the study outcome as compared to the firm's outcome for this study (please see details in Section 5.1.4.4).
5. Similar as the fasting study MGR001-1006, on Day -1 and Day 1 prior to dosing for both study periods, subjects were trained to achieve an appropriate inhalation maneuver. On Day -1 for Period 1, subjects trained for both the CRC749 and Diskus[®] inhalers. On Day 1 of the subsequent study period, subjects trained using only the inhaler from which they were assigned to receive study drug.
6. Same as the fasting study MGR001-1006, the research unit staff prepared (as per the instruction for use) each inhaler ready for dosing, before handing to the subject for dosing. The inhaler was re-prepared by the research unit staff following each inhalation and prior to the next inhalation. There was an interval of approximately 30 seconds between each inhalation.
7. Same as in the fasting study MGR001-1006, subjects were instructed to rinse their mouths (without swallowing) with approximately 50 mL water after completing the three inhalations, and to spit the water out after rinsing. This is in line with the product-specific guidance, which states that "[s]ubjects should adhere to labeling as follows: 'Rinse your mouth with water after breathing in the medicine. Spit the water out, do not swallow.'"

The firm's study design is **acceptable**.

⁹⁶ <\\cdsnas\OGDS6\CONTROLS\2012-docs\12-0731.pdf> p. 26 of 34.

5.1.4.2 Clinical Results

Table 53A. Demographics Profile of Subjects Completing the Bioequivalence Study

Study Number MGR001-1014			
		Treatment Groups	
		Test Product (MGR001 250/50mcg) N = 66	Reference Product (Advair® Diskus®) N = 66
Age (years)	Mean ± SD Range	36.2 ± 10.11 18.0 – 54.0	36.4 ± 10.14 18.0 – 54.0
Age Groups	<18 18-40 41-64 65-75 >75	0 (0.0%) 40 (61.5%) 25 (38.5%) 0 (0.0%) 0 (0.0%)	0 (0.0%) 40 (60.6%) 26 (39.4%) 0 (0.0%) 0 (0.0%)
Sex	Male Female	35 (52.3%) 30 (47.7%)	35 (53.0%) 31 (47.0%)
Race	White Black or African American American Indian or Alaska Native Asian White, Black or African American	44 (67.7%) 18 (27.7%) 1 (1.5%) 1 (1.5%) 1 (1.5%)	44 (66.7%) 19 (28.8%) 1 (1.5%) 1 (1.5%) 1 (1.5%)
BMI	Mean ± SD Range	26.82 ± 2.5 (20.4 – 30.4)	26.84 ± 2.5 (20.4 – 30.4)
Other Factors		N/A	N/A

Table 53B. Demographics Profile of Individual Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. MGR001-1014				
Subject No	Age	Gender	Race	BMI
(b) (6)	45	F	BLACK OR AFRICAN AMERICAN	29.6
	35	F	WHITE	22.3
	42	M	WHITE	29.4
	43	F	WHITE	26.9
	27	M	BLACK OR AFRICAN AMERICAN	28.5
	53	M	BLACK OR AFRICAN AMERICAN	29.0
	21	F	BLACK OR AFRICAN AMERICAN	27.6
	49	M	WHITE	29.4
	48	F	WHITE	28.1
	19	M	WHITE	29.6
	27	F	WHITE	29.6
	47	M	WHITE	26.5
	41	F	WHITE	23.6
	49	F	WHITE	25.1
	35	F	WHITE	23.7
	46	M	AMERICAN INDIAN OR ALASKA NATIVE	27.8
	46	F	BLACK OR AFRICAN AMERICAN	29.6
	54	F	WHITE	30.4
	36	F	WHITE	29.0
	45	F	WHITE	25.5
	43	M	BLACK OR AFRICAN AMERICAN	21.9

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(b) (6)	28	M	WHITE	29.1
	28	M	BLACK OR AFRICAN AMERICAN	28.5
	49	M	ASIAN	25.4
	35	M	WHITE	29.6
	48	M	BLACK OR AFRICAN AMERICAN	28.1
	48	M	WHITE	27.2
	23	F	WHITE	21.1
	30	M	WHITE	29.8
	20	F	WHITE	25.4
	30	M	BLACK OR AFRICAN AMERICAN	27.9
	40	F	BLACK OR AFRICAN AMERICAN	27.9
	22	F	WHITE	20.4
	30	M	WHITE	25.5
	41	M	BLACK OR AFRICAN AMERICAN	27.6
	25	F	BLACK OR AFRICAN AMERICAN	23.8
	33	M	BLACK OR AFRICAN AMERICAN	25.8
	53	M	BLACK OR AFRICAN AMERICAN	26.8
	40	F	BLACK OR AFRICAN AMERICAN	26.7
	53	F	WHITE	23.1
	48	F	WHITE	23.6
	31	F	WHITE	27.8
	44	M	BLACK OR AFRICAN AMERICAN	28.9
	41	F	WHITE	26.5
	34	M	MULTIPLE	26.1
	38	F	WHITE	29.6
	35	M	WHITE	29.0
	30	F	BLACK OR AFRICAN AMERICAN	26.3
	37	F	WHITE	26.1
	54	M	WHITE	27.5
	18	F	WHITE	27.8
	23	F	BLACK OR AFRICAN AMERICAN	26.5
	26	M	WHITE	29.9
	20	F	WHITE	21.1
	28	F	WHITE	29.4
	26	F	WHITE	23.6
	33	M	WHITE	23.6
	26	F	WHITE	28.1
	35	F	WHITE	29.5
	32	M	BLACK OR AFRICAN AMERICAN	29.5
	33	F	WHITE	27.1
	34	M	WHITE	27.0
	30	M	WHITE	27.3
	25	M	WHITE	23.1
	42	F	WHITE	27.0
	51	M	WHITE	26.4

Table 54. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
(b) (6)	Withdrawal of informed consent Subject withdrew from the study prior to Period 2 and did not receive MGR001 250/50 mcg Date: (b) (6) Treatment: Prior to receiving Test	1	No

Table 55. Study Adverse Events, Fasting Bioequivalence Study

System Organ Class/ Preferred Term	Reported Incidence by Treatment Groups	
	Study Number MGR001-1014*	
	Test Product (N=65) (MGR001 250/50 mcg) No. of Subjects n (%)	Reference Product (N=66) (Advair® Diskus® 250/50 mcg) No. of Subjects n (%)
Nervous system disorders		
Headache	4 (6.2%)	3 (4.5%)
Dizziness	0 (0.0%)	1 (1.5%)
Gastrointestinal disorders		
Constipation	1 (1.5%)	0 (0.0%)
Diarrhoea	0 (0.0%)	1 (1.5%)
Dyspepsia	0 (0.0%)	1 (1.5%)
Nausea	1 (1.5%)	0 (0.0%)
General disorders and administration site conditions		
Vessel puncture site pain	0 (0.0%)	3 (4.5%)
Infections and infestations		
Urinary tract infection	1 (1.5%)	0 (0.0%)
Viral upper respiratory tract infection	0 (0.0%)	1 (1.5%)
Blood and lymphatic system disorders		
Neutropenia	1 (1.5%)	0 (0.0%)
Cardiac disorders		
Tachycardia	0 (0.0%)	1 (1.5%)
Immune system disorders		
Seasonal allergy	0 (0.0%)	1 (1.5%)
Injury, poisoning and		

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procedural complications		
Skin abrasion	1 (1.5%)	0 (0.0%)
Psychiatric disorders		
Insomnia	1 (1.5%)	1 (1.5%)
Respiratory, thoracic and mediastinal disorders		
Nasal congestion	0 (0.0%)	1 (1.5%)
Total	10 (15.4%)	14 (21.2%)
*3 Inhalations (total dose 750/150 mcg FP/salmeterol)		
Adverse Events were coded using MedDRA version 18.0		

Do any of the adverse events require statistical analysis consideration (e.g. emesis)?

No

If yes, does the time exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products) according to the *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products*?

N/A

Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Please comment.

Yes. The frequency of insomnia was same for both test and reference treatments. Four and three incidence each of headache was observed for test and reference product, respectively. One incidence each of constipation, nausea, urinary tract infection, neutropenia, skin abrasion was observed for test treatment. One incidence each of dizziness, diarrhea, dyspepsia, viral upper respiratory tract infection, tachycardia, seasonal allergy, and nasal congestion; three incidences of vessel puncture site pain, were observed for test products.

The firm considered diarrhoea, dyspepsia, insomnia, nausea, tachycardia and 5 incidences of headache (4 from test and 1 from RLD treatment group) to be possibly related to treatment; seasonal allergy and viral upper respiratory tract infection to be unlikely related to treatment; and all the rest AE incidences to be unrelated/not related to treatment.

All adverse events were mild in severity, except neutropenia and urinary tract infection, which were considered moderate in severity. All symptoms of adverse events reported during the study were resolved, except for nasal congestion and neutropenia, which were recovering/resolving.

Are there any safety concerns based on the adverse event profile?

The firm reported two AEs (neutropenia and tachycardia) that were judged by the investigator to be of clinical significance.

Subject (b) (6) was noted to have neutropenia on the clinical laboratory evaluation performed at the end of the study. The AE was considered by the firm to be moderate in severity, unrelated/not related to the study treatment, and was recovering/resolving.

Subject (b) (6) experienced tachycardia after dosing with the RLD product in Period 1. The time of onset of the AE was approximately 4 minutes after dosing. The subject was asymptomatic. The AE was considered by the firm to be mild in severity, possibly related to the study treatment, and was resolved. It is noted that tachycardia is among the adverse reactions that are listed in the RLD labeling.³⁰

No deaths or serious AEs were reported during the study.

There is no strong evidence suggesting that the test drug caused substantially more serious adverse events compared to the reference drug.

Table 56. Protocol Deviations, Fasting Bioequivalence Study

Study No. MGR001-1014		
Type	Subject #s (Test)	Subject #s (Ref.)
Blood collection time deviations	(b) (6)	
Missed assessments (blood samples not collected per protocol)		
Inhalation technique refresher training conducted more than 1 hour prior to dosing		
Blood sample not centrifuged within 45 minutes		
Unable to verify 0.5h centrifuge and verification of settings time due to documentation error		
Restricted concomitant medication		

Did dropouts/adverse events/protocol deviations affect the study outcome?

Please see comments below.

Comments on Dropouts/Adverse Events/Protocol Deviations:

- A total of 66 subjects were randomized into the study. Sixty-five (65) subjects who completed both periods of the study were included in both of the PK parameter set (i.e. had PK parameters derived) and PK analysis set (i.e. contributed to the statistical analysis of BE). One (1) dropout subject (b) (6) that completed 1 period of the study were included in the PK parameter set but not the PK analysis set.
- For Subject (b) (6) that was dropped out of the study (due to withdrawal of informed consent), the reviewer verified from their corresponding CRF that this

subject was not dosed in Period 2. According to the CRF, this subject did not experience AE.

- Concomitant medications were given to Subject (b) (6) who experienced constipation and urinary tract infection in the test drug treatment group. This subject was included in the firm's PK analysis.

For this Subject (b) (6) laxative (1 oral tablet, ingredients unknown as per CRF) was administered orally at 35.8 hrs post-dose to treat constipation during Period 2. Since the ingredient is unknown and this concomitant medication is administered during the elimination phase of the study drug, the reviewer will exclude the samples collected after this concomitant medication (Period 2, 36 hrs and 48 hrs) from statistical analysis as a conservative approach.

This Subject (b) (6) was also orally administered with Nitrofurantoin Capsule (1 capsule twice per day, ongoing) and Phenazopyridine Tablet (1 oral tablet as needed, ongoing) starting (b) (6), which was after completion of PK blood sampling (8:13, (b) (6)), to treat urinary tract infection. Therefore, these 2 concomitant medications are not expected to affect the study outcome.

- The use of the following concomitant medications as birth controls was also reported: etonogestrel, and norgestimate/ethinyl estradiol. The firm evaluated the specificity of the analytical methods in the presence of etonogestrel and ethinyl estradiol. Based on representative chromatograms provided, none of the tested compounds significantly interfere with the analysis of FP, SA and the internal standards.



The reviewer verified from Micromedex that there are no known drug-drug interactions between the aforementioned concomitant medications and the study drug FP/SX.⁹⁷

- There were sampling time deviations. Since the firm used the actual sampling time points for the PK analysis, these deviations do not affect the study outcome.
- Five (5) subjects had missing blood sample collections (due to restick or subject not showing up), and the firm included all these 5 subjects into the statistical analysis⁹⁸. However, the reviewer noticed that some of these missing sample blood collection time points are close to Tmax, thus may potentially affect Cmax of these subjects (please see table below. For representative plots of plasma concentration vs time of subjects with missing samples that potentially affect Cmax, please see reviewer's comments in Section 5.1.1.2.).

Subject	Randomization Code	Period	Treatment	Time of missing blood collection	Potentially affect Cmax for FP?	Potentially affect Cmax for SA?
[REDACTED]	(b) (6)	1	R	2 min (0.03 hr)	No	Yes
		2	R	2 min (0.03 hr)	No	Yes
		1	T	2 min (0.03 hr)	No	Yes
				30 min (0.5 hr)	Might (might be a double peak)	No
		2	R	2 min (0.03 hr)	No	Yes
		2	T	36 hrs	No	No
		1	R	15 min (0.25 hr)	No	No
48 hrs	No			No		

The reviewer will **exclude** subjects with missing time point(s) that are **very likely to impact Cmax**. For subjects with missing time point(s) that **might affect Cmax**, the reviewer will also exclude them as a conservative approach. However, it should be noted that excluding the latter subjects does not change study outcome (please see tables below). Please note that the subject numbers mentioned in the rest of this bullet point is their corresponding randomization codes as listed in table above.

⁹⁷ Micromedex:
<http://www.micromedexsolutions.com/micromedex2/librarian/PFDefaultActionId/evidencexpert.ShowDrugInteractionsResults> Last accessed: 9/30/2016.

⁹⁸ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.1.2. mgr001-1014...\Statistical Methods Interim Analysis Plan, p. 80-85 of 95).

FP

Excluding Subjects ^{(b) (6)} (with missing samples that **might affect C_{max}**) [and excluding Subject ^{(b) (6)} (analytical run with carryover blank issue, please see details in Section 5.1.4.3) and last 2 time points for Subject ^{(b) (6)} Period 2 (administered with laxative with unknown ingredient, please see details above)]

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
Group 1, 2 and 3 (trt*troup = 2)					
LAUCT (hr *pg/ml)	1449.73	1516.15	0.96	91.43	100.00
LAUCI (hr *pg/ml)	1531.99	1581.09	0.97	92.60	101.39
LCMAX (pg/ml)	189.23	228.89	0.83	79.03	86.48

Note: The subjects were dosed in 3 groups, and the treatment*group interaction was not statistically significant (p>0.1) for LAUC_{0-t}, LAUC_{0-∞} and LC_{max}.

Not excluding Subjects ^{(b) (6)} (with missing samples that **might affect C_{max}**) [but excluding Subject ^{(b) (6)} (analytical run with carryover blank issue, please see details in Section 5.1.4.3) and last 2 time points for Subject ^{(b) (6)} Period 2 (administered with laxative with unknown ingredient, please see details above)]

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
Group 1, 2 and 3 (trt*troup = 2)					
LAUCT (hr *pg/ml)	1452.00	1519.34	0.96	91.45	99.87
LAUCI (hr *pg/ml)	1534.20	1584.57	0.97	92.60	101.24
LCMAX (pg/ml)	189.55	228.43	0.83	79.36	86.78

Note: The subjects were dosed in 3 groups, and the treatment*group interaction was not statistically significant (p>0.1) for LAUC_{0-t}, LAUC_{0-∞} and LC_{max}.

- Two blood samples (Subject ^{(b) (6)}, Period 1, 24 hrs; and Subject ^{(b) (6)}, Period 1, 24 hrs) were not centrifuged within 45 mins of sample collection. According to the firm's protocol deviation document, these 2 samples were centrifuged 59 mins and 52 mins, respectively, following sample collection. Since the firm has demonstrated whole blood stability for 80 mins in the pre-study method validation, these 2 protocol deviations are not expected to affect the study outcome.
- According to the firm's Documentation of Statistical Methods⁹⁹, 1 subject coughed after holding breath for 10 seconds and 1 subject reported a feeling of powder in their throat after the 3rd inhalation. The firm did not report these in protocol deviations. They checked the concentration vs. time plots of these subjects, and considered that the PK profile of these subjects did not appear to be affected. Subsequently, the firm included both subjects in the PK analysis.

⁹⁹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.1.2. mgr001-1014...\Statistical Methods Interim Analysis Plan, p. 78-79 of 95).

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Subject	Randomization Code	Period	Treatment	Study Drug Administration Deviation
	(b) (6)	1	R	Subject coughed after they held their breath for 10 seconds after inhalations 2 and 3.
		1	R	Subject reported a feeling of powder in their throat after the third inhalation.

Based on internal discussion with ORS, it is acceptable to include these subjects in the statistical analysis.

- Other protocol deviations mentioned above do not affect study outcome.

5.1.4.3 Bioanalytical Results

Table 57. Sample Analysis Calibration and Quality Control – Within the Fasting Bioequivalence Study

Bioequivalence Study MGR001-1014 ANALYTE FP										
Parameter	Standard Curve Samples									
Concentration (pg/mL)	1.000	2.000	3.000	10.00	30.00	100.0	300.0	400.0	500.0	600.0
Inter day Precision (% CV)	3.21	5.99	5.68	3.81	3.29	2.84	2.93	2.89	3.06	2.98
Inter day Accuracy (% Actual)	102.20	97.75	96.70	99.02	100.10	100.20	101.37	100.90	100.78	100.78
Linearity	0.9935 - 0.9996									
Linearity Range (pg/mL)	1.000 - 600.0									
Sensitivity/LOQ (pg/mL)	1.000									

Bioequivalence Study MGR001-1014 ANALYTE FP						
Parameter	Quality Control Samples					
Concentration (pg/mL)	3.000	15.00	90.00	240.0	450.0	450.0 diluted
Inter day Precision (% CV)	6.32	8.76	3.83	3.58	3.53	5.33
Inter day Accuracy (% Actual)	98.87	101.93	101.61	101.29	101.76	102.56

Bioequivalence Study MGR001-1014 ANALYTE SA										
Parameter	Standard Curve Samples									
Concentration (pg/mL)	1.000	2.000	3.000	10.00	30.00	100.0	300.0	400.0	500.0	600.0
Inter day Precision (% CV)	2.32	4.43	3.95	3.70	2.90	1.88	2.48	2.28	2.17	2.82
Inter day Accuracy (% Actual)	102.50	97.40	97.13	97.37	99.80	101.00	101.47	101.98	100.64	100.67
Linearity	0.9913 - 0.9999									
Linearity Range (pg/mL)	1.000 - 600.0									
Sensitivity/LOQ (pg/mL)	1.000									

Bioequivalence Study MGR001-1014 ANALYTE SA						
Parameter	Quality Control Samples					
Concentration (pg/mL)	3.000	15.00	90.00	240.0	450.0	450.0 diluted
Inter day Precision (% CV)	4.94	4.26	3.39	3.14	3.31	3.61
Inter day Accuracy (% Actual)	97.73	100.27	102.71	102.92	102.96	104.27

Number of Acceptable Runs	FP: 69 SA: 70
Number of Rejected Runs (Run ID, volume/page location)	FP: 2 rejected runs [Runs 48 (reassay run) and 74 (ISR)] and 1 “N/A” run (Run 50. Please see reviewer’s comments in Section 4.6.4 for more details.) SA: 1 rejected run [Run 74 (ISR)] and 1 “N/A” run (Run 50. Please see reviewer’s comments in Section 4.6.1 for more details.) (1/29/2015 submission, Module 5.3.1.4. mgr001-1014...MGR001-

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If sample and QC diluted during study, specify all dilution factors	2-fold
Was 100% of raw numerical data submitted?	Yes

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes (maximum sample concentration: 430 pg/mL for FP, and 916.7 pg/mL for SA)
Do you agree with the firm's accepted and rejected runs?	No (please see comments below and additional comments in Section 4.6.4)

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes (Run IDs 7-20, which includes subjects with randomization numbers (b) (6))
Were chromatograms serially or randomly selected?	Serially
Were the chromatograms submitted by the firm acceptable?	Yes

Table 58. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
MPI-SOP-BIO-GEN-0018 (v. 4.0)	8/27/2015	Evaluation and Acceptance Criteria for Analytical Runs
MPI-SOP-BIO-GEN-0019 (v. 2.0)	2/4/2015	Chromatography Acceptance Criteria
MPI-SOP-BIO-GEN-0020 (v. 4.0)	8/27/2015	Re-assay or Re-injection of Clinical Samples

Table 59. Additional Comments on Repeat Assays

Were all SOPs followed?	No (please see comments below)
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Were Calibration and Quality Control for the Sample Analysis acceptable?

Yes (maximum sample concentration: 430 pg/mL for FP, and 916.7 pg/mL for SA)

Summary/Conclusions, Study Assays:

General Comments

- The firm referenced 3 SOPs that dealt with bioanalytical repeats of study samples, which were the same versions of SOP as used in the fasting study MGR001-1005. As detailed in the aforementioned study, these updated versions of SOPs included

minor changes and did not affect the actual procedure for sample re-assay as compared to the SOPs referenced in MGR001-1006 and MGR001-1007.

- Prior to biosample analysis, the firm conducted 1 run of QC pool qualification (Run 1), 4 runs of qualification experiment accuracy and precision (Runs 2, and 4-6) and 1 run of simulated study run (Run 3). According to raw data provided, no biosamples were pre-analyzed in these runs.
- According to the firm's SOP MPI-SOP-BIO-GEN-0018, “[t]he carryover check blank will be considered acceptable provided that the analyte peak (or an interfering peak as defined by MPI-SOP-BIO-GEN-0019) response ratio does not exceed 20% of the response ratio at the LLOQ. In situations where this criterion is not met, runs may be acceptable with written justification approved by a Principal Scientist, Associate Director, or higher level employee.” The firm reported 2 runs with carryover check blank¹⁰⁰ issues (but the firm accepted both runs) as detailed below:
 - In Run 27, the carry-over check blank slightly exceeded 20% of the LLOQ peak response ratio for FP (23.6%). All other blanks in the run were free of detectable analyte peaks. The carryover check blank sample was re-injected to determine whether the initial result was due to autosampler carryover or to a small amount of FP present in the sample. The firm stated that the re-injection confirmed the presence of the FP peak, “indicating that there had been no significant carryover in the run”. In the 9/22/2016 amendment, the firm further supported this statement by providing chromatograms of the initial and reinjection of this check blank sample showing that the magnitude of the fluticasone peak was similar between these 2 injections. Thus, the firm considered this observation not consistent with autosampler carryover.

In addition, the firm further justified the above statement by noting that the carryover check blank sample in the runs immediately preceding and following Run 27 (Runs 26 and 36, respectively) exhibited no detectable peak at the retention time of fluticasone. In addition, the double blank sample at the start of Run 27, which immediately followed the high QC sample from Run 26, also had no detectable peak at the retention time of FP. The firm stated that these observations reinforce the conclusion made based on the re-injection of the Run 27 carryover check blank.

The reviewer considers the firm's justification acceptable.

¹⁰⁰ According to SOP MGWBIO-SOP-BIO-GEN-0018, carryover check blank should be placed after calibration standards and before QCs and subject samples in the run [firm's example run order: 00M (double blank), 0M1 (blank), calibration standards, carryover check blank, QCs, subject samples, 0M2 (blank), QCs].

- The firm stated that in Run 61 (for Subject (b) (6)), the carryover check blank and its succeeding QC were lost during the extraction procedure due to cracked sample vials. The firm then assessed carryover by evaluating the double blank sample from the run (Run 72) that was injected on the same instrument immediately following Run 61. However, since the loss of carryover check blank precluded evaluation of the run for carryover per SOP, the reviewer will exclude this subject from statistical analysis as a conservative approach.

It should be noted that excluding this Subject (b) (6) does not change study outcome (please see tables below).

FP

Excluding Subjects (b) (6) [and excluding Subject (b) (6) (with missing samples that potentially affect Cmax, please see details in Section 5.1.4.2), and last 2 time points for Subject (b) (6) Period 2 (administered with laxative with unknown ingredient, please see details in Section 5.1.4.2)]

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
Group 1, 2 and 3 (trt*troup = 2)					
LAUCT (hr *pg/ml)	1449.73	1516.15	0.96	91.43	100.00
LAUCI (hr *pg/ml)	1531.99	1581.09	0.97	92.60	101.39
LCMAX (pg/ml)	189.23	228.89	0.83	79.03	86.48

Note: The subjects were dosed in 3 groups, and the treatment*group interaction was not statistically significant (p>0.1) for LAUC_{0-t}, LAUC_{0-∞} and LCmax.

Not excluding Subject (b) (6) [but excluding (b) (6) (with missing samples that potentially affect Cmax, please see details in Section 5.1.4.2), and last 2 time points for Subject (b) (6) Period 2 (administered with laxative with unknown ingredient, please see details in Section 5.1.4.2)]

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
Group 1, 2 and 3 (trt*troup = 2)					
LAUCT (hr *pg/ml)	1440.92	1500.98	0.96	91.82	100.37
LAUCI (hr *pg/ml)	1522.91	1565.01	0.97	93.01	101.81
LCMAX (pg/ml)	187.65	226.06	0.83	79.38	86.81

Note: The subjects were dosed in 3 groups, and the treatment*group interaction was not statistically significant (p>0.1) for LAUC_{0-t}, LAUC_{0-∞} and LCmax.

SA

Excluding Subjects (b) (6) [and excluding Subjects (b) (6) (with missing samples that potentially affect Cmax, please see details in Section 5.1.4.2), and last 2 time points for Subject (b) (6) Period 2 (administered with laxative with unknown ingredient, please see details in Section 5.1.4.2)]

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
Group 1, 2 and 3 (trt*troup = 2)					
LAUCT (hr *pg/ml)	723.85	745.80	0.97	93.78	100.45

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Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
LAUCI (hr *pg/ml)	758.82	782.61	0.97	93.77	100.26
LCMAX (pg/ml)	329.05	400.73	0.82	76.87	87.71

Note: The subjects were dosed in 3 groups, and the treatment*group interaction was not statistically significant (p>0.1) for LAUC_{0-t}, LAUC_{0-∞} and LCmax.

Not excluding Subject ^{(b) (6)} [but excluding Subjects ^{(b) (6)} (with missing samples that potentially affect C_{max}, please see details in Section 5.1.4.2), and last 2 time points for Subject ^{(b) (6)} Period 2 (administered with laxative with unknown ingredient, please see details in Section 5.1.4.2)]

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
Group 1, 2 and 3 (trt*troup = 2)					
LAUCT (hr *pg/ml)	722.86	746.20	0.97	93.64	100.21
LAUCI (hr *pg/ml)	757.63	782.72	0.97	93.65	100.04
LCMAX (pg/ml)	327.74	398.75	0.82	77.04	87.69

Note: The subjects were dosed in 3 groups, and the treatment*group interaction was not statistically significant (p>0.1) for LAUC_{0-t}, LAUC_{0-∞} and LCmax.

Comments for FP

- ISR was performed on 8.71% of the samples (216 out of 2481 total samples). It is noted that the firm conducted ISR on 27 subjects (samples from 66 subjects were analyzed). Based on the data provided, it appeared that for each subject period of these 30 subjects, the firm selected 4 samples with at least one sample near C_{max} and at least one sample in the elimination phase. As mentioned in fasting study MGR001-1007, the firm will be advised about the ISR recommendation in the bioanalytical guidance for their future study. 97.7% of the ISR were within 20% of the mean of original and ISR concentration.

Comments for SA

- For reassay of samples above ULOQ, the firm used 2-fold dilution, which was covered by the dilution integrity study in pre-study method validation. Similar to the fasting study MGR001-1006, the firm did not include DQCs (the firm diluted HQC instead as per SOP) in the analytical run. However, since the method validation guidance did not require DQC in the reassay run, the reviewer will not pursue this issue further.
- ISR was performed on 8.71% of the samples (216 out of 2481 total samples). It is noted that the firm conducted ISR on 27 subjects (samples from 66 subjects were analyzed). Please refer to the FP section above for the firm's ISR sample selection. As mentioned above, the firm will be advised about the ISR recommendation in the bioanalytical guidance for their future study. 100% of the ISR were within 20% of the mean of original and ISR concentration.

The bioanalytical results are **acceptable**.

5.1.4.4 Pharmacokinetic Results

Table 60. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 64 and Figure 4

Fasting Bioequivalence Study, Study No. MGR001-1014									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	%CV	Min	Max	
FP									
AUC _{0-t} (hr *pg/ml)	1506.014	32.45	669.31	2971.88	1548.974	25.78	713.47	2382.67	0.97
AUC _∞ (hr *pg/ml)	1591.245	32.58	723.16	3182.15	1613.481	25.43	788.19	2488.33	0.99
C _{max} (pg/ml)	194.109	28.85	95.58	345.30	233.403	26.16	101.20	430.00	0.83
T _{max} * (hr)	1.000	.	0.25	2.00	0.750	.	0.17	2.00	1.33
Kel (hr ⁻¹)	0.056	18.94	0.04	0.11	0.059	17.42	0.04	0.09	0.94
T _{1/2} (hr)	12.795	16.55	6.08	19.42	12.022	17.79	7.96	17.56	1.06
SA									
AUC _{0-t} (hr *pg/ml)	778.157	38.18	415.59	2042.50	803.125	38.55	353.07	2004.13	0.97
AUC _∞ (hr *pg/ml)	815.265	38.32	441.56	2151.76	841.732	38.49	374.16	2089.75	0.97
C _{max} (pg/ml)	356.487	44.59	121.20	829.00	423.875	36.69	175.60	916.70	0.84
T _{max} * (hr)	0.080	.	0.03	1.00	0.080	.	0.03	0.10	1.00
Kel (hr ⁻¹)	0.059	17.59	0.04	0.09	0.058	15.73	0.04	0.09	1.02
T _{1/2} (hr)	12.075	16.84	7.67	18.25	12.239	16.28	7.82	17.69	0.99

* T_{max} values are presented as median, range.

Table 61. Geometric Means and 90% Confidence Intervals - Firm Calculated

Individual analysis of Study MGR001-1014

MGR001 250/50 MCG AND ADVAIR® DISKUS®						
Dose: 3 Inhalations; Total Dose 750/150 mcg FP/salmeterol						
Number of Subjects Completed = 65						
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study Number MGR001-1014): FP						
Parameter	Test	N	Reference	N	Ratio*	90% C.I.**
AUC _{last} (pg h/mL)	1400	65	1452	65	96.38	92.24% - 100.71%
AUC _{inf} (pg.h/mL)	1497	65	1507	65	99.35	94.99% - 103.92%
C _{max} (pg/mL)	185.7	65	222.5	65	83.44	79.81% - 87.23%
Fasting Bioequivalence Study (Study Number MGR001-1014): SA						
Parameter	Test	N	Reference	N	Ratio*	90% C.I.**
AUC _{last} (pg h/mL)	729.8	65	751.8	65	97.08	93.91% - 100.35%
AUC _{inf} (pg.h/mL)	763.3	65	786.6	65	97.04	93.95% - 100.23%
C _{max} (pg/mL)	329.5	65	402.9	65	81.78	76.84% - 87.05%

Pooled analysis of Studies MGR001-1005 and MGR001-1014

MGR001 250/50 MCG AND ADVAIR® DISKUS® Dose: 3 Inhalations; Total Dose 750/150 mcg FP/salmeterol Number of Subjects Completed = 131 Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Studies (Study Numbers MGR001-1005 and MGR001-1014): FP						
Parameter	Test	N	Reference	N	Ratio*	90% C.I.**
AUClast (pg.h/mL)	1620	131	1477	131	109.71	106.57% - 112.95%
AUCinf (pg h/mL)	1720	124	1534	124	112.10	108.90% - 115.40%
C _{max} (pg/mL)	215.5	131	219.2	131	98.32	95.45% - 101.28%
Fasting Bioequivalence Studies (Study Numbers MGR001-1005 and MGR001-1014): SA						
Parameter	Test	N	Reference	N	Ratio*	90% C.I.**
AUClast (pg.h/mL)	782.0	131	727.5	131	107.50	104.87% - 110.18%
AUCinf (pg h/mL)	819.1	131	762.8	131	107.38	104.82% - 110.00%
C _{max} (pg/mL)	399.3	131	400.5	131	99.69	95.61% - 103.95%

*Ratio (A/B) = e^[LSMEAN of LNA - LSMEAN of LNB] **Used Natural Log Transformed Parameter

Table 62. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder 3 x 250/50 mcg Fasting Bioequivalence Study, Study No. MGR001-1014, N=65 (Male=35 and Female=30) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
FP							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
Group 1, 2 and 3 (trt*troup = 2)							
LAUCT (hr *pg/ml)	1449.73	63*^#	1516.15	63*^#	0.96	91.43	100.00
LAUCI (hr *pg/ml)	1531.99	63*^#	1581.09	63*^#	0.97	92.60	101.39
LCMAX (pg/ml)	189.23	63*^#	228.89	63*^#	0.83	79.03	86.48
SA							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
Group 1, 2 and 3 (trt*troup = 2)							
LAUCT (hr *pg/ml)	723.85	61^#@	745.80	61^#@	0.97	93.78	100.45
LAUCI (hr *pg/ml)	758.82	61^#@	782.61	61^#@	0.97	93.77	100.26
LCMAX (pg/ml)	329.05	61^#@	400.73	61^#@	0.82	76.87	87.71

* Subject ^{(b) (6)} was excluded by the reviewer due to missing samples that potentially affect Cmax.

^ Subject ^{(b) (6)} was excluded by the reviewer due to carryover blank issue in the corresponding bioanalytical run.

The last 2 time points (36 and 48 hrs) for Subject ^{(b) (6)} Period 2 was treated as missing by the reviewer due to administration of laxative with unknown ingredient.

@ Subjects ^{(b) (6)} were excluded by the reviewer due to missing samples that potentially affect Cmax.

Table 63. Additional Study Information, Fasting Study No. MGR001-1014

FP

DB SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALKE	
Reason(s) for Selecting Above SAS Program Macro	Please provide comment below the table	
Root mean square error, AUC _{0-t}	0.1492	
Root mean square error, AUC _∞	0.1510	
Root mean square error, C _{max}	0.1499	
	Test	Reference
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC _∞	63	63
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC _∞	Mostly agree*	Mostly agree^
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C _{max}	0	0
C _{max} at the first time point	0	0
Were the subjects dosed as more than one group?	Yes	

* Mostly agree, except for 3 subjects (subjects (b) (6)) that don't agree. The firm excluded these subjects from Kel and AUC_i determination, whereas the reviewer thinks that these parameters could be determined for these subjects.

^ Mostly agree, except for 4 subjects (subjects (b) (6)) that don't agree with the same reason mentioned above.

SA

DB SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALKE	
Reason(s) for Selecting Above SAS Program Macro	Please provide comment below the table	
Root mean square error, AUC _{0-t}	0.1123	
Root mean square error, AUC _∞	0.1093	
Root mean square error, C _{max}	0.2153	
	Test	Reference
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC _∞	61	61
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC _∞	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C _{max}	4	11
C _{max} at the first time point	4	11
Were the subjects dosed as more than one group?	Yes	

Group Analysis Consideration (FP)

If more than one group were dosed, did you use the statistical model with group effect included?	Yes
Was the group*treatment interaction term statistically significant at alpha=0.1 (i.e., p< 0.1)?	No
If yes, specify which PK parameter(s)	N/A
If yes (group*treatment term is significant), was each group analyzed separately?	N/A
If each group was analyzed, did any individual group meet BE criteria?	N/A
If none of individual group meets the BE criteria, did you have other justifications for accepting the data? If yes, please provide justifications. Additional justification comments may be provided under the Comments section below.	N/A

Group Analysis Consideration (SA)

If more than one group were dosed, did you use the statistical model with group effect included?	Yes
Was the group*treatment interaction term statistically significant at alpha=0.1 (i.e., p< 0.1)?	No
If yes, specify which PK parameter(s)	N/A
If yes (group*treatment term is significant), was each group analyzed separately?	N/A
If each group was analyzed, did any individual group meet BE criteria?	N/A
If none of individual group meets the BE criteria, did you have other justifications for accepting the data? If yes, please provide justifications. Additional justification comments may be provided under the Comments section below.	N/A

Ratio of AUC _{0-t} /AUC _∞				
FP				
Treatment	n	Mean	Minimum	Maximum
Test	63	0.95	0.86	0.97
Reference	63	0.96	0.89	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.				N/A
SA				
Treatment	n	Mean	Minimum	Maximum
Test	61	0.95	0.90	0.98
Reference	61	0.95	0.89	0.98
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.				N/A

Was the fasting bioequivalence study MGR001-1014 acceptable?
No

Comments on SAS Program selected, Subject variability, any Tmax differences (if applicable), Pharmacokinetic and Statistical Analysis:

- The reviewer specified linear range used to calculate Kel; therefore, SAS code CALKE was used for statistical analysis.
- The subjects were dosed in 3 groups; therefore, analysis of variance was performed with the group effect incorporated in the model.

For FP and SA, there was no statistically significant difference ($p > 0.1$) in terms of treatment*group for LnAUCt ($p = 0.7581$ for FP, $p = 0.6552$ for SA), LnAUCi ($p = 0.7533$ for FP, $p = 0.6688$ for SA), LnCmax ($p = 0.7046$ for FP, $p = 0.7334$ for SA). All of the subjects in this study were recruited from the same geographic region and were dosed at the same clinical facility within 3 days. Accordingly, the reviewer combined three groups for statistical analysis as per current DB practice¹⁰¹.

- There are differences between the firm and the reviewer calculated geometric means and 90% confidence intervals for AUC_{0-t} , AUC_{∞} and Cmax (Tables 61 and 62). It should be noted that the reviewer excluded subjects that had missing samples that could potentially affect Cmax, subject with bioanalytical issues, and samples from subject administered with concomitant medication of unknown ingredient. In addition, according to the study report, the firm's AUC was calculated by the linear-log trapezoidal method, whereas the Agency's SAS code used the linear trapezoidal method. Also, as mentioned in the study design section, the firm calculated AUClast (the firm defined AUClast as AUC "from time 0 to the time of the last measurable concentration"¹⁰²) instead of AUC_{0-t} . Moreover, the reviewer also suspects that the firm did not incorporate group effect in their calculation, as leaving out the group effect (let trtgroup=" " instead of "2" in SAS code) using the firm's dataset leads to exactly the same results as firm-calculated Cmax (verified by the reviewer, results not shown).
- The study still fail to meet BE acceptance criteria after statistical analysis was completed under the assumption that all groups are homogenous and can therefore be treated as a single group for statistical analysis purposes¹⁰³ (please see table below).

¹⁰¹ V:\FIRMSNZ\ (b) (4) \CONTROLS\98-392A.doc

¹⁰² GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.1.2. mgr001-1006...\Study Report Body\MGR001-1006 Study Report, p. 12 of 98).

¹⁰³ Because the study met the following criteria, it is not necessary to include group*treatment interaction in the statistical model: 1) the clinical study took place at once site; 2) all subjects were recruited from the same enrollment pool; 3) all of the subjects had similar demographics and; 4) all enrolled subjects were randomly assigned to treatment groups at study outset. Therefore, statistical analysis was performed with the group*treatment interaction set to null.

trtgroup=null

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
FP					
LAUCT (hr *pg/ml)	1431.65	1495.84	0.96	91.49	100.12
LAUCI (hr *pg/ml)	1513.24	1560.04	0.97	92.70	101.50
LCMAX (pg/ml)	186.29	225.11	0.83	79.13	86.54
SA					
LAUCT (hr *pg/ml)	733.21	756.21	0.97	93.66	100.38
LAUCI (hr *pg/ml)	768.47	793.17	0.97	93.68	100.20
LCMAX (pg/ml)	323.63	396.60	0.82	76.35	87.21

- For SA, 4 subjects for the test product and 11 for the RLD had the first measurable drug concentration as Cmax as well as first post-dose time point as Cmax. However, it should be noted that the firm included sufficient PK sampling times to cover the expected Tmax range per the RLD label (i.e. about 5 min for SA and 1 to 2 hrs for FP). The firm included early time points (2, 5, 10, 15 min) in addition to 4 more time points within the first hour. This time point selection is in line with *Draft Guidance for Industry – Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (posted Dec 2013).

It is noted that subjects treated with reference product had more first time point Cmax as compared to subjects treated with test product (11 subjects for the reference product vs. 4 subjects for the test product). However, it should be noted that Tmax values for the test and reference product are considered comparable (please see details in the bullet point below).

- Tmax (hr) for the test and reference product are provided below:

FP

	Test	Reference	Ratio
Median	1.00	0.75	1.33
Min	0.25	0.17	1.47
Max	2.00	2.00	1.00

SA

	Test	Reference	Ratio
Median	0.08	0.08	1.00
Min	0.03	0.03	1.00
Max	1.00	0.10	10.00

For SA, it is noted that Tmax range for the test product has a higher maximum value than the reference product (1.00 hrs vs. 0.10 hrs). This is due to one individual (Subject ^{(b) (6)}) with a Tmax of 1.00 hr and two individuals (Subject ^{(b) (6)} ^{(b) (6)} with Tmax of 0.50 hrs. All other Tmax values for the test product are no greater than 0.10 hrs.

Therefore, the T_{max} for the test and reference product is considered comparable for FP and SA.

- The overall results indicate that the FP and SA results for fasting BE study MGR001-1014 do not meet the acceptance criteria of 80%-125%.

5.1.4.4.1 Pooled Analysis of MGR001-1005 and MGR001-1014

- It is noted that the firm conducted pooled analysis on 2 failed PK studies (MGR001-1005 and MGR001-1014) for the 200/50 mcg strength.
- The firm stated that both studies were conducted at the same site, in healthy adult volunteers fulfilling the same inclusion/exclusion criteria, within 2 months of each other and had exactly the same design. The same batch of MGR001 (test lot 631-009) product was used in both studies, but a different batch of RLD was used in each study (MGR001-1005: 5ZP9304; MGR001-1014: 5ZP9882).
- According to the pooled analysis report, the RLD batch used in MGR001-1014 (RLD batch 5ZP9882) was selected to represent the RLD population. The firm stated that the test versus RLD fine particle mass (FPM) ratio for FP and SA for batches measured during the MGR001-1014 study was approximately (b) (4) than those for (the same test and different RLD) batches measured during the MGR001-1005 study (please see figures below), creating the expectation that lower test versus RLD Geometric Mean Ratios (GMRs) would be observed in MGR001-1014 (please note that for MGR001-1005, firm-calculated AUC for FP and C_{max} for SA were above the 125% acceptance limit to establish BE).

FPM of FP



FPM of SA

(b) (4)



However, it should be noted that the study results of MGR001-1014 still failed to meet BE criteria (firm-calculated C_{max} for FP and SA were below the 75% acceptance limit to establish BE).

- It is also noted that, according to the firm's FPM figures above, FPM for each of FP and SA is smaller in the test product used in MGR001-1014 as compared to that used in MGR001-1005, even though same lot of the test product (lot 631-009) was used in these 2 studies.

In addition, it is noted that although same lot of test product was used in these 2 studies, the PK parameters of the test product differ (please see in tables below). In contrast, although 2 different RLD lots were used in these 2 studies, their PK parameters were comparable.

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MGR001-1005					
FP					
Parameter (units)	Test	RLD	Ratio	90% C.I.	
Group 1					
LAUCT (hr *pg/ml)	1882.22	1493.75	1.26	115.59	137.36
LAUCI (hr *pg/ml)	1966.71	1548.13	1.27	116.35	138.70
LCMAX (pg/ml)	242.69	201.03	1.21	110.85	131.47
Group 2					
LAUCT (hr *pg/ml)	1901.97	1460.99	1.30	123.85	136.85
LAUCI (hr *pg/ml)	2007.77	1516.38	1.32	126.20	138.91
LCMAX (pg/ml)	253.74	209.02	1.21	114.12	129.13
Group 3					
LAUCT (hr *pg/ml)	1963.37	1628.03	1.21	113.35	128.31
LAUCI (hr *pg/ml)	2079.71	1689.37	1.23	115.82	130.85
LCMAX (pg/ml)	263.01	242.29	1.09	103.34	114.02
SA					
Parameter (units)	Test	RLD	Ratio	90% C.I.	
Group 1, 2 and 3					
LAUCT (hr *pg/ml)	851.86	708.72	1.20	115.51	125.07
LAUCI (hr *pg/ml)	893.17	744.37	1.20	115.44	124.72
LCMAX (pg/ml)	485.94	401.57	1.21	114.44	127.96

MGR001-1014					
FP					
Parameter (units)	Test	RLD	Ratio	90% C.I.	
Group 1, 2 and 3					
LAUCT (hr *pg/ml) (GRP 1,2,3)	1449.73	1516.15	0.96	91.43	100.00
LAUCI (hr *pg/ml) (GRP 1,2,3)	1531.99	1581.09	0.97	92.60	101.39
LCMAX (pg/ml) (GRP 1,2,3)	189.23	228.89	0.83	79.03	86.48
SA					
Parameter (units)	Test	RLD	Ratio	90% C.I.	
Group 1, 2 and 3					
LAUCT (hr *pg/ml) (GRP 1,2,3)	723.85	745.80	0.97	93.78	100.45
LAUCI (hr *pg/ml) (GRP 1,2,3)	758.82	782.61	0.97	93.77	100.26
LCMAX (pg/ml) (GRP 1,2,3)	329.05	400.73	0.82	76.87	87.71

- The firm stated that the reason why MGR001-1005 and MGR001-1014 failed to fully demonstrate BE across all endpoints is not evident from comparison of the in vitro data measured for the T and R product batches included in these studies,

which were well matched.¹⁰⁴ In addition, the *in vitro* data do not predict the extent to which lower test/reference ratios of PK parameters were observed in the latter study compared to the former study.

- On 10/21/2016, DBI sent a biostatistics consult²³ to Division of Biometrics VIII (DBVIII), Office of Biostatistics for a statistical evaluation of the firm's pooled analysis of these 2 failed PK studies. In the consult response²⁴, the biostatistics reviewer stated that the firm's pooled analysis is not acceptable from the statistical point of view. The biostatistics reviewer also provided the following comments to be conveyed to the firm.
 - 1) The pooled analysis consisted of only two studies with opposite findings. It is apparent that by pooling such data together, the differences between the two studies could be balanced out and therefore, yielding a result somewhere toward to the middle and making the pooled study pass bioequivalence.
 - 2) Study MGR001-1005 failed to show bioequivalence. Study MGR001-1014 also failed to show bioequivalence even though the batch of Advair Diskus® was selected to represent the Advair Diskus® population. Therefore, whether the pooled analysis results can truly represent all the 250/50 µg strength data is questionable.
 - 3) The pooled analysis is a post-hoc analysis, not pre-specified in a protocol or a statistical analysis plan. Therefore, the finding from the pooled analysis is viewed as hypothesis generating and is not acceptable from the statistical point of view.
 - 4) Your statistical model for the pooled analysis included terms for study, subject within study, period within study, treatment, and study by treatment interaction, but did not take sequence-related effects such as sequence within study into consideration. In addition, the batch-to-batch variability was not addressed in the model. Even had the pooled analysis approach/concept been accepted, the suitability of the statistical model is still questionable.

The *in vivo* fasting BE study MGR001-1014 is **unacceptable**.

¹⁰⁴ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 2.7.1\Summary of Biopharmaceutical Studies and Associated Analytical Methods, p. 29-30 of 32).

Table 64. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

FP

Time (hr)	Test (n=63)		Reference (n=63)		Ratio (T/R)
	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	
0.00	0.00	.	0.00	.	.
0.03	25.44	66.20	33.88	68.08	0.75
0.08	57.25	47.37	78.32	54.70	0.73
0.17	80.75	39.77	105.74	43.15	0.76
0.25	110.84	36.04	146.77	37.37	0.76
0.33	135.12	34.55	167.13	35.52	0.81
0.50	161.92	31.86	201.52	31.74	0.80
0.75	179.54	31.49	218.60	27.61	0.82
1.00	183.01	29.98	216.39	26.18	0.85
1.50	169.07	28.61	196.81	25.51	0.86
2.00	158.28	31.40	181.54	26.85	0.87
3.00	132.54	33.97	148.86	27.51	0.89
4.00	113.37	36.35	121.05	28.58	0.94
6.00	68.97	37.36	71.24	30.40	0.97
8.00	52.73	37.81	52.82	30.99	1.00
12.00	31.27	37.13	29.72	33.52	1.05
24.00	13.43	40.97	11.09	32.04	1.21
36.00	6.70	44.73	5.39	33.12	1.24
48.00	4.50	42.26	3.60	34.98	1.25

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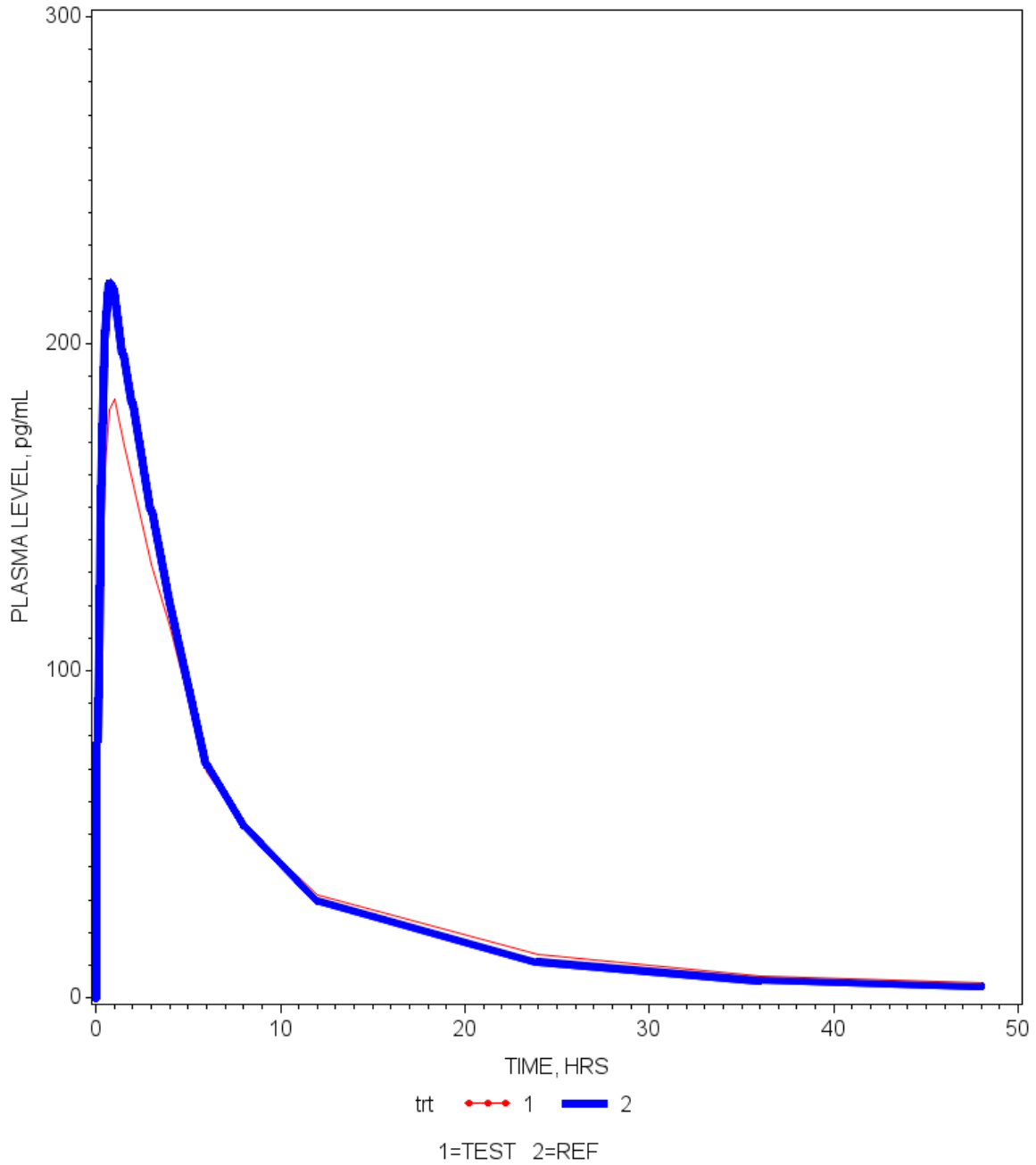
SA

Time (hr)	Test (n=61)		Reference (n=61)		Ratio (T/R)
	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	
0.00	0.00	.	0.00	.	.
0.03	271.79	59.19	360.36	48.24	0.75
0.08	352.07	43.63	412.01	33.56	0.85
0.17	242.70	36.40	267.80	28.24	0.91
0.25	176.13	33.34	194.05	26.80	0.91
0.33	147.85	30.94	159.45	27.77	0.93
0.50	121.63	33.34	127.96	30.77	0.95
0.75	109.59	39.57	108.14	34.93	1.01
1.00	103.02	41.08	98.12	38.35	1.05
1.50	87.80	41.50	88.08	42.12	1.00
2.00	76.28	42.80	76.15	46.68	1.00
3.00	55.11	46.05	55.05	47.26	1.00
4.00	41.86	48.03	42.21	45.81	0.99
6.00	30.38	47.48	30.45	47.56	1.00
8.00	22.46	44.02	23.08	47.10	0.97
12.00	14.40	46.62	14.98	47.14	0.96
24.00	7.21	48.00	7.59	48.02	0.95
36.00	3.04	48.18	3.23	52.76	0.94
48.00	1.89	64.94	1.99	58.65	0.95

Figure 4. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

FP

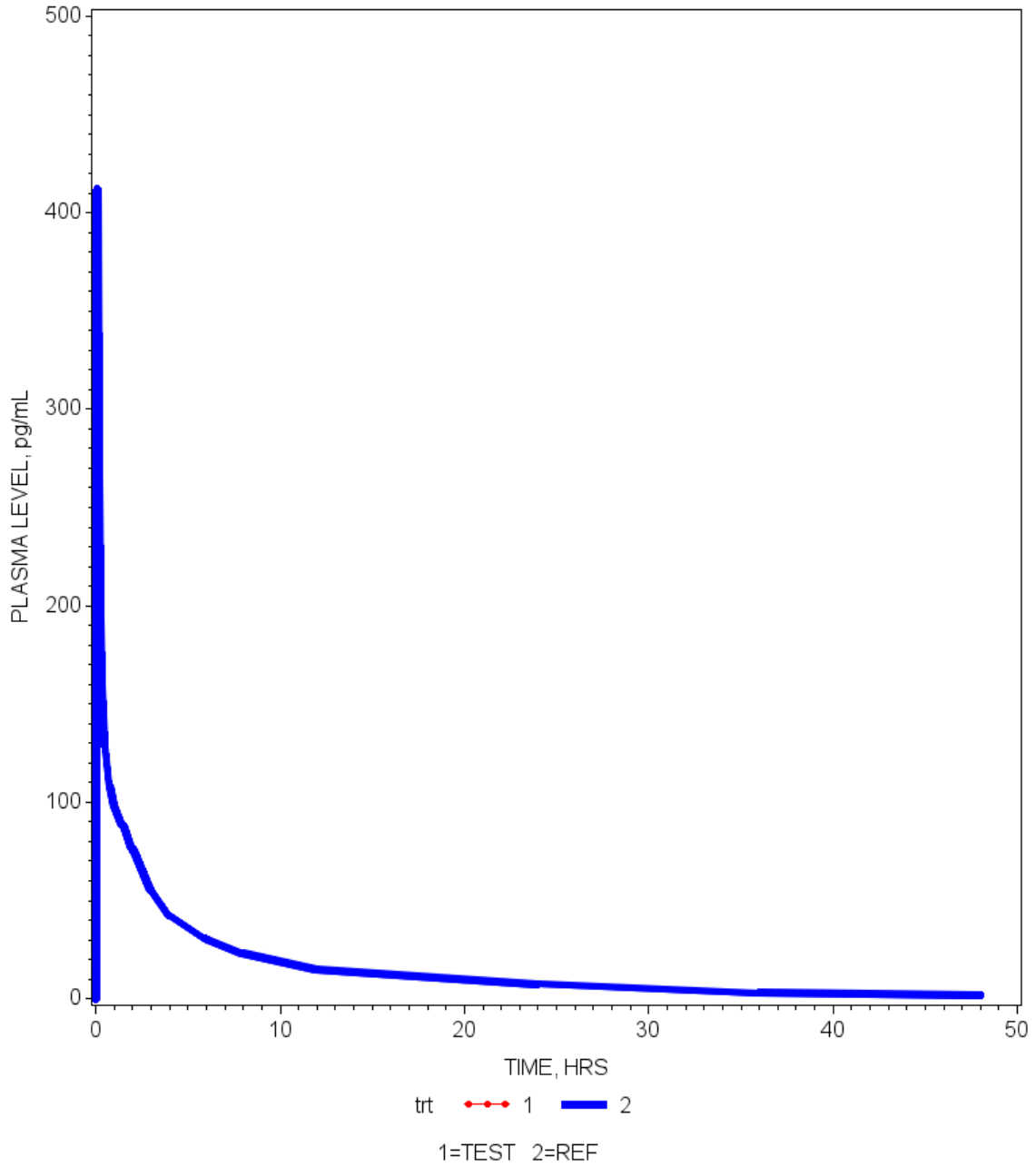
PLASMA Fluticasone Propionate LEVELS
Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder, ANDA 208891
UNDER Fasting CONDITIONS
DOSE= 3 x 250/50 MCG



ANDA 208891
Single-Dose Fasting Bioequivalence Study Review

SA

PLASMA Salmeterol LEVELS
Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder, ANDA 208891
UNDER Fasting CONDITIONS
DOSE= 3 x 250/50 MCG



5.2 Formulation

Formulation of the test product (commercial batch)¹⁰⁵ (from the firms' batch formula)

Ingredients	Commercial Batch Formula per Strength			Quality standard
	MGR001 100/50	MGR001 250/50	MGR001 500/50	
Salmeterol Xinafoate ^{1,2}	(b) (4)			USP
Fluticasone Propionate ²	(b) (4)			USP
Lactose monohydrate (b) (4)	(b) (4)			USP
(b) (4)	(b) (4)			USP
Total Weight (Batch Size)	(b) (4)			--

Reviewer's Comment on Test Product Formulation:

1. It should be noted that the firm's formulation above is for commercial batches. The firm stated that "[t]here are no difference between the batch formula of the registration and commercial batches (b) (4) (b) (4) as outlined below:

(b) (4)

¹⁰⁵ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.3.2\Batch Formula, p. 1 of 2).

(b) (4)



(b) (4)



and registration batches were used to conduct in vitro studies, PK studies as well as clinical endpoint studies, the firm will be asked to conduct in vitro BE studies (SAC and APSD studies) comparing RLD product and the test product with formulation of the commercial batches

(b) (4)

as bridging studies. These studies should be conducted for each strength of the product, and these in vitro studies should be conducted according to the product specific guidance, and use at least 3 batches each of T and R products with no fewer than 10 units from each batch.

¹⁰⁶ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.3.2\Batch Formula, p. 2 of 2).

The impact of lactose amount based on API amount will be evaluated in reviewer's comment #3 below.

2.



3. Based on USP-specified potency of FP (NLT 98.0% and NMT 101.0%)¹¹⁰ and SX (NLT 98.0% and NMT 102.0%)¹¹¹, the maximum and minimum amount and % w/w of APIs and lactose monohydrate in the test product is listed in table below. Please note that information for both of the commercial batches ()

¹⁰⁷ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.2\Pharmaceutical Development, p. 430 of 676).

¹⁰⁸ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.2\Pharmaceutical Development, p. 541, 544, 667 and 671 of 676).

¹⁰⁹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.2\Pharmaceutical Development, p. 430, 667, 671 and 675 of 676).

¹¹⁰ USP monograph for fluticasone propionate:

http://www.uspnf.com/uspnf/pdf/download?usp=39&nf=34&s=1&q=usp39nf34s1_m34220.pdf&officialOn=August%201,%202016&target=oldwindow&time=1472340029342 Last accessed: 8/27/2016.

¹¹¹ USP monograph for salmeterol xinafoate:

http://www.uspnf.com/uspnf/pdf/download?usp=39&nf=34&s=1&q=usp39nf34s1_m74389.pdf&officialOn=August%201,%202016&target=oldwindow&time=1472340217917 Last accessed: 8/27/2016.

(b) (4) and registration batches (b) (4) is listed below. The %w/w calculated below will be used for Q1/Q2 evaluation.

Table 66. Amount and %w/w of each ingredient in the test product formulation based on potency and/or overage adjustment in commercial batches and registration batches

100/50 mcg strength

Ingredients	Amount Based on 100% Potency of Each API	Commercial Batches				Registration Batches			
		Minimum Amount of API [@]		Maximum amount of API [#]		Minimum Amount of API [@]		Maximum amount of API [#]	
		Amount (g)	%w/w	Amount (g)	%w/w	Amount (g)	%w/w	Amount (g)	%w/w
Salmeterol (as xinafoate) [*]	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Fluticasone Propionate	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Lactose monohydrate	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total			100.00		100.00		100.00		100.00

250/50 mcg strength

Ingredients	Amount Based on 100% Potency of Each API	Commercial Batches				Registration Batches			
		Minimum Amount of API [@]		Maximum amount of API [#]		Minimum Amount of API [@]		Maximum amount of API [#]	
		Amount (g)	%w/w	Amount (g)	%w/w	Amount (g)	%w/w	Amount (g)	%w/w
Salmeterol (as xinafoate) [*]	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Fluticasone Propionate	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Lactose monohydrate	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total			100.00		100.00		100.00		100.00

500/50 mcg strength

Ingredients	Amount Based on 100% Potency of Each API	Commercial Batches				Registration Batches			
		Minimum Amount of API [@]		Maximum amount of API [#]		Minimum Amount of API [@]		Maximum amount of API [#]	
		Amount (g)	%w/w	Amount (g)	%w/w	Amount (g)	%w/w	Amount (g)	%w/w
Salmeterol (as xinafoate) [*]		(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Fluticasone Propionate									
Lactose monohydrate									
Total			100.00		100.00		100.00		100.00

4.

¹¹² GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.4.1\Specifications – Compendial – MDR-SPEC-0002 – (b) (4) p. 2 of 3).
¹¹³ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.4.1\Specifications – Compendial – MDR-SPEC-0015 – (b) (4) p. 2 of 3).

Table 67. Formulation of the RLD Product (batch formula based on (b) (4) batch size)¹¹⁴

Ingredients	100/50 mcg strength ¹¹⁵	250/50 mcg strength ¹¹⁶	500/50 mcg strength ¹¹⁶
Salmeterol xinafoate (micronized)			(b) (4)
Fluticasone propionate (micronized)			
Lactose monohydrate			

(b) (4)

Reviewer’s Comment on RLD Product Formulation:

1. According to the footnote “^{\$}” in the RLD formulation above, the amount of FP is based on the 100% potency. The actual input weigh is adjusted depending on the potency of the FP as received. Based on USP-specified potency of FP (NLT 98.0% and NMT 101.0%)¹¹⁷, the maximum and minimum amount and % w/w of FP and lactose monohydrate in the RLD product is listed in table below. Please note that RLD formulation did not mention about how to calculate the amount of FP when potency is >100%. The reviewer will use >100% (instead of 100% as indicated in the test product) to cover the worst case scenario.

The %w/w calculated below will be used for Q1/Q2 evaluation.

¹¹⁴ According to the most recent Annual Report [GS Review: NDA 021077, New/Annual Report, 7/20/2016 (Module 1.13.5\Drug Product Index of Approved Changes, p. 1 of 4)], the most recent approved composition are in Supplement S-034 submitted in 12/21/2007. (b) (4)

and this supplement or its corresponding CMC review does not include formulation table. According to the aforementioned most recent Annual Report, the next most recent approved composition information is in Annual Report submitted on 10/21/2005, which contains batch formula table for the 100/50 mcg strength only¹¹⁵. According to the aforementioned most recent Annual Report, the next most recent approved composition information is in original NDA. Therefore, RLD formulation information for the 100/50 mcg strength is from Annual Report submitted on 10/21/2005, while for the 250/50 mcg and 500/50 mcg strengths are from original NDA. Please note that these formulation information is also consistent with the most recent electronically available batch formula available in GS Review [GS Review: NDA 021077, New/Annual Report, 10/9/2009 (Module 3.2.P.3.2\Batch Formula)].

¹¹⁵ NDA 021077, Annual Report-5, 10/21/2005 (Volume 160.2, Volume 2 of 3, Attachment 1, p. 8).

¹¹⁶ NDA 021077 Action Package (Mercado search term: action package NDA 21077), p. 1058 of 1368.

¹¹⁷ USP monograph for fluticasone propionate:

http://www.uspnf.com/uspnf/pdf/download?usp=39&nf=34&s=1&q=usp39nf34s1_m34220.pdf&officialOn=August%201,%202016&target=oldwindow&time=1472340029342 Last accessed: 8/27/2016.

Table 68. Amount and %w/w of each ingredient in the RLD product formulation based on potency adjustment

100/50 mcg strength

Ingredients	Amount Based on 100% Potency of FP	Minimum Amount of FP [@]		Maximum amount of FP [#]	
		Amount (g) (b) (4)	%w/w (b) (4)	Amount (g) (b) (4)	%w/w (b) (4)
Salmeterol (as xinafoate)*					
Fluticasone Propionate					
Lactose monohydrate					
Total			100.00		100.00

250/50 mcg strength

Ingredients	Amount Based on 100% Potency of FP	Minimum Amount of FP [@]		Maximum amount of FP [#]	
		Amount (g) (b) (4)	%w/w (b) (4)	Amount (g) (b) (4)	%w/w (b) (4)
Salmeterol (as xinafoate)*					
Fluticasone Propionate					
Lactose monohydrate					
Total			100.00		100.00

500/50 mcg strength

Ingredients	Amount Based on 100% Potency of FP	Minimum Amount of FP [@]		Maximum amount of FP [#]	
		Amount (g) (b) (4)	%w/w (b) (4)	Amount (g) (b) (4)	%w/w (b) (4)
Salmeterol (as xinafoate)*					
Fluticasone Propionate					
Lactose monohydrate					
Total			100.00		100.00

(b) (4)

Table 69. Comparison of Test and Reference Formulations (based on theoretical formulation)

Ingredient	100/50 mcg strength			250/50 mcg strength			500/50 mcg strength		
	Reference Product (%w/w)	Test Product (%w/w)	Difference [(T-R)/R x 100%]	Reference Product (%w/w)	Test Product (%w/w)	Difference [(T-R)/R x 100%]	Reference Product (%w/w)	Test Product (%w/w)	Difference [(T-R)/R x 100%]
Salmeterol (as xinafoate)		(b) (4)	0		(b) (4)	0		(b) (4)	0
Fluticasone Propionate			0			0			0
Lactose monohydrate			0			0			0

Table 70. Comparison of Test and Reference Formulations (based on actual formulation adjusted for API potency/and or overage) (numbers used to calculate maximum possible difference is highlighted in green)

100/50 mcg strength

Ingredient	Reference Product (%w/w)		Commercial Batches			Registration Batches		
	Min amount of API	Max amount of API	Test Product (%w/w)		Maximum Possible % Difference [(T-R)/R x 100%]	Test Product (%w/w)		Maximum Possible % Difference [(T-R)/R x 100%]
			Min amount of API	Max amount of API		Min amount of API	Max amount of API	
Salmeterol (as xinafoate)				(b) (4)	0 (vs RLD label claim)		(b) (4)	0 (vs RLD label claim)
Fluticasone Propionate					0 (vs RLD label claim)			0 (vs RLD label claim)
Lactose monohydrate					-0.05			-0.02

250/50 mcg strength

Ingredient	Reference Product (%w/w)		Commercial Batches			Registration Batches		
	Min amount of API	Max amount of API	Test Product (%w/w)		Maximum Possible % Difference [(T-R)/R x 100%]	Test Product (%w/w)		Maximum Possible % Difference [(T-R)/R x 100%]
			Min amount of API	Max amount of API		Min amount of API	Max amount of API	
Salmeterol (as xinafoate)	(b) (4)		(b) (4)		0 (vs RLD label claim)	(b) (4)		0 (vs RLD label claim)
Fluticasone Propionate	(b) (4)		(b) (4)		0 (vs RLD label claim)	(b) (4)		0 (vs RLD label claim)
Lactose monohydrate	(b) (4)		(b) (4)		-0.09	(b) (4)		-0.03

500/50 mcg strength

Ingredient	Reference Product (%w/w)		Commercial Batches			Registration Batches		
	Min amount of API	Max amount of API	Test Product (%w/w)		Maximum Possible % Difference [(T-R)/R x 100%]	Test Product (%w/w)		Maximum Possible % Difference [(T-R)/R x 100%]
			Min amount of API	Max amount of API		Min amount of API	Max amount of API	
Salmeterol (as xinafoate)	(b) (4)		(b) (4)		0 (vs RLD label claim)	(b) (4)		0 (vs RLD label claim)
Fluticasone Propionate	(b) (4)		(b) (4)		0 (vs RLD label claim)	(b) (4)		0 (vs RLD label claim)
Lactose monohydrate	(b) (4)		(b) (4)		-0.15	(b) (4)		-0.06

Is the formulation of the Test product Q ₁ and Q ₂ same as the Reference product?	Yes
Is the formulation acceptable?	ACCEPTABLE FROM BE PERSPECTIVE (b) (4), the acceptability of which will be evaluated by OPQ)
If not, why?	N/A

Comments on Formulation:

1. As mentioned in the reviewer's comments for test product formulation, the test product has formulation for registration batches and commercial batches that differ in whether potency adjustment is involved. However, in each of the registration batch formulation and commercial batch formulation, the test product contains the same active ingredient in the same dosage form as the RLD product. The theoretical amount of the active ingredients is the same between test and RLD product.
2. Both the RLD product and commercial batch of the test product contain adjustment of API amount based on potency (RLD formulation adjusts for FP, while test formulation adjust for both FP and SX based on their potency). For commercial batches of the test product, where the assay value or potency is >100%, a value of 100% will be used.
3. The test product also contained [REDACTED] (b) (4) for the commercial batches is to be provided by the firm and its acceptability will be deferred to OPQ.
4. According to the product-specific guidance, the test product is recommended to be Q1 and Q2 the same as the R product. Q1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product, and Q2 (quantitative sameness) means that concentrations of inactive ingredient(s) used in the test product are within $\pm 5\%$ of those used in the reference product.

The firm's test formulation for registration batches and commercial batches differs in whether a potency adjustment during dispensing is included (please see details in reviewer's comments on test formulation #1 and 3). Nevertheless, the only inactive ingredient (lactose monohydrate) in each of the registration and commercial batch formulation is Q1 and Q2 the same as the approved RLD product with less than 5% difference based on the % w/w.

The formulation is **acceptable** from BE perspective. It should be noted that the firm did not provide information on [REDACTED] (b) (4), and thus will be asked to provide so. The acceptability of [REDACTED] (b) (4) will be deferred to OPQ.⁸

* Data obtained from Certificate of Analysis (COA). For test product, data is obtained from the “Uniformity of Emitted Dose” section of COA. For RLD product, data is obtained from the “Mean Delivered Dose” section of COA.

^ Clinical device: (b) (4)

@ Commercial device: (b) (4)

In vitro BE studies

§ 4 kPa fixed pressure drop studies

Comments: Incomplete.

- According to CC13-0422¹²¹, the Agency recommends the firm to use same batches of the RLD and the test for their proposed clinical program and for in vitro BE studies, whenever feasible.

The test and RLD lots used in the PK BE studies as well as the test lots used in the clinical endpoint study were included in the lots used in in vitro BE studies (please see highlights with the same color in the table above). However, the RLD lot (lot #4ZP4083) used in the clinical endpoint study was not included in in vitro BE studies. Since the RLD lot was unexpired during the duration of the clinical study, the reviewer will not pursue this issue further.

- According to the guidance-generating review¹²², it is important that 3 batches of the T product be manufactured from 3 different batches of the drug substance, excipient(s) and container closure system to account for the variability arising from each of these key components of the drug product.

The 3 exhibit batches for each strength were manufactured using different combination of API lots, excipient lots, filling component lots and device component lots. It is also noted that several exhibit lots used multiple filling components and device component lots in a single exhibit lot (please see table below for exhibit lots of the 100/50 mcg strength as an example).

¹²¹ <\\cdsnas\OGDS6\CONTROLS\2013-docs\13-0422.pdf>, p. 18 of 28.

¹²² V:\Science Group\Master Files BE Posting\Fluticasone Propionate_Salmeterol Xinafoate_021077\ Fluticasone Propionate_Salmeterol Xinafoate_21077_RC09-13.doc, p. 12 of 62.

(b) (4)

¹²³ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.2\Pharmaceutical Development, p. 530 of 676).

- [Redacted] (b) (4)

[Redacted] (b) (4)

Therefore, the firm will be asked to conduct the aforementioned bridging studies at all 3 flow rates of 30 L/min, 60 L/min and 90 L/min. This is decision is concurred by OB management in 1/18/2017-1/19/2017 meeting.¹²⁷

- The reviewer could not locate COAs for the following RLD batches used in the clinical endpoint study or in vitro BE studies: 4ZP4083 (clinical endpoint study), 5ZP8178, 5ZP8397, 5ZP0114, 4ZP7022, and 5ZP8689 (in vitro studies). Therefore, the firm will be asked to provide so.

The batch information is **incomplete**.

¹²⁴ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.2\Pharmaceutical Development, p. 566 of 676).

¹²⁵ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 2.3.P\Drug Product Part 1 – FPSX – Mylan Dublin, p. 97 of 107).

¹²⁶ GDRP: Pre-ANDA Briefing Package + Meeting Request, Ref 13-0422, Primary Review, 844398_Review.doc, 10/19/2015 (p. 14 of 16).

¹²⁷ \DIVISION\BIO\BIO1\Meeting Minutes\DBI non-Bio Management Meeting\2016\01182017-03202017 ANDA 208891_ [Redacted] (b) (4) Fluticasone_salmeterol DPI.doc.

5.3.1.2 Device Comparability

100/50 mcg strength

	100/50 mcg	
Parameter	Advair® Diskus®	Mylan MGR001
Dosage Type	Oral Inhalation Powder	Oral Inhalation Powder
Description	60 dose inhalation powder pre-dispensed	60 dose inhalation powder pre-dispensed
Mode of Action	Passive breath actuated	Passive breath actuated
Dose Counter	Dose counter counts down from sixty to zero with numbers five to zero showing in red.	Dose counter counts down from sixty to zero with an adjacent red indicator in the window to show that nine or fewer doses remain.
Device Resistance	Medium (b) (4)	Medium (b) (4)
Operating Sequence	Step 1. Open your Advair Diskus Step 2. Slide the lever until you hear it click Step 3. Inhale your medicine Step 4. Close the Diskus	Step 1. Open Step 2. Push Down Step 3. Inhale Step 4. Close
Container/Closure Design	Sealed foil pouch	Sealed foil pouch
Photograph ^{a,b}		

^a The purpose of the blank label of the test product is to illustrate the label shape, size and positioning. Please refer to firm's Module 1 for actual labels.

^b Photographs are for illustration and do not represent the actual inhaler sizes

^c Firm's test results

250/50 mcg strength

	250/50 mcg	
Parameter	Advair® Diskus®	Mylan MGR001
Dosage Type	Oral Inhalation Powder	Oral Inhalation Powder
Description	60 dose inhalation powder pre-dispensed	60 dose inhalation powder pre-dispensed
Mode of Action	Passive breath actuated	Passive breath actuated
Dose Counter	Dose counter counts down from sixty to zero with numbers five to zero showing in red.	Dose counter counts down from sixty to zero with an adjacent red indicator in the window to show that nine or fewer doses remain.
Device Resistance	Medium (b) (4)	Medium (b) (4)
Operating Sequence	Step 1. Open your Advair Diskus Step 2. Slide the lever until you hear it click Step 3. Inhale your medicine Step 4. Close the Diskus	Step 1. Open Step 2. Push Down Step 3. Inhale Step 4. Close
Container/Closure Design	Sealed foil pouch	Sealed foil pouch
Photograph ^{a,b}		

^a The purpose of the blank label of the test product is to illustrate the label shape, size and positioning. Please refer to firm's Module 1 for actual labels.

^b Photographs are for illustration and do not represent the actual inhaler sizes

^c Firm's test results

500/50 mcg strength

	500/50 mcg	
Parameter	Advair® Diskus®	Mylan MGR001
Dosage Type	Oral Inhalation Powder	Oral Inhalation Powder
Description	60 dose inhalation powder pre-dispensed	60 dose inhalation powder pre-dispensed
Mode of Action	Passive breath actuated	Passive breath actuated
Dose Counter	Dose counter counts down from sixty to zero with numbers five to zero showing in red.	Dose counter counts down from sixty to zero with an adjacent red indicator in the window to show that nine or fewer doses remain.
Device Resistance	Medium (b) (4)	Medium (b) (4)
Operating Sequence	Step 1. Open your Advair Diskus Step 2. Slide the lever until you hear it click Step 3. Inhale your medicine Step 4. Close the Diskus	Step 1. Open Step 2. Push Down Step 3. Inhale Step 4. Close
Container/Closure Design	Sealed foil pouch	Sealed foil pouch
Photograph ^{a,b}		

^a The purpose of the blank label of the test product is to illustrate the label shape, size and positioning. Please refer to firm's Module 1 for actual labels.

^b Photographs are for illustration only and do not represent the actual inhaler sizes

^c Firm's test results

Size of Test Device¹²⁸

Please note the firm did not provide a diagram with dimension measured for the whole test device. Based on the components of the test device (please see figures of the test device in closed and open position below), the reviewer listed out diagrams with dimensions of subassembly components and mouthpiece cover component of the test device so that to give a general idea of device dimensions.

Image of the CRC749 device in the closed position



Image of the CRC749 device with the mouthpiece cover open



¹²⁸ GS Review: ANDA 208891, 12/29/2015 submission (Module 3.2.P.7\Container Closure System, p. 5, 8, 24 and 29 of 229)

¹²⁹ GS Review: NDA 021077, New/Annual Report with PMR/PMC Status, 7/16/2015 (Module 3.2.P.7\Container Closure System – Diskus, p. 3-4 of 28).

Reviewer's Comments:

1. According to the product-specific guidance, the test product should have the following characteristics:
 - Passive (breath-actuated) device
 - Pre-metered multi-dose format
 - 60 doses
 - External operating procedures consisting of (1) Open, (2) Click, (3) Inhale, and (4) Close
 - Similar size and shape to the RLD product
 - Comparable device resistance to the RLD product
 - Dose counter

In addition, the robustness of the test product should be demonstrated.

2. According to the firm's description and composition of the drug product¹³⁰, MGR001 is a fixed dose combination product of FP and SX inhalation powder for oral use in the CRC749 device. In addition, the CRC749 device is the same for all 3 product strengths, which are differentiated by the product label.
3. The firm stated that CRC749 is a passive (breath-actuated) multi dose inhaler containing 60 pre-metered doses.¹³¹ The doses are contained within 2 foil sealed discs each with 30 pre-metered doses.
4. According to the firm, CRC749 external operating principles are (1) open, (2) push down, (3) inhale and (4) close¹³², which are comparable to those of the RLD device Diskus®. It is noted that due to the difference in device orientation, the description of step (2) is different between the test and RLD product. The RLD product instructs patients to slide the lever until you hear a click, whereas the test product instructs patients to "push the yellow lever down to the end of the purple arrows (you may hear a click).
5. Based on the device photographs and device diagrams with measurements above, the test device has similar size and shape to the RLD product, and has a dose counter.

¹³⁰ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.1\Description and Composition of the Drug Product).

¹³¹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 2.2\Introduction).

¹³² GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 2.3.P\Drug Product Part 2 _ FPSX – Mylan Dublin, p. 42 of 103).

6. Airflow resistance of the test (CRC749) and RLD (Diskus®) devices¹³³ are listed in the table below. Please note that the device resistance for the test device is almost (b) (4) higher than that of RLD.

A large rectangular area of the document is redacted with a solid grey box. The redaction covers what appears to be a table or list of data. The label (b) (4) is visible in the top right corner of the redacted area.

According to guidance-generating review¹³⁴, “in order to ensure that the targeted patient population is able to operate the T device effectively and receive medication without any significant change in inspiratory effort relative to use of the R DPI, it is generally preferable that the device resistance of the T and R DPIs be comparable, i.e., within $\pm 15\%$ of the R product.¹³⁵ ... If the device resistance of the T DPI product varies by more than 15% from the R DPI product, additional justification/ data (e.g., comparisons of inspiratory flow rates or profiles generated by healthy subjects and patients who participate in the PK and clinical endpoint studies for the T and R devices) from the ANDA sponsor should be submitted to support that this difference in the device resistance does not impact therapeutic equivalence of the T and R products.”

As listed in the table above, the device resistance of the T device varies by more than 15% (b) (4) from the R device. As mentioned in CC12-0731¹³⁶, the Agency does not fully agree with the firm’s claim that MGR001 has comparable device resistance to the RLD.

As mentioned in Section 3.1, according to CC12-0731¹³⁷, the Agency considers the test device still appropriate for the 505(j) regulatory pathway. However, to address some residual uncertainties due to the device resistance difference, the Agency recommends the firm to *either*

- i) Modify the device to attain similar resistance as the RLD, i.e., $\pm 15\%$ of the RLD,

or

- ii) Provide justification/data (e.g., comparisons of inspiratory flow rates or profiles generated by relevant patients for the test and reference DPIs) to

¹³³ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 2.3.P\Drug Product Part 1 _FPSX – Mylan Dublin, p. 71 of 107).

¹³⁴ V: (b) (4) \Master Files BE Posting\Fluticasone Propionate_Salmeterol Xinafoate_021077\Fluticasone Propionate_Salmeterol Xinafoate_21077_RC09-13.doc, p. 29 of 62.

¹³⁵ Footnote as in the guidance-generating review: “The recommendation is in part based on the release specification of Advair® Diskus for the specific device resistance and is consistent with the EMEA recommendation. The release specification for Advair® Diskus is 1.7-3.1 kPa for the pressure drop measured at 60 LPM (labeled flow rate). (b) (4)

(b) (4) The resistance range span around $\pm 15\%$ across the mean. Additionally, the EMEA also recommends that airflow resistance of a test DPI should be within $\pm 15\%$ of that of reference DPI.”

¹³⁶ [\\cdsnas\OGDS6\CONTROLS\2012-docs\12-0731.pdf](#), p. 16 of 34 (Question 8).

¹³⁷ [\\cdsnas\OGDS6\CONTROLS\2012-docs\12-0731.pdf](#), p. 13 of 34 (Question 3a).

support that this difference in the device resistance does not impact therapeutic equivalence of the proposed generic and the RLD.

In the same CC¹³⁸, the Agency provided additional information regarding justification/data as mentioned in ii) above. The Agency stated that data from patients (or from BE studies in healthy volunteers) showing similarity of flow rates would be helpful in the Agency's evaluation. The firm were also advised to consider flow rate dependency of product performance. If there is little flow rate dependency, this mitigates impact of difference in device resistance.

Later in CC13-0422¹³⁹, the Agency made additional recommendations to the firm regarding the device resistance issue. The firm was recommended to provide:

- iii) The SAC and APSD results for MGR001 and RLD measured at flow rates that produce 4 kPa pressure drop¹⁴⁰ across the corresponding inhalers.
and
- iv) Justification that the airflow resistance difference between MGR001 and RLD does not impact the usability of their proposed generic product. This may be achieved by conduct of a patient survey as part of the clinical endpoint BE study to evaluate/capture patients' experience with the use of MGR001.

(b) (4)

¹³⁸ [\\cdsnas\OGDS6\CONTROLS\2012-docs\12-0731.pdf](#), p. 33 of 34 (Question 8).

¹³⁹ [\\cdsnas\OGDS6\CONTROLS\2013-docs\13-0422.pdf](#) p. 28 of 28.

¹⁴⁰ According to CC13-0422 (p. 21 of 28), “[i]n literature, it has been reported that patients produce around 4 kPa pressure drop across the inhaler when inhale against resistances typical for the marketed DPIs. Comparable emitted dose and fine particle mass measured at 4kPa pressure drop for both the devices can provide additional confirmation that resistance difference between the RLD and MGR001 is acceptable.”

¹⁴¹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.2\Pharmaceutical Development, p. 663 of 676).

7. As detailed in Section 3.2, the test product has different orientation (vertical) as the reference device (horizontal). In CC12-0731¹⁴², the Agency raised concerned about the difference in the orientation of use between the MGR001 and the RLD. Some patients may use MGR001 horizontal orientation (i.e., the orientation that patients use for Advair Diskus). Such an error may result in incomplete lip sealing around the mouthpiece and lead to different air flow pattern through the inhaler

¹⁴² <\\cdsnas\OGDS6\CONTROLS\2012-docs\12-0731.pdf>, p. 16-17 of 34 (Question 8).

compared to when the test product is used correctly (i.e. vertically). The Agency recommends that the firm to demonstrate *one of the following*:

- i) Low likelihood of the orientation-related errors when MGR001 is used by the patients including prior Advair Diskus users.
- ii) Inhalation profiles through inhaler (i.e. peak inhalation flow rate (PIFR) and total inhalation volume through inhaler)¹⁴³ when used by the patients and the device retention (i.e. amount of drug retains in the device and air channel following inhalation) are comparable at both the (vertical and horizontal) orientations.

In the current application, the firm provided information on i) above (device orientation study MGR000-1004), which is evaluated in Section 5.6.

8. The firm conducted device robustness study MGR001-1010, which is evaluated by OPQ.
9. According to Clinical Overview⁵⁷, the CRC749 design development program resulted in the *clinical device* that was used in the in vivo flow profiling study and the majority of the pivotal clinical studies (i.e., pivotal PK BE studies MGR001-1006 and MGR001-1007 and pivotal clinical endpoint BE study MGR001-3001).

(b) (4)
the final *commercial device* which was used in the pivotal PK BE studies MGR001-1005 and MGR001-1014 and the device robustness study MGR001-1010. It should be also noted that similar to pivotal PK BE studies and the clinical endpoint study, in vitro studies (as evaluated in Section 5.3) were using clinical device for the 100/50 mcg and 500/50 mcg strengths, and commercial device for the 250/50 mcg strength.

(b) (4)
. As mentioned in Sections 5.1.1.1 and 5.1.2.1, due to the device difference, the firm will be asked to conduct in vitro BE study comparing the test product with commercial device and RLD product as bridging studies.

The firm's device comparability is **incomplete**.

¹⁴³ Footnote as in the CC review: "In the event of incomplete lip sealing around the mouthpiece of the inhaler, the patient may draw some portion of from the unsealed area around the mouthpiece. As a result, the amount and flow rate of air drawn through the inhaler by the patient may be less compared to the situation when the patient has complete lip sealing around the mouthpiece."

5.3.1.3 Actuation Methods

Which tests (if any) used MANUAL actuation?	SAC, APSD		
If some tests used manual actuation(s), describe methods used to avoid T to RLD bias in dose release.	The firm used randomization scheme to minimize potential laboratory bias during testing.		
Which tests (if any) used AUTOMATED actuation?	N/A		
What were the parameters of automated actuation? (units)*		T	RLD
	Force	N/A	N/A
	Velocity	N/A	N/A
	Acceleration	N/A	N/A
	Initial Delay	N/A	N/A
	Hold Time	N/A	N/A
	Final Delay	N/A	N/A
Are the actuation parameters the same for the test and reference products?	N/A		

Comments: Incomplete.

According to the study protocols, the firm used randomization scheme to minimize potential laboratory bias during testing. The firm will be asked to clarify if they used any blinding/unblinding approach during each of the SAC and APSD study. If yes, they will be asked to provide details on what procedures were taken for blinding/unblinding.

5.3.2 Individual In Vitro-Test Reviews – Pivotal Studies

Reviewer’s note: Instead of recording actuation numbers, the firm recorded “dose counter number” for each of their in vitro BE studies. Please note that dose counter number starts with 60, and counts down by 1 following each adequate actuation. Test performed on dose counter # 60 corresponds to actuation #1, and test performed on dose counter #59 corresponds to actuation #2, and so on. To be consistent with the firm, the reviewer will refer to dose counter number instead of actuation number in this Section 5.3.2.

5.3.2.1 Single Actuation Content through Container Life – 100/50 mcg strength

5.3.2.1.1 Study Information

Study No.	057755-02-04 Protocol #: P20987.00
Study Site	(b) (4)
Principal Investigator	(b) (4)
Study Dates	6/2/2015 to 9/28/2015
SOP No.	MGR-METH-546070 (v. 7.0)
SOP Effective Date	12/22/2014
SOP Title	Determination of emitted dose of MGR001 (PF-04764793) from multidose powder inhalation devices using (b) (4)
Test Method Description	(b) (4) for Dry Powder Inhalers (DPIs) is used to determine the emitted dose (ED) of MGR001 (PF-04764793) in 100/50, 250/50 and 500/50 µg multidose dry powder inhalers containing 100, 250 or 500 µg Fluticasone propionate and 50 µg salmeterol as xinafoate salt respectively and for Advair® and Seretide® Accuhaler® Reference Listed Drug (RLD).
Testing Equipment Used (e.g., name, model, etc)	USP <601> Apparatus B with modified end caps
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	30, 60 or 90 L/min flow rate; 2 L volume. Testing carried out at ambient laboratory conditions.
Analytical Method Description	(b) (4)
Analytical Equipment Used (e.g., name, model, etc.)	(b) (4) LC (b) (4) UPLC

Comments:

Reviewer’s note: The firm conducted SAC and APSD tests on the same device. Therefore, some of the comments below are common to both SAC and APSD study design (please see “General Comments” below). For reviewer’s comments specific for SAC study, please see “Comments for SAC” below.

General Comments

- The firm stated in the study protocol P20987.00 that testing on devices was to be completed within 1 month of unpouching from the overwrap. This is in line with the RLD labeling, which states that “[s]afely throw away ADVAIR DISKUS in the trash 1 month after you open the foil pouch or when the counter reads 0, whichever comes first”.
- The test was conducted on 3 lots of test and 3 lots of RLD product. For each lot, 20 test and 20 RLD devices were tested, with 3 replicates of SAC (beginning, middle, and end), and 2 replicates of APSD (beginning and end) collected from each device. Each SAC and APSD study was conducted at 3 flow rates (30 L/min, 60 L/min and 90 L/min). This is in accordance with the product-specific guidance.
- According to the study protocol, the following are the dose counter #s used for SAC and APSD testing. Please note that the firm conducted SAC (ED) and APSD (b) (4) test on the same device.

Test Sequence Dose counter number	Procedure	Testing to be Performed	Test Day
60	ED Beginning	Emitted Dose at target flow	1
59	(b) (4) Beginning	(b) (4) at target flow	
58-33	Waste	Wasting at target flow	
Leave device to rest at least overnight			
32-31	Waste	Wasting at target flow	2
30	ED Middle	Emitted Dose at target flow	
29-5	Waste	Wasting at target flow	
Leave device to rest at least overnight			
4-3	Waste	Wasting at target flow	3
2	(b) (4) End	(b) (4) at target flow	
1	ED End	Emitted Dose at target flow	

NA = Not Applicable

- According to the study protocol, to clear the test device of any potentially extraneous powder, an extra solenoid activation of 2 seconds was recommended after a final waste shot, just prior to an ED or (b) (4) collection.
- In Method #s MGR-METH-546070 (Version 7.0, p. 7 of 38) for SAC study and MGR-METH-546069 (Version 6.0, p. 6 of 37) for APSD study, the firm stated that during sample preparation, (b) (4).
The firm will also be asked to clarify if they did sealing for the RLD device.
- According to Method # MGR-METH-546070 (Version 7.0, p. 8 of 38), for emitted dose test set-up, the firm stated that when attaching the mouthpiece

adaptor to the (b) (4), “ensuring that the raised notch is pointing downwards at the 6 o’clock position. (Diskus/Accuhaler attach the mouthpiece adaptor to the (b) (4) ensuring that the raised notch is pointing horizontally at the 9 o’clock position.)” The firm also had a similar statement about mouthpiece adapter attachment to the throat in Method # MGR-METH-546069 (Version 6.0, p. 8 of 37) for APSD study. It is unclear what “raised notch” is. Therefore, the firm will be asked to provide picture(s) to illustrate how test and RLD devices were set up with the testing apparatus in SAC and APSD studies. Whether devices were set up in the correct orientation will be evaluated upon receipt of this information.

- The firm provided 100% raw analytical data for SAC and APSD testing. However, the raw data format provided by the firm is too granular, as each page only contains information for one sample. The firm will be asked to compile the raw data of each run. An example for this compiled raw data format can be seen in 9/22/2016 submission, Module 3.2.P.2\Attachment 4-4 – MGR-PRO-2015-080 – 250/50 mcg – APSD Raw Data – Comment 4 – Sequence 0009. The raw data should include all samples (including blank/diluent, standards, etc.) in a run in run sequence order.

-  (b) (4)

 (b) (4)

Therefore, the firm will be asked to explain for this inconsistency of SA retention time among different studies. In addition, the firm will be asked to explain wide range of SA retention time as well as deviation from expected SA retention time, and justify its impact on reliability of sample analysis.

Comments for SAC

- According to the study protocol, flow rates and actuation times for testing are as follow:

Flow Rate (L/min)	ED Actuation Time (seconds)	Wasting Actuation Time (seconds)
30	4.0	4.0
60	2.0	2.0
90	1.3	1.3

This is in line with product-specific guidance's recommendation that the volume of air drawn through the delivery system should be 2L for SAC study.

- In the study protocol, the firm also stated that the target emitted dose for both T and RLD product are FP = 93 mcg, and SA = 45 mcg. This is the target emitted dose specified in the USP monograph for Fluticasone Propionate and Salmeterol Inhalation Powder¹⁴⁴ when tested at a flow rate of 60 L/min for 2 seconds. According to the RLD labeling, these values are also what RLD product delivers under standardized in vitro test conditions when tested at a flow rate of 60 L/min for 2 seconds. Please note that RLD labeling and USP monograph did not mention delivered dose or target emitted dose for flow rate at 30 L/min and 90 L/min.

5.3.2.1.2 Analytical Method Validation for UPLC

Information Requested	
Analytical method validation report location	12/29/2015 submission, Module 3.2.P.5.3\Uniformity of delivered dose Validation Report – MDR-RGMETH-0032
Study Report Number	Validation of MDR-RGMETH-0032
Analyte	Fluticasone propionate (FP) and Salmeterol (SA)
Internal Standard (IS)	N/A
Method description	Determination of Emitted Dose for Fluticasone propionate and Salmeterol Xinafoate Dry Powder Inhalation Products by UPLC
Selectivity or Specificity	Resolution between the peak being quantified and the closest eluting peak in the chromatogram with a peak area more than 1% of the peak being quantified is no less than 1.5 for FP and SA.
Limit of quantitation	0.4 mcg/mL (FP) 0.2 mcg/mL (SA)
Detection Limit	N/A
Linearity Range (mcg/mL)	0.4, 1.0, 2.0, 5.0, 10.0, 15.0 mcg/mL (FP) 0.2, 0.5, 0.75, 1.0, 1.25, 1.5 mcg/mL (SA)
Linearity (R ²)	1.0000 (FP) 1.0000 (SA)
Accuracy (% recovery at the high and low concentrations)	Not provided (please see comments below)

¹⁴⁴ USP Monograph for Fluticasone and Salmeterol Inhalation Powder:
http://www.uspnf.com/uspnf/pdf/download?usp=39&nf=34&s=1&q=usp39nf34s1_m3467.pdf&officialOn=August%201.%202016&target=oldwindow&time=1472465975258, p. 5 of 7. Last accessed: 8/28/2016.

Precision -- Repeatability	Not provided (please see comments below)
Precision --Intermediate Precision	Not provided (please see comments below)
Bench-top stability (hrs(CV%)) (working std solution)	7 days (both FP and SA) Storage condition: ambient laboratory temperature protected from light
Refrigerator stability (hrs(CV%)) (working std solution)	N/A
Stock solution stability (days (CV %))	7 days (20.0 mcg/ml) (FP) 7 days (20.0 mcg/ml and 10.0 mcg/ml) (SA) Storage condition: ambient laboratory temperature protectd from light
Freeze-thaw stability (cycles (CV %))	N/A
Robustness	<u>Effect on retention time of FP and SA:</u> • % organic and column have a significant effect. • Buffer pH, buffer concentration, column temperature, and SDS concentration do not have a significant effect. <u>Effect on tailing factor of SA:</u> • % organic and column temperature have a significant effect. • % organic-by-buffer concentration interaction has a significant effect. • Buffer pH, buffer concentration alone and SDS concentration do not have a significant effect. <u>Effect on tailing factor of FP:</u> • % organic, column, buffer pH, buffer concentration, column temperature, and SDS concentration do not have a significant effect. The statistical analysis of the results indicates that the % organic is the main factor affecting SA peak retention time and therefore particular care should be taken when diluting the buffer solution component with methanol during preparation of the mobile phase.
Dilution integrity	N/A

Does Firm's SOP include validation criteria? (Y/N)	The firm did not submit SOP for UPLC method validation, but acceptance criteria were listed in the method validation report. <u>Specificity:</u> • Resolution between the peak being quantified and the closest eluting peak in the chromatogram with a peak more than 1% of the peak being quantified is not less than 1.5. <u>Linearity:</u> • R^2 is not less than 0.999 • Intercept is not more than 2% of the response for 90% of the lowest test sample concentration • No trends observed in residuals <u>Solution stability:</u>

	• Mean result for each sample and standard concentration is 98.0% to 102.0% of the initial concentration.
Comments on Firm's SOPs and Criteria (Acceptable/ or Explain)	Acceptable.

Comments on Method Validation:

- It is noted that method validation results for the current Method # MGR-METH-546070 (Section C of this method) is almost the same as method validation results for Method # MDR-RGMETH-0032 (12/29/2015 submission, Module 3.2.P.5.3\Uniformity of delivered dose Validation Report – MDR-RGMETH-0032). According to the firm¹⁴⁵, the former method is equivalent (i.e. employ the same preparation, the same chromatographic conditions and the same method of quantification) to the latter method. The firm will be asked to clarify if these are the same method validation studies, and provide street address as well as study dates for their method validation studies for each of these 2 methods.

Based on the firm's submissions to the current ANDA, it is unclear whether the method validation studies were conducted at the same study site as the in vitro BE studies. As detailed in Section 5.8.3.1, during OSIS inspection of (b) (4) (in vitro BE study site for the 100/50 and 500/50 mcg strengths), it was found out that the analytical methods performed by (b) (4) were developed and validated by the sponsor (Mylan Global Respiratory Group) prior to the transfer to (b) (4) according to (b) (4) method transfer protocol. The method was initially transferred to (b) (4), and was then transferred from (b) (4). Therefore, it is clear that method validation and pivotal in vitro BE studies for the 100/50 and 500/50 mcg strengths were conducted at different sites.

Since OSIS mentioned the existence of (b) (4) method transfer protocol, it is likely that the firm conducted studies for method transfer from Mylan Global Respiratory Group to (b) (4). Since the firm did not provide method transfer report in the current submission, the firm will be asked to provide so, as method transfer studies (e.g. precision and accuracy studies for the HPLC method) are needed to support method transfer between different study sites.

- Instead of evaluating accuracy, method precision, and intermediate precision for the UPLC analytical method, the firm evaluated them for the SAC method (b) (4). The firm will be asked to validate accuracy (% recovery at the high and low concentrations) and precision/intermediate precision of the UPLC method. Accuracy and precision should be evaluated with known amounts of FP and SA relevant to expected sample concentrations spiked into placebo solution.

¹⁴⁵ GS Review: ANDA 208891, Response to ECD/Bioequivalence, 9/22/2016 (Module 1.2\Cover Letter..., p. 2 of 18).

- The firm conducted solution stability study for stock standard solutions and working standard solutions of 7 days at ambient laboratory temperature, which covers the storage period of up to 7 days for all SAC studies (057755-02-04, MGF-PRO-2015-080, 057755-02-07, MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093).
- As mentioned in the table above, based on statistical analysis of the robustness study results, the firm stated that % organic is the main factor affecting SA peak retention time and therefore particular care should be given when diluting the buffer solution component with methanol during preparation of the mobile phase. The firm will be asked to specify their approaches taken during sample processing regarding % organic affecting SA peak retention time. Please note that as detailed in Section 5.3.2.1.1, 5.3.2.5.1 and 5.3.3.1.1, chromatograms from a few studies show a wide range of SA retention time as well as deviation from expected SA retention time. As mentioned above, the firm will be asked to explain for that and justify its impact on sample analysis.

The firm's UPLC method validation is **incomplete**.

5.3.2.1.3 Calibration of Manual and/or Automated Actuator (For Single Actuation Content Study)

Reviewer's Note: As indicated by the table below, the firm conducted intermediate precision study for each of the 100/50 and 500/50 mcg strength for each of the T and R products 32 times (using a combination of 2 days, 2 analysts, 2 ED workstation, and 4 devices).

Experiment	Day	Analyst	ED workstation	Device number	DCN Number ¹⁴⁶
1	1	1	2	1	60
2	1	1	1	1	59
3	1	2	2	1	58
4	1	2	1	1	57
5	1	1	2	2	60
6	1	2	2	2	59
7	1	1	1	2	58
8	1	2	1	2	57
9	1	2	1	3	60
10	1	1	2	3	59
11	1	2	2	3	58
12	1	1	1	3	57
13	1	1	1	4	60

¹⁴⁶ According to Method #MGR-METH-546070 (Version 7.0), DCN stands for dose counter number.

14	1	2	1	4	59
15	1	1	2	4	58
16	1	2	2	4	57
17	2	1	1	1	56
18	2	2	1	1	55
19	2	1	2	1	54
20	2	2	2	1	53
21	2	1	2	2	56
22	2	2	2	2	55
23	2	1	1	2	54
24	2	2	1	2	53
25	2	2	2	3	56
26	2	2	1	3	55
27	2	1	2	3	54
28	2	1	1	3	53
29	2	1	2	4	56
30	2	2	1	4	55
31	2	1	1	4	54
32	2	2	2	4	53

Test Product

MGR 001	100/50µg product strength				500/50µg product strength			
	FP (µg)	% mean	S (µg)	% mean	FP (µg)	% mean	S (µg)	% mean
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								

20	(b) (4)							
21								
22								
23								
24								
25								
26								
27								
28								
29								
30								
31								
32								
Mean	95.151	100.0	43.420	100.0	456.520	100.0	44.935	100.0
% RSD	11.09	11.1	3.53	3.5	2.89	2.9	2.60	2.6
Min	(b) (4)							
Max								

Reviewer's note: For the values highlighted above, the firm stated that "[a] single high result was see for FP in the 100/50 product, possibly due to contamination." (b) (4)

RLD Product

ADVAIR	100/50µg product strength				500/50µg product strength			
	FP (µg)	% mean	S (µg)	% mean	FP (µg)	% mean	S (µg)	% mean
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								

20	(b) (4)							
21	(b) (4)							
22	(b) (4)							
23	(b) (4)							
24	(b) (4)							
25	(b) (4)							
26	(b) (4)							
27	(b) (4)							
28	(b) (4)							
29	(b) (4)							
30	(b) (4)							
31	(b) (4)							
32	(b) (4)							
Mean	94.103	100.0	45.855	100.0	458.266	100.0	44.992	100.0
% RSD	2.97	3.0	2.73	2.7	4.11	4.1	4.21	4.2
Min	(b) (4)							
Max	(b) (4)							



Comments on Firm's SOPs and Criteria (Acceptable/ or Explain)	Acceptable.

Comments on Method Validation:

- As mentioned above, the firm will be asked to provide street address and study dates for method validations studies. Based on the firm's submissions to the current ANDA, it is unclear whether the method validation studies were conducted at the same study site as the in vitro BE studies. However, based on OSIS findings, it is clear that method validation and in vitro BE studies for the 100/50 and 500/50 mcg strengths were conducted at different sites. Similar to the HPLC method validation in Section 5.3.2.1.2, the firm will be asked to provide method transfer report, as method transfer studies (e.g. precision study for the SAC method) are needed to support method transfer between different study sites. The firm will be advised that method transfer studies for the SAC method should be conducted using unexpired RLD product.
- The firm conducted intermediate precision study using test products MGR001 529-005-1DE (100/50 mcg strength) and MGR001 529-005-16DE (500/50 mcg strength) as well as RLD product Advair Diskus (A025222) Lot 3ZP6443 (100/50 mcg strength) and Advair Diskus (A048356) Lot 3ZP6615 (500/50 mcg strength).
- According to the validation report, "DCN number" (dose counter number) 60-57 were used for the intermediate precision study.
- The firm did not specify the flow rate, actuation time and volume of air drawn through the delivery system for the intermediate precision study of the SAC method, and thus will be asked to specify so.
- As mentioned above, the firm conducted intermediate precision study using different days, analysts, ED workstations, and device numbers. (b) (4)

[REDACTED]

[REDACTED]. It should be noted that all other results complies with the limits of 75% to 125% of mean. Therefore, the reviewer will not pursue this issue further.

5.3.2.1.4 Results Summary

Firm's results

Flow Rate (L/min)	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
30	FP	BoL	(b) (4)					
		EoL						
		MoL						
	Sal	BoL						
		EoL						
		MoL						
60	FP	BoL						
		EoL						
		MoL						
	Sal	BoL						
		EoL						
		MoL						
90	FP	BoL						
		EoL						
		MoL						
	Sal	BoL						
		EoL						
		MoL						

Reviewer's Comments:

- The firm did not provide actual dose counter numbers in the SAS .xpt dataset, thus the reviewer is unable to verify whether the actuation used was at the beginning, middle and end lifestages of the device. Therefore, the firm will be asked to add a column for dose counter number in their SAC SAS .xpt dataset.
- It is noted that the firm's study protocol has the following statement for lost sample collections:

"If during sample preparation, a sample is lost due to an assignable cause (e.g., (b) (4) tube leakage, dropped (b) (4) plate, etc.) during Beginning or Middle-of-Life, the lost sample will be documented and supervisory approval will be obtained to cease further collection/recovery of the sample. A new sample will be prepared from the next dose(s) of the same device per the test method. The tests ...may be performed within ± 3 doses..."

For sample lost at the End-of-Life due to an assignable cause, the lost sample will be documented and supervisory approval will be obtained to cease further collection/recovery of the sample. Beginning and Middle-of-Life collections/results, as well as any successfully collected End-of-Life results from

this device will be used as-is. Where possible, a new device will be used to repeat any lost End-of-Life collections and/or continue testing any End-of-Life collections not originally performed.”

As mentioned above, the firm did not provide dose counter numbers in the SAS .xpt dataset, thus it is unclear if the firm lost any sample and measured the “next dose” of the same device. Therefore, as mentioned above, the firm will be asked to add a column for dose counter number in their SAC SAS .xpt dataset. In addition, for each sample that was lost and “next dose” of the same device was measured, the firm will be asked to provide detailed cause of sample loss as well as supporting documents (e.g. investigational report) for these sample loss.

- It is also noted that the firm repeated 14 samples using new devices, and each of these 14 samples were repeated for both FP and SA. Please note that beginning, middle and end lifestages should be from the same device. Nevertheless, given the multiple incidences of alternative actuation/alternative devices throughout the in vitro BE studies, the firm will be asked to explain and provide supporting documents for them (please see details below), and explain why there are multiple incidences of alternative actuation/replacement device, and the impact of it on the in vitro BE studies.

Among these 14 samples, the firm provided the repeat reasons for 13 samples below. The firm also stated that these samples did not have the original data generated due to analysis being stopped prior to data generation.

Number	Product	Batch number	Original inhaler number	Replacement inhaler number	Flow rate (L/min)	Reason for replacement
1	MGR001	631-003	9	112	30	Leak in sample collection tube, analysis halted.
2	Advair	4ZP3863	2	117	30	For ten instances of SAC, tested in the same chromatography run there were bracketing standard agreement failures and a standard preparation error. Hence no original analytical data was generated for these replicates.
3	MGR001	631-001	19	115	30	
4	MGR001	631-002	10	112	30	
5	MGR001	631-001	15	114	30	
6	MGR001	631-001	5	116	30	
7	MGR001	631-003	10	115	30	
8	Advair	4ZP3863	5	118	30	
9	MGR001	631-003	20	113	30	
10	Advair	5ZP8178	17	116	30	
11	MGR001	631-003	7	114	30	
12	Advair	5ZP8178	38	111	60	Leak in sample collection tube, analysis halted.
13	Advair	4ZP3863	39	111	60	

- For sample #s 1, 12 and 13 above, the reviewer considers the firm’s reason for original sample rejection (please see details in the table above)

acceptable. However, it should be noted that the firm only repeated the sample at the end lifestage in the replacement device.

- For sample #s 2-11 above, the reviewer calculated out that the % RSD of bracketing standards for these 10 samples in the original run was 78.2% for FP and 77.1% for SA, which did not meet the acceptance criteria ($\leq 1.4\%$ RSD). Therefore, these samples were rejected as per the study method MGR-METH-546070 (Version 7.0). According to the study report, these samples are at the beginning lifestage (the firm did not specify actuation number/dose counter number). Since rejecting the original samples happened after chromatograph results were analyzed, and by that time, the suitable “next dose” likely has already been wasted as per protocol, the reviewer considers the firm’s usage of a replacement device acceptable. However, it should be noted that the firm only repeated the sample at the beginning lifestage in the replacement device.
- The firm did not provide reason and supporting document for the rejection of the following sample (p. 8 of 178 of the firm’s MGR-REP-2015-096 version 1.0). Therefore, the firm will be asked to provide so.

Product	Batch Number	(b) (4) Device ID	Mylan Unit	Flow Rate (L/min)
REF	5ZP8397	40	180	60

- Due to aforementioned missing information, the reviewer could not verify the firm’s results summary at this time.
- The firm did not provide % of label claim in their SAS dataset, and thus will be asked to add a column for this in the SAS .xpt file.
- Based on the firm’s results, it is noted that RLD product had lower FP and SA emitted dose as compared to the test product at beginning lifestages at 30 L/min flow rate. It is also noted that RLD had high variability for FP under this condition. The firm also noted the same observation, and considered it to reflect a considerable number of actuations with low dose emission from the RLD at this flow rate.¹⁴⁷ The reviewer checked study data for each individual unit, and found that RLD batch #5ZP8397 had multiple samples that had very low emitted dose for FP (b) (4) at beginning lifestages at 30 L/min flow rate.

5.3.2.1.5 In Vitro PBE Analysis

As detailed above, analysis will be carried out pending the firm’s additional information on actual dose counter number, % of label claim, lost samples and repeat samples.

¹⁴⁷ GS Review: ANDA 208891, 12/29/2015 (Module 3.2.P.2\Pharmaceutical Development, p. 341 of 676).

5.3.2.1.6 Conclusions

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE		
REVIEW OF TESTING METHODS:		
Is the testing method validated?	Yes, but with deficiencies	
Is the Quantitative Analytical Method Validated? (e.g., HPLC)	Yes, but with deficiencies	
Is the method sufficiently sensitive?	Yes	
Is testing performed as per RLD labeling?	To be determined	
Are data measured at both beginning, middle & end lifestages?	Yes	
Is testing a single actuation per determination?	Yes	
If yes, what is the actuation number tested?	Study protocol states that dose counter #s 60 (beginning), 30 (middle) and 1 (end) were to be used. The firm did not provide actual dose counter number , and thus will be asked to provide so.	
Are the testing methods acceptable?	INCOMPLETE	
If not, why?	Due to deficiencies in method validation and study information.	
STUDY RESULTS:		
Are data expressed as actual amount and % of label claim?	No	
Is the geo-mean of the test product (% of label claim) within 95-105%?	Beginning	To be determined
	Middle	To be determined
	End	To be determined
Are the PBE results acceptable?	To be determined	
If not, why?	Pending additional information about actual dose counter numbers, % of label claim, and repeated samples.	

Comments:

The firm’s pivotal SAC study for the 100/50 mcg strength is **incomplete**.

5.3.2.1.7 Deficiencies / Recommendations

Please see Section 4.10.

5.3.2.2 Aerodynamic Particle Size Distribution (APSD) – 100/50 mcg strength

5.3.2.2.1 Study Information

Study No.	057755-02-04 Protocol #: P20987.00
Study site	(b) (4)
Principal Investigator	(b) (4)
Study dates	6/2/2015 to 9/28/2015
SOP No.	MGR-METH-546069 (v. 6.0)
SOP Effective Date	12/22/2014
SOP Title	Determination of aerodynamic particle size distribution of MGR001 (PF-04764793) dry powder inhaler products at 60 l per minute using a (b) (4) Impactor (b) (4) by UPLC.
Testing Method Description	(b) (4) Impactor (b) (4) is used to determine the aerodynamic particle size distribution (APSD) of PF-04764793 in 100/50, 250/50 and 500/50 µg MGR001 dry powder inhaler products containing 50 µg salmeterol as xinafoate salt and 100, 250 or 500 µg fluticasone propionate respectively and for Advair® Diskus® and Seretide® Accuhaler®.
Testing Equipment Used (e.g., name, model, etc)	USP <601> Apparatus 5
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	30, 60 or 90 L/min flow rate; 4 L volume. Testing carried out at ambient laboratory conditions.
Analytical Method Description	(b) (4)
Analytical Equipment Used (e.g., name, model, etc)	(b) (4) LC (b) (4) UPLC

Comments:

Reviewer's note: The firm conducted SAC and APSD tests on the same device. Therefore, some of the comments are common to both SAC and APSD study design (please refer to reviewer's general comments in Section 5.3.2.1.1). For reviewer's comments specific for APSD study, please see below.

Comments for APSD

- According to the study protocol, flow rates and actuation times for testing are as follow:

Flow Rate (L/min)	(b) (4) Actuation Time (seconds)	Wasting Actuation Time (seconds)
30	8.0	4.0
60	4.0	2.0
90	2.7	1.3

This is in line with product-specific guidance’s recommendation that the volume of air drawn through the delivery system should be 4L for APSD study.

- According to the study protocol, the firm evaluated each individual (b) (4) component, total recovery, and impactor sized mass (ISM) for each determination. Total recovery and ISM is defined as below:
 - Total recovery: The sum of all recovered components [mouthpiece adapter/induction port through micro orifice collector (MOC)], as determined by (b) (4) chromatographic software.
 - ISM: The sum of results from Cup 2 through MOC. The mass on all impactor components with a defined upper cut-off. This is in accordance with the Agency’s previous response in Control # 12-0731 as well as the product-specific guidance.

In addition, the firm also had the following statement for FPM and mass balance (MB):

- FPM: According to the study method MGR-METH-546068 (version 6.0, p. 15 of 37), FPM is calculated (b) (4) (b) (4) when operated at 60 L/min. The firm did not specify calculation method for FPM at 30 and 90 L/min. According to the pharmaceutical development report¹⁴⁸, (b) (4)

The reviewer spot checked the firm’s SAS dataset, and found that for FPM, (b) (4)

Therefore, the firm will be asked to explain why they changed the calculation method for FPM.

- Mass Balance (MB): calculated as % “TDD”. TDD values are taken from patient information for Advair® Diskus® (45 mcg for SA and 93 mcg for FP).

¹⁴⁸ GS Review: ANDA 208891, 12/29/2015 (Module 3.2.P.2\Pharmaceutical Development, p. 26 of 676).

Please note that according to the RLD labeling³⁰, under standardized in vitro test conditions, RLD delivers 93 mcg of FP and 45 mcg of SA per blister from Advair Diskus 100/50, when tested at a flow rate of 60 L/min for 2 seconds. This is also the target emitted dose in USP monograph for Fluticasone Propionate and Salmeterol Inhalation Powder. Please note that RLD labeling and USP monograph did not mention delivered dose or target emitted dose for flow rate at 30 L/min and 90 L/min.

According to the guidance-generating review¹⁴⁹, the total mass of drug collected on all stages¹⁵⁰ and accessories should be between 85 and 115%¹⁵¹ of label claim on a per actuation basis¹⁵².

- The firm will be asked to provide detailed calculations for calculating MMAD and GSD.
- The firm provided mass balance in the study report, but did not include it in the SAS .xpt file. Therefore, the firm will be asked to add a column for mass balance in their SAS xpt file for APSD studies.
- According to the *Guidance for Industry - Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal sprays for Local Actions* (posted April 2003): “analytical runs include at least three or more concentrations of quality control samples that represent the entire range of the standard curve or the expected concentration range of samples from the various stages of the CI.”

According to the study method MGR-METH-546069 (version 6.0), each run contains standard high (b) (4)



Based on the raw data, for APSD studies on the 250/50 mcg strength, typical sample concentration range across the cascade impactor is (b) (4)

(b) (4)
Therefore, the reviewer will not pursue the no QC issue at this

¹⁴⁹ V:\Science Group\Master Files BE Posting\Fluticasone Propionate_Salmeterol Xinafoate_021077\Fluticasone Propionate_Salmeterol Xinafoate_21077_RC09-13.doc, p. 14 of 62.

¹⁵⁰ Footnote as in the guidance-generating review: “Total mass of drug includes drug deposition on each individual site, to include the mouthpiece adapter, throat, preseparator, and each stage of the impactor including the filter, is requested.”

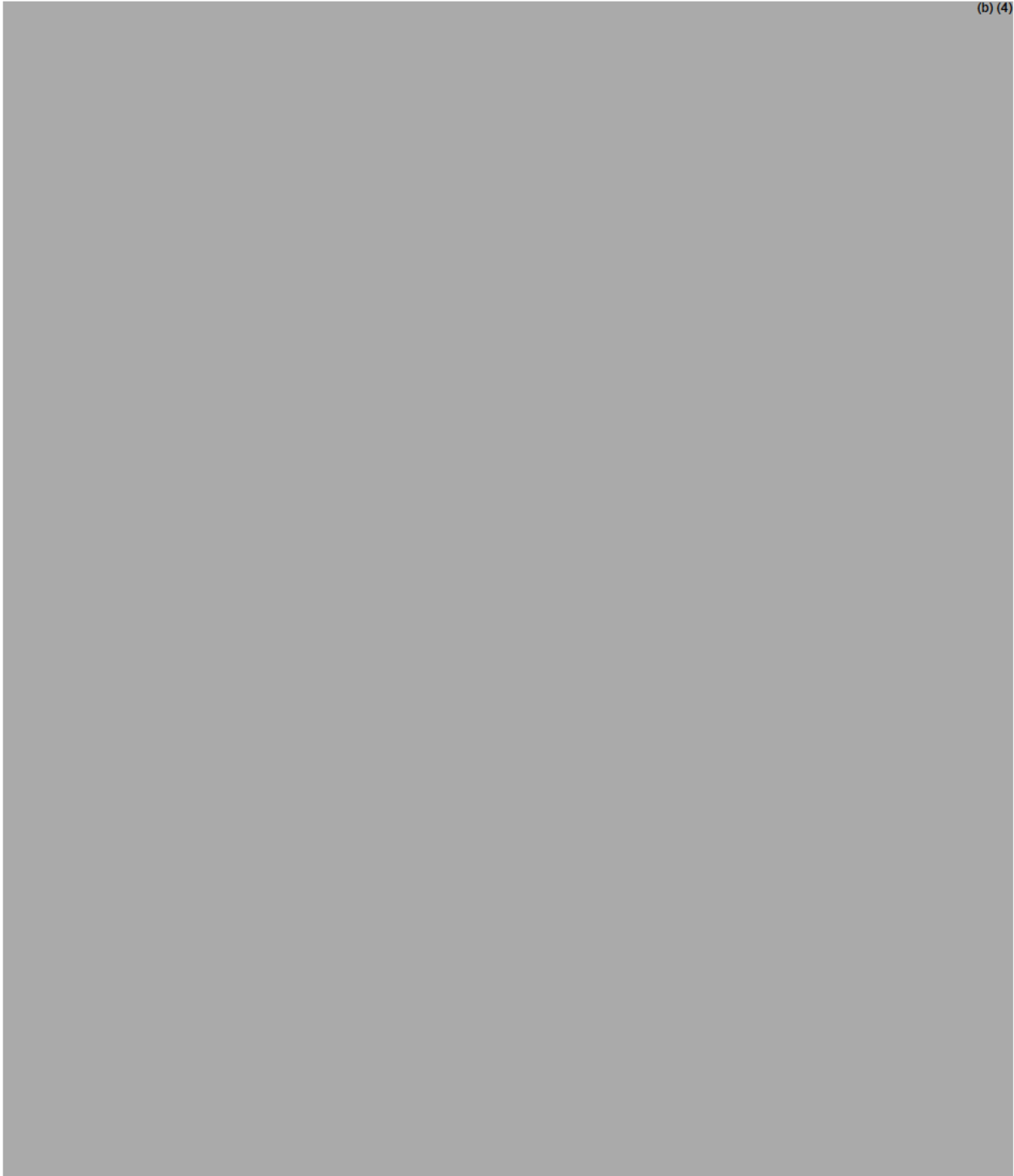
¹⁵¹ Footnote as in the guidance-generating review:

“<http://www.fda.gov/downloads/Drugs/Guidances/ucm070573.pdf>”

¹⁵² Footnote as in the guidance-generating review: “As determined by USP <601> apparatus B.”

strength. However, for the 100/50 mcg and 250/50 mcg strengths, typical sample concentration range is difficult to check as the raw data for these strengths are too granular. Therefore, the no QC issue for APSD studies at these 2 strengths will be evaluated upon receipt of the firm's complied raw data.

5.3.2.2.2 Validation Summary Table for Aerodynamic Particle Size Distribution



Comments on Method Validation:

- Similar to the SAC study, it is noted that method validation results for the current Method # MGR-METH-546069 (Section C of this method) is almost the same as method validation results for Method # MDR-RGMETH-0031 (12/29/2015 submission, Module 3.2.P.5.3\Aerodynamic Particle Size Distribution Validation Report – MDR-RGMETH-0031). For the former method validation results, the firm also included “achievable LOQ of method” that was not reported in the latter method validation report. According to the firm¹⁵³, the former method is equivalent (i.e. employ the same preparation, the same chromatographic conditions and the same method of quantification) to the latter method. The firm will be asked to clarify if these are the same method validation studies, and

¹⁵³ GS Review: ANDA 208891, Response to ECD/Bioequivalence, 9/22/2016 (Module 1.2\Cover Letter..., p. 2 of 18).

provide street address as well as study dates for their method validation studies for each of these 2 methods.

Based on the firm's submissions to the current ANDA, it is unclear whether the method validation studies were conducted at the same study site as the in vitro BE studies. However, based on OSIS findings, it is clear that method validation and in vitro BE studies for the 100/50 and 500/50 mcg strengths were conducted at different sites. Similar to the HPLC method validation in Section 5.3.2.1.2, the firm will be asked to provide method transfer report, as method transfer studies (e.g. precision and accuracy study for the SAC method) are needed to support method transfer between different study sites.

- The firm conducted method validation of APSD at 60 L/min using (b) (4).
- The firm did not evaluate UPLC analytical method accuracy, method precision, and intermediate precision. Instead, the firm evaluated repeatability, and intermediate precision for the APSD method validation. In addition, for accuracy/recovery study, the firm (b) (4). The firm will be asked to validate accuracy (% recovery at the high and low concentrations) and precision/intermediate precision of the UPLC method. Accuracy and precision should be evaluated with known amounts of FP and SA relevant to expected sample concentrations spiked into placebo solution.
- The firm conducted solution stability study for stock standard solutions and working standard solutions of 7 days at ambient laboratory temperature, which covers the storage period of up to 7 days for all APSD studies (057755-02-04, MGF-PRO-2015-080, 057755-02-07, MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093).

The firm also conducted solution stability study for test sample solutions of 6 days at refrigerated temperature. The firm did not specify what test sample solution is in the APSD method validation report, but according to the SAC method validation report, which also contains test sample solution stability study, test sample solution appears to involve the use of test devices. The firm stated that in all APSD studies, test sample solutions were stored at 5°C for periods up to 5 days, except that one set of APSD test solutions generated from a single test sample (test lot #631-003, beginning lifestage testing, (b) (4)) was injected up to 4 hrs beyond the 6-day period. The reviewer will exclude this set of data from statistical analysis.

- Please refer to Section 5.3.2.1.2 for reviewer's comment on the issue regarding % organic affecting SA peak retention time.

¹⁵⁴ GS Review: ANDA 208891, Response to ECD/Bioequivalence, 1/12/2017 (Module 1.2\Cover Letter..., p. 15 of 21)

The firm's UPLC method validation is **incomplete**.

5.3.2.2.2 Validation Table for Cascade Impaction

According to the firm, the intermediate precision was performed on the test and RLD products on each of the 100/50 mcg and 500/50 mcg strengths. Each analyst prepared one (b) (4) replicate per experiment, and prepared a total of 2 (b) (4) replicates per device, per day using the following test plan.

Experiment	Day	Analyst	(b) (4) workstation	Device number	UPLC system and column*
1	1	1	2	1	1
2	1	2	2	2	2
3	1	2	1	1	2
4	1	1	1	2	1
5	2	2	2	1	1
6	2	1	2	2	2
7	2	1	1	1	2
8	2	2	1	2	1

* Firm's note: 3 columns were used for this study. As this increased the sources of variability it was an approved deviation.

Does Firm's SOP include validation criteria? (Y/N)	The firm did not submit SOP for method validation, and the validation report provided did not have acceptance criteria.
Comments on Firm's SOPs and Criteria (Acceptable/ or Explain)	The firm stated that since intermediate precision is performed on drug product (and therefore method and product both contribute to variability), no acceptance criteria were set. Since the firm's %RSD for the intermediate precision study are reasonable, and the product specific guidance or Nasal Spray Guidance does not have specific requirement for method validation acceptance criteria, the reviewer will not pursue this issue further.

Comments on Method Validation:

- As mentioned above, the firm will be asked to provide street address and study dates for method validation studies. Based on the firm's submissions to the current ANDA, it is unclear whether the method validation studies were conducted at the same study site as the in vitro BE studies. However, based on OSIS findings, it is clear that method validation and in vitro BE studies for the 100/50 and 500/50 mcg strengths were conducted at different sites. Similar to the HPLC method validation in Section 5.3.2.1.2, the firm will be asked to provide method transfer report, as method transfer studies (e.g. precision study for the APSD method) are needed to support method transfer between different study sites. The firm will be advised that method transfer studies for the APSD method should be conducted using unexpired RLD product.
- The firm conducted method validation for APSD at 60 L/min using (b) (4). However, the firm did not specify the actuation time or volume of air drawn through the delivery system for the intermediate precision study of APSD, and thus will be asked to clarify so.
- The firm will be asked to provide dose counter number used for this intermediate precision study for each of the test and RLD device.
- For the intermediate precision study for APSD, the firm used the same test and RLD devices as compared to those used in the intermediate precision study for SAC. As mentioned in Section 5.3.2.1.3, the firm will be asked to provide COA of these test and RLD devices lots.
- According to the method validation report, 3 columns were used in the study. However, in the firm's test plan table on p. 9 of 26 of the method validation report

for MDR-RGMETH-0031, only 2 columns were listed. Therefore, the firm will be asked to clarify this discrepancy.

- According to the method validation report (p. 12 of 26), the firm stated that “testing for the 100/50 strength was not completed within 30 days of removing the device from the pouch. Testing started 7/3/2013 and the final test date was 8/13/2013. The intermediate precision data demonstrated that there was no adverse effect on the product. The out of pouch stability has been confirmed in the registration stability studies.” RLD labeling states that “[s]afely throw away ADVAIR DISKUS in the trash 1 month after you open the foil pouch or when the counter reads 0, whichever comes first.” Since the test product is 41 days after removing from the pouch (vs. 1 month as recommended in the RLD labeling), and intermediate precision data are still within a reasonable range, the reviewer will not pursue this issue further.
- As mentioned above, the firm conducted intermediate precision study using different days, analysts, (b) (4) workstations, devices and UPLC system and columns. It is noted that for RLD device at the 100/50 mcg strength, one experiment [experiment#7 (highlighted in table above): Day 2, Analyst 1, (b) (4) workstation 1, Device number 1, UPLC system and column 2] had FP amount in the mouth piece and throat (MT) markedly higher than other experiments (95.735 mcg in experiment #7 vs. mean of 20.1 mcg for other experiments). The firm stated that this was possibly due to contamination of the MT sample. It should be noted that all other results showed reasonable %RSD. Therefore, the reviewer will not pursue this issue further.

5.3.2.2.3 Results Summary – Aerodynamic Particle Size Distribution

Firm’s results - ISM

Flow Rate (L/min)	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
30	FP	BoL	(b) (4)					
		EoL						
	Sal	BoL						
		EoL						
60	FP	BoL						
		EoL						
	Sal	BoL						
		EoL						
90	FP	BoL						
		EoL						
	Sal	BoL						
		EoL						

* The firm provided mass balance of individual unit in the study report in pdf format, but not in the SAS dataset. In the SAS dataset, the firm provided values for mass balance in amount (mcg), not % of labeled claim. Therefore, the reviewer calculated the arithmetic mean and range of mass balance using the firm's mass balance (mcg) data in the SAS dataset divided by target emitted dose of 93 mcg for FP and 45 mcg for SA, which is the calculation method stated by the firm in the study report. Please note that these target emitted dose values are from USP monograph under testing condition with air flow rate of 60 L/min for 2 seconds. According to the RLD labeling, these values are also what RLD product delivers under standardized in vitro test conditions when tested at a flow rate of 60 L/min for 2 seconds. The RLD labeling and USP monograph does not mention delivered dose or target emitted dose for flow rate at 30 L/min and 90 L/min.

Reviewer's Comments:

- According to study protocol, the APSD study should be performed at dose counter #59 for beginning lifestage and #2 for end lifestage. As detailed in the SAC study, if a sample is lost due to an assignable cause (e.g., (b) (4) tube leakage, dropped (b) (4) plate, etc.) during sample preparation in beginning or middle lifestage, further collection/recovery of the lost sample will be ceased, and a new sample will be prepared from the next dose(s) (may be performed within ± 3 doses of those stated) of the same device per the test method.

The reviewer checked the firm's SAS dataset, and noticed that the following samples had dose counter number other than #59 and #2, thus the original samples were likely lost. The firm will be asked to explain the detailed reason of their corresponding sample loss and provide supporting document as well as corrective action taken. The firm will also be asked to provide the same information for any additional "next dose" repeat they identified in the study.

¹⁵⁵ Please note that for reference product at 60 L/min, n=119. This is because the firm stated that 1 sample in reference batch 5ZP8178 at 60 L/min flow rate had "No acceptable data generated for both FP and Sal" (please see details in the reviewer's comment below).

Flow Rate	Product	Batch	Unit	Stage	Dose Counter Number
30	REF	4ZP3863	4	BOL	58
30	REF	5ZP8178	12	BOL	58
30	REF	5ZP8178	9	BOL	58
30	TEST	631-001	9	BOL	58
30	TEST	631-002	5	BOL	58
30	TEST	631-003	2	BOL	58
30	TEST	631-003	3	BOL	58
60	REF	4ZP3863	33	BOL	58
60	REF	4ZP3863	40	BOL	57
60	REF	5ZP8178	34	BOL	58
60	REF	5ZP8178	36	BOL	58
60	REF	5ZP8397	27	BOL	58
60	REF	5ZP8397	33	BOL	58
60	REF	5ZP8397	37	BOL	58
60	TEST	631-003	27	BOL	58
90	TEST	631-002	56	BOL	58

- It is also note that the firm repeated 15 samples using new devices, and each of these 15 samples were repeated for both FP and SA. Please note that beginning and end lifestages should be from the same device. Nevertheless, given the multiple incidences of alternative actuation/alternative devices throughout the in vitro BE studies, the firm will be asked to explain and provide supporting documents for them (please see details below), and explain why there are multiple incidences of alternative actuation/replacement device, and the impact of it on the in vitro BE studies.

The firm provided the reason for original sample rejection below.

- Among the 15 samples, the firm stated that the following 12 samples did not have the original data generated due to analysis being stopped prior to

- data generation.

Number	Product	Batch number	Original inhaler number	Replacement inhaler number	Flow rate (L/min)	Reason for replacement
1	Advair	4ZP3863	10	116	30	For 10 instances of APSD at end of life the mouth and throat samples were stored at ambient rather than 5°C prior to analysis in error. Hence the original preparations were not tested and new replacement inhalers were tested.
2	MGR001	631-002	7	111	30	
3	Advair	5ZP8178	18	115	30	
4	Advair	5ZP8397	2	112	30	
5	Advair	5ZP8178	1	113	30	
6	MGR001	631-001	8	112	30	
7	MGR001	631-001	20	113	30	
8	MGR001	631-003	5	111	30	
9	Advair	5ZP8178	7	114	30	
10	Advair	4ZP3863	1	115	30	
11	MGR001	631-001	57	111	90	Pipetting error into cup 4 observed during preparation; analysis halted
12	Advair	4ZP3863	53	114	90	Incorrect volume pipetted into cup 6; analysis halted.

- For all the 12 samples above, the reviewer considers the firm's reason for original sample rejection (please see details in the table above) acceptable. According to the study report, these are end of lifestages samples. The reviewer checked the dose counter number provided in the SAS dataset, and noticed that dose counter #2 were used. Therefore, the reviewer agrees that these samples were at the end lifestage. However, it should be noted that the firm only repeated the sample at the end lifestage in the above replacement devices.
- For the remaining 3 samples, the firm stated that the original data was generated, and the firm provided reason for original sample rejection below:

Number	Product	Batch number	Original inhaler number	Replacement inhaler number	Flow rate (L/min)	Reason for replacement
13	Advair	4ZP3863	21	112	60	Very low results for mouth and throat stage for both APIs. (b) (4) investigation (b) (4), concluded lab error and replacement device was tested.
14	Advair	5ZP8178	32	112	60	High Fluticasone propionate result for mouth and throat sample. Salmeterol value as expected. (b) (4) investigation (b) (4), concluded lab error and replacement device was tested.
15	Advair	4ZP3863	25	113	60	Poor chromatography (broad peaks) in mouth and throat test sample. (b) (4) (b) (4), concluded lab error and replacement device tested.

- According to study protocol (P20987.00, p. 8 of 9), atypical results will be handled according to the current version of (b) (4) SOP (b) (4). Therefore, the firm will be asked to provide SOP (b) (4) that was effective at the time of the in vitro studies in current application.
- For sample #s 13 and 14 above, the firm provided (b) (4) (b) (4). In this investigation report, the firm considered that during sample collection using methanol and buffer and then top off the volumetric flask with methanol, these 2 samples were not mixed well. It was suspected that for sample #13, an area of the volumetric flask was sampled that contained a lower concentration of analytes, whereas for sample #14, an area of high concentration was sampled.

For the lack of increased SA (compared to corresponding increased FP) in sample #14, the firm suspected that it was due to lesser solubility properties of FP compared to SA, which leads to an area being sampled containing a high concentration of FP, and because SA is more soluble, it was already fully dissolved and more homogenous with the sample solution.

The firm also conducted solution verification by injecting the original and duplicated vial (retained) solutions in duplicate (please see results below). The originally prepared solutions stored

in volumetric flask were not re-injected as they were discarded after obtaining duplicate aliquots.

			Original Vial, re-capped	Duplicate, retained vial
Sample #13	FP (mcg)	Replicate 1	4.467	6.929
		Replicate 2	4.465	7.131
	SA (mcg)	Replicate 1	2.940	2.927
		Replicate 2	3.397	2.780
Sample #14	FP (mcg)	Replicate 1	123.318	123.358
		Replicate 2	123.246	123.256
	SA (mcg)	Replicate 1	10.278	10.074
		Replicate 2	10.002	10.060

The firm stated that as once aliquot of sample solution in a transfer pipette can be used to fill the duplicate vials, it explains the consistency of analyte values obtained during solution verification for sample #14, and does not contradict the idea that the sample solutions were not homogenous as seen in the inconsistent values for FP in sample #13.

These sample repeats will be evaluated upon receipt of the firm’s SOP (b) (4) which contains information on atypical result handling.

- For sample #15 that was repeated due to poor chromatograms (broad peaks), the reviewer checked the chromatography for the original sample, and noticed that SA had a broad peak as compared to typical SA peaks. Therefore, the reviewer considers the original sample rejection acceptable. However, it should be noted that the firm only repeated the sample at the beginning lifestage in the above replacement devices.

Please note that the firm did not perform solution verification, as the time elapsed between analysis and when the atypical chromatography was found during QC review well after the solutions were expired. The originally prepared solutions stored in volumetric flasks were not re-injected as they were not retained from the day of testing.

- According to study report MGR-REP-2015-096, version 1.0, p. 40 of 178, the firm stated that “No acceptable data generated for both FP and Sal” for the following sample. The firm will be asked to provide the data obtained as well as supporting document for why this data was not acceptable. The firm will also be asked to provide SOP that pre-defines data acceptability.

Product	Batch Number	Unit	Flow Rate (L/min)	Lifestage
REF	5ZP8178	159	60	BOL

- Due to aforementioned missing information, the reviewer could not verify the firm's results summary at this time.

5.3.2.2.4 In Vitro PBE Analysis

As detailed above, analysis will be carried out pending the firm's additional information lost samples and repeat analysis.

5.3.2.2.5 Conclusions

AERODYNAMIC PARTICLE SIZE DISTRIBUTION		
REVIEW OF TESTING METHODS:		
Is the testing method for CI test validated?	Yes, but with deficiencies	
Is the analytical method (e.g. HPLC) validated?	Yes, but with deficiencies	
Is the analytical method sufficiently sensitive?	Yes	
Is testing conducted as per RLD labeling?	To be determined	
What is the size of the induction port (or expansion chamber) used for testing?	N/A	
Are ≤ 10 actuations used for cascade impactor study?	Yes (1 actuation)	
If >1 actuation, what is the # of actuations used?	N/A	
Are the testing methods acceptable?	INCOMPLETE	
If not, why?	Due to deficiencies in method validation and study information.	
STUDY RESULTS:		
Is drug deposition reported in mass units?	Yes	
Is the mass balance data reported?	Yes in the study report (pdf format) for individual units, but not in the summary table or SAS .xpt file.	
Results	Does Impactor Size Mass data pass PBE?	To be determined
	Does ISM data pass modified chi-square ratio test?	To be determined
	Do mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle dose (FPD) pass PBE?	To be determined
If not, why?	Pending the firm's additional information on repeat analysis.	

Comments:

The firm's pivotal APSD study for the 100/50 mcg strength is **incomplete**.

5.3.2.2.6 Deficiencies / Recommendations

Please see Section 4.10.

APPEARS THIS WAY ON
ORIGINAL

5.3.2.3 Single Actuation Content through Container Life – 250/50 mcg strength

5.3.2.3.1 Study Information

Study No.	MGR-PRO-2015-080
Study Site	Mylan Global Respiratory Group IPC008, Discovery Park House, Floor 3 Sandwich, Kent. CT13 9ND. UK
Principal Investigator	Elizabeth Clift Karen Weaver
Study Dates	9/21/2015 to 10/30/2015
SOP No.	MGR-METH-546070 (v. 7.0)
SOP Effective Date	12/22/2014
SOP Title	Determination of emitted dose of MGR001 (PF-04764793) from multidose powder inhalation devices using (b) (4)
Test Method Description	(b) (4) for Dry Powder Inhalers (DPIs) is used to determine the emitted dose (ED) of MGR001 (PF-04764793) in 100/50, 250/50 and 500/50 µg multidose dry powder inhalers containing 100, 250 or 500 µg Fluticasone propionate and 50 µg salmeterol as xinafoate salt respectively and for Advair® Diskus® and Seretide® Accuhaler® Reference Listed Drug (RLD).
Testing Equipment Used (e.g., name, model, etc)	USP <601> Apparatus B with modified end caps
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	30, 60 or 90 L/min flow rate; 2 L volume. Testing carried out at ambient laboratory conditions.
Analytical Method Description	(b) (4)
Analytical Equipment Used (e.g., name, model, etc.)	(b) (4) UPLC

Comments:

Reviewer's note: The firm's study protocol (MGR-PRO-2015-080, version 3.0) for the current study is similar to the study protocol (P20987.00) for the 100/50 mcg strength SAC study. The reviewer has the same comments regarding the study information as compared to the 100/50 mcg strength SAC study (please see reviewer's comments in Section 5.3.2.1.1) except the firm did not specify target emitted dose and reviewer have different comments regarding raw data and chromatograms as detailed below. The reviewer also have additional comments about study protocol as detailed below.

- (b) (4)
However, it is noted that the firm did not submit 100% raw data, as there are many instances that the result IDs in the run are not consecutive (e.g. 9/22/2016 submission, Module 3.2.P.2\Attachment 4-4 – MGR-PRO-2015-080 –

250/50 mcg – SAC Raw Data – Comment 4 – Sequence 0009, p. 4 of 740, result IDs 30078, 30088-30077 were missing). In addition, it is noted that raw data for blank/diluent, system suitability S1 or S2, standard check S1 and S2 are not included in raw data for SAC studies. Similarly, blank/diluent, system suitability standard SHL, LOQ, standard check SHL and SLL were not included in raw data for APSD studies. Moreover, raw data for stage 7, stage 8 for many samples (e.g. p. 6 of aforementioned document) were not included in the raw data for APSD study. Therefore, the firm will be asked to submit 100% raw data (including blank/diluent, standards, etc.) in run sequence order.

- It is noted that the study protocol provided by the firm is version 3.0 [version updates included details about the repeat testing at 90 L/min to be conducted (please see Section 5.3.2.4.3 for details)], and was signature on 11/13/2015, which was after the study completion date (10/30/2015). The firm will be asked to provide the effective date of the 2 previous versions of the protocol, and study dates of the repeated APSD study for the 90 L/min flow rate.

5.3.2.3.2 Analytical Method Validation for UPLC

- It is noted that this study was conducted at a different study site (Mylan Global Respiratory Group, Sandwich, Kent, UK) as compared to SAC studies for the other 2 strengths ((b) (4)). Currently it is unknown where the method validation studies were conducted. Therefore, the firm will be advised that if any in vitro BE studies were conducted at different site as compared to the method validation studies, the firm should provide partial method validation data (e.g. accuracy and precision test of the UPLC method) to support method transfer between study sites.
- The firm conducted method validation for method MDR-RGMETH-0032, which, according to the firm¹⁵⁶, is equivalent (i.e. employ the same preparation, the same chromatographic conditions and the same method of quantification) to the method MGR-METH-546070 used for this SAC study.

The firm also stated that the (b) (4) methods differs only in the system suitability requirement for the SA retention time, which was due to the dwell volume of the ultra-HPLC instruments used by (b) (4) . However, the reviewer noticed that all of MDR-RGMETH-0032 (12/29/2015 submission, Module 3.2.P.5.2\Analytical Procedures – Uniformity of Delivered Dose by UPLC – MDR-RGMETH-0032, p. 5 of 8), Mylan’s (9/22/2016 submission, Module 3.2.P.2\Attachment 1-1..., p. 13 of 41) and (b) (4) (9/22/2016 submission, Module 3.2.P.2\Attachment 1-4..., p. 11 of 40) method MGR-METH-546070 had system suitability requirement for SA retention time (b) (4) . Therefore, the firm will be asked to clarify this discrepancy.

¹⁵⁶ GS Review: ANDA 208891, Response to ECD/Bioequivalence, 9/22/2016 (Module 1.2\Cover Letter..., p. 2 of 18).

5.3.2.3.3 Calibration of Manual and/or Automated Spray Pump Actuator (For the Single Actuation Content Study)

- As detailed above, it is noted that this study was conducted at a different study site as compared to SAC studies for the other 2 strengths. Currently it is unknown where the method validation studies were conducted. Therefore, the firm will be advised that if any in vitro BE studies were conducted at different site as compared to the method validation studies, the firm should provide partial method validation data (e.g. precision study for the SAC method using unexpired RLD product) to support method transfer between study sites.

5.3.2.3.4 Results Summary

Firm's results

Flow Rate (L/min)	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
30	FP	BoL	231.06	195.91	1.18	8.51	39.73	0.21
		EoL	235.25	229.26	1.03	8.14	20.73	0.39
		MoL	236.66	239.46	0.99	9.75	11.87	0.82
	Sal	BoL	46.76	38.61	1.21	1.44	7.86	0.18
		EoL	47.47	45.11	1.05	1.23	4.07	0.30
		MoL	47.47	47.10	1.01	1.53	2.36	0.65
60	FP	BoL	240.25	229.60	1.05	11.98	7.12	1.68
		EoL	241.73	246.77	0.98	9.61	9.90	0.97
		MoL	244.18	240.70	1.01	13.11	8.73	1.50
	Sal	BoL	48.21	45.37	1.06	1.66	1.48	1.12
		EoL	48.61	48.51	1.00	1.53	1.93	0.79
		MoL	48.90	47.30	1.03	2.23	1.78	1.26
90	FP	BoL	242.21	232.07	1.04	8.85	8.15	1.09
		EoL	245.03	249.79	0.98	8.36	5.49	1.52
		MoL	249.78	242.85	1.03	10.60	7.89	1.34
	Sal	BoL	48.65	45.73	1.06	1.60	1.69	0.95
		EoL	49.06	49.07	1.00	1.52	1.10	1.39
		MoL	49.61	47.64	1.04	1.98	1.56	1.27

Reviewer's Comments:

- The firm did not provide actual dose counter numbers in the SAS .xpt dataset, thus the reviewer is unable to verify whether the actuation used was at the beginning, middle and end lifestages of the device. Therefore, same as the SAC study for the 100/50 mcg strength, the firm will be asked to add a column for dose counter number in their SAC SAS .xpt dataset. In addition, for those samples that were lost and "next dose" of the same device was measured, the firm will be

asked to provide detailed cause of sample loss as well as supporting documents (e.g. investigational report) for these sample loss.

- It is also noted that the firm repeated 1 sample using new devices for both FP and SA. Please note that beginning, middle and end lifestages should be from the same device. Nevertheless, given the multiple incidences of alternative actuation/alternative devices throughout the in vitro BE studies, the firm will be asked to explain and provide supporting documents for them (please see details below), and explain why there are multiple incidences of alternative actuation/replacement device, and the impact of it on the in vitro BE studies.

The firm provided the reason for its original sample rejection below. The firm also stated that this sample did not have the original data generated due to analysis being stopped prior to data generation.

Number	Product	Batch Number	Unit	Flow Rate (L/min)	Lifestage	Reason for replacement
1	TEST	631-009	293R	90	EOL	Incorrect actuation time for initial replicate.

For this original sample, the firm stated that incorrect actuation time was used for the initial replicate. Since actuation time is set the same for all units, the firm will be asked to explain how this incorrect actuation time was found out and whether other units also had incorrect actuation time.

- The firm did not provide % of label claim in their SAS dataset, and thus will be asked to add a column for this in the SAS .xpt file.
- Due to aforementioned missing information, the reviewer could not verify the firm's results summary at this time.
- The firm did not provide % of label claim in their SAS dataset, and thus will be asked to add a column for this in the SAS .xpt file.
- Based on the firm's results, it is noted that RLD product had lower FP and SA emitted dose as compared to the test product at beginning lifestages at 30 L/min flow rate. It is also noted that RLD had high variability for FP at beginning and end lifestages at 30 L/min flow rate. The reviewer checked study data for each individual unit, and found that RLD batches had multiple samples that had low emitted dose for FP and SA at beginning lifestages at 30 L/min flow rate.

5.3.2.3.5 In Vitro PBE Analysis

As detailed above, analysis will be carried out pending the firm's additional information on actual dose counter number, % of label claim, lost samples and repeat samples.

5.3.2.3.6 Conclusions

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE		
REVIEW OF TESTING METHODS:		
Is the testing method validated?	Yes, but with deficiencies	
Is the Quantitative Analytical Method Validated? (e.g., HPLC)	Yes, but with deficiencies	
Is the method sufficiently sensitive?	Yes	
Is testing performed as per RLD labeling?	To be determined	
Are data measured at both beginning, middle & end lifestages?	Yes	
Is testing a single actuation per determination?	Yes	
If yes, what is the actuation number tested?	Study protocol states that dose counter #s 60 (beginning), 30 (middle) and 1 (end) were to be used. The firm did not provide actual dose counter number , and thus will be asked to provide so.	
Are the testing methods acceptable?	INCOMPLETE	
If not, why?	Due to deficiencies in method validation and study information.	
STUDY RESULTS:		
Are data expressed as actual amount and % of label claim?	No	
Is the geo-mean of the test product (% of label claim) within 95-105%?	Beginning	To be determined
	Middle	To be determined
	End	To be determined
Are the PBE results acceptable?	To be determined	
If not, why?	Pending additional information about actual dose counter numbers, % of label claim, and repeat samples.	

Comments:

The firm's pivotal SAC study for the 250/50 mcg strength is **incomplete**.

5.3.2.3.7 Deficiencies / Recommendations

Please see Section 4.10.

5.3.2.4 Aerodynamic Particle Size Distribution (APSD) – 250/50 mcg strength

5.3.2.4.1 Study Information

Study No.	MGR-PRO-2015-080
Study site	Mylan Global Respiratory Group IPC008, Discovery Park House, Floor 3 Sandwich, Kent. CT13 9ND. UK
Principal Investigator	Elizabeth Clift Karen Weaver
Study dates	9/21/2015 to 11/25/2015
SOP No.	MGR-METH-546069 (v. 6.0)
SOP Effective Date	12/22/2014
SOP Title	Determination of aerodynamic particle size distribution of MGR001 (PF-04764793) dry powder inhaler products at 60 l per minute using a (b) (4) Impactor (b) (4) by UPLC.
Testing Method Description	(b) (4) Impactor (b) (4) is used to determine the aerodynamic particle size distribution (APSD) of PF-04764793 in 100/50, 250/50 and 500/50 µg MGR001 dry powder inhaler products containing 50 µg salmeterol as xinafoate salt and 100, 250 or 500 µg fluticasone propionate respectively and for Advair® and Seretide® Accuhaler®.
Testing Equipment Used (e.g., name, model, etc)	USP <601> Apparatus 5
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	30, 60 or 90 L/min flow rate; 4 L volume. Testing carried out at ambient laboratory conditions.
Analytical Method Description	(b) (4)
Analytical Equipment Used (e.g., name, model, etc)	(b) (4) UPLC

Comments:

Reviewer's note: The firm's study protocol (MGR-PRO-2015-080, version 3.0) for the current study is similar to the study protocol (P20987.00) for the 100/50 mcg strength APSD study. The reviewer has the same comments regarding the study information as compared to the 100/50 mcg strength APSD study (please see reviewer's comments in Section 5.3.2.2.1), except that the firm has different definition for mass balance as detailed below.

- Mass Balance (MB): calculated as % "TDD". TDD values are taken from patient information for Advair® Diskus® (45 mcg for SA and 233 mcg for FP).

Please note that according to the RLD labeling³⁰, under standardized in vitro test conditions, RLD delivers 233 mcg of FP and 45 mcg of SA per blister from

Advair Diskus 250/50, when tested at a flow rate of 60 L/min for 2 seconds. This is also the target emitted dose in USP monograph for Fluticasone Propionate and Salmeterol Inhalation Powder. Please note that RLD labeling and USP monograph did not mention delivered dose or target emitted dose for flow rate at 30 L/min and 90 L/min.

According to guidance-generating review¹⁵⁷, the total mass of drug collected on all stages¹⁵⁸ and accessories should be between 85 and 115%¹⁵⁹ of label claim on a per actuation basis¹⁶⁰.

5.3.2.4.2 Validation Summary Table for Aerodynamic Particle Size Distribution

5.3.2.4.2.1 Analytical Method Validation for UPLC

- Similar to the SAC study for the 250/50 mcg strength, It is noted that this study was conducted at a different study site as compared to SAC studies for the other 2 strengths. Currently it is unknown where the method validation studies were conducted. Therefore, the firm will be advised that if any in vitro BE studies were conducted at different site as compared to the method validation studies, the firm should provide partial method validation data (e.g. accuracy and precision test of the UPLC method) to support method transfer between study sites.
- The firm conducted method validation for method MDR-RGMETH-0031, which, according to the firm¹⁶¹, is equivalent (i.e. employ the same preparation, the same chromatographic conditions and the same method of quantification) to the method MGR-METH-546069 used for this APSD study.

The firm also stated that the (b) (4) methods differs only in the system suitability requirement for the SA retention time, which was due to the dwell volume of the ultra-HPLC instruments used by (b) (4). However, the reviewer noticed that all of MDR-RGMETH-0031 (12/29/2015 submission, Module 3.2.P.5.2\Analytical Procedures – Aerodynamic Particle Size Distribution by UPLC – MDR-RGMETH-0031, p. 4 of 8), Mylan’s (9/22/2016 submission, Module 3.2.P.2\Attachment 1-2..., p. 14 of 40) and (b) (4) (9/22/2016 submission, Module 3.2.P.2\Attachment 1-4..., p. 14 of 40) method MGR-METH-546070 had system suitability requirement for SA retention time (b) (4). Therefore, the firm will be asked to clarify this discrepancy.

¹⁵⁷ V:\Science Group\Master Files BE Posting\Fluticasone Propionate_Salmeterol Xinafoate_021077\Fluticasone Propionate_Salmeterol Xinafoate_21077_RC09-13.doc, p. 14 of 62.

¹⁵⁸ Footnote as in the guidance-generating review: “Total mass of drug includes drug deposition on each individual site, to include the mouthpiece adapter, throat, preseparator, and each stage of the impactor including the filter, is requested.”

¹⁵⁹ Footnote as in the guidance-generating review:
“<http://www.fda.gov/downloads/Drugs/Guidances/ucm070573.pdf>”

¹⁶⁰ Footnote as in the guidance-generating review: “As determined by USP <601> apparatus B.”

¹⁶¹ GS Review: ANDA 208891, Response to ECD/Bioequivalence, 9/22/2016 (Module 1.2\Cover Letter..., p. 2 of 18).

5.3.2.4.2.2 Validation Table for Cascade Impaction

- As detailed above, it is noted that this study was conducted at a different study site as compared to APSD studies for the other 2 strengths. Currently it is unknown where the method validation studies were conducted. Therefore, the firm will be advised that if any in vitro BE studies were conducted at different site as compared to the method validation studies, the firm should provide partial method validation data (e.g. precision study for the APSD method using unexpired RLD product) to support method transfer between different study sites.

5.3.2.4.3 Results Summary – Aerodynamic Particle Size Distribution

Firm's results - ISM

Flow Rate (L/min)	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
30	FP	BoL						
		EoL						
	Sal	BoL						
		EoL						
60	FP	BoL						
		EoL						
	Sal	BoL						
		EoL						
90	FP	BoL						
		EoL						
	Sal	BoL						
		EoL						

(b) (4)

(b) (4)

Reviewer's Comments:

- According to study protocol, the APSD study should be performed at dose counter #59 for beginning lifestage and #2 for end lifestage. Same to the 100/50 mcg strength in vitro BE study, if a sample is lost due to an assignable cause (e.g., (b) (4) tube leakage, dropped (b) (4) plate, etc.) during sample preparation in beginning or middle lifestage, further collection/recovery of the lost sample will be ceased, and a new sample will be prepared from the next dose(s) (may be performed within ± 3 doses of those stated) of the same device per the test method.

The reviewer checked the firm's SAS dataset, and noticed that the following samples had dose counter number other than #59 and #2, thus the original samples were likely lost. The firm will be asked to explain the detailed reason of their corresponding sample loss and provide supporting document as well as corrective action taken. The firm will also be asked to provide the same information for any additional "next dose" repeat they identified in the study.

Flow Rate	Product	Batch	Unit	Stage	Dose Counter Number
30	REF	5ZP0114	97	BOL	58
60	REF	5ZP9304	187	BOL	57
60	REF	5ZP9304	192	BOL	58
60	REF	5ZP9882	237	BOL	58
60	TEST	631-008	147	BOL	58
60	TEST	631-009	175	BOL	58
90	REF	5ZP9304	425	EOL	1
90	TEST	631-008	383	BOL	58

- It is also noted that the firm repeated 9 samples using new devices, and each of these 9 samples were repeated for both FP and SA. Please note that beginning and end lifestages should be from the same device. Nevertheless, given the multiple incidences of alternative actuation/alternative devices throughout the in vitro BE studies, the firm will be asked to explain and provide supporting documents for them (please see details below), and explain why there are multiple incidences of alternative actuation/replacement device, and the impact of it on the in vitro BE studies.

The firm provided the reason for their original sample rejections below.

- Among the 9 samples, the firm stated that the following 3 samples did not have the original data generated due to analysis being stopped prior to data generation.

Number	Product	Batch Number	Unit	Flow Rate (L/min)	Lifestage	Reason for replacement
1	REF	5ZP0114	91R	30	BOL	Error during sampling. Mouth and throat samples were washed into the same volumetric flask.
2	TEST	631-008	37R	30	BOL	
3	REF	5ZP0114	327R	90 (original)	EOL	Error during firing of the initial device

- For sample #s 1 and 2 above, since according to the study method (MDR-RGMETH-0031, Section 6.2.2, step 1), mouth and throat samples were to be washed into the same flask for each device, the firm will be asked to explain why this was considered as an error.
 - For sample #3 above, since it is with the original run that was rejected due to flow meter issue (please see details below), they will not be evaluated.
- For the following 5 samples, the firm stated that the original data was generated, and provided reason for original sample rejection below:

Number	Product	Batch Number	Unit	Flow Rate (L/min)	Lifestage	Reason for replacement
1	REF	5ZP9304	198R	60	BOL	Poor chromatography affecting integration. Samples reached expiry therefore could not be re-injected
2	REF	5ZP9882	240R	60	BOL	Stage 5 being sampled instead of stage 4.
3	TEST	631-007	248R	90 (original)	BOL	Poor chromatography affecting API peak resolution
4	REF	5ZP9882	348R	90 (original)	EOL	Lack of cup coating reagent applied to at least some of the ^{(b) (4)} cups used for the replicate
5	TEST	631-007	367R	90 (repeat)	BOL	Poor chromatography (broad peaks)

- For samples #s 3 and 4, since they are with the original run that was rejected due to flow meter issue (please see details below), they will not be evaluated.

- For samples #s 1 and 5 above, the reviewer verified that the original samples had poor chromatography, and agrees that these samples be repeated. However, it should be noted that the firm only repeated the sample at the beginning lifestage in the replacement devices.
- For sample #2 above, the firm will be asked to explain how this “stage 5 being sampled instead of stage 4” was found out.
- For the following sample, the study report showed that it was repeated with a new device [study report MGR-PRO-REP-2015-080 version 1.0 (p. 83 and 95 of 192)], and the firm stated in their 9/22/2016 ECD response that original data was generated. However, the firm did not provide reason for device replacement in their study report or their 9/22/2016 ECD response. Therefore, the firm will be asked to explain why its original assay was rejected, and provide supporting documents (e.g. investigational report) for this sample rejection.

Number	Product	Batch Number	Unit	Flow Rate (L/min)	Lifestage	Reason for replacement
1	REF	5ZP9304	433R	90 (repeat)	EOL	Not provided

- The firm stated that after completion of the initial testing for this study, it was discovered that the flow meter used for the APSD testing at 90 L/min failed its calibration and was subsequently reading incorrect flow values. Therefore, the APSD testing was repeated for the 90 L/min flow rate (MGR-PRO-2015-080 v3.0).

To support the above statement, the firm provided calibration certificates of the flow meter used in the original study. Based on these calibration certificates, this flow meter was calibrated successfully in 11/2014, but when sent in 10/2015 for annual calibration, its required pre-calibration test was out of tolerance^{162 (b) (4)}

It was decided that the APSD results generated at 90 L/min could have potentially been impacted by this failure and that the testing should be repeated. Therefore, the repeat testing was carried out using 3 different flow meters that were all within calibration throughout the testing. The reviewer agrees with the repeat of this study at 90 L/min flow rate.

The firm also stated that the original data and repeat testing data were comparable and hence, there was negligible impact. According to the firm, that all other data was generated using other flow meters that were in calibration.

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(b) (4)

- Due to aforementioned missing information, the reviewer could not verify the firm's results summary at this time.

5.3.2.4.4 In Vitro PBE Analysis

As detailed above, analysis will be carried out pending the firm's additional information lost samples and repeat analysis.

5.3.2.4.5 Conclusions

AERODYNAMIC PARTICLE SIZE DISTRIBUTION		
REVIEW OF TESTING METHODS:		
Is the testing method for CI test validated?	Yes, but with deficiencies	
Is the analytical method (e.g. HPLC) validated?	Yes, but with deficiencies	
Is the analytical method sufficiently sensitive?	Yes	
Is testing conducted as per RLD labeling?	To be determined	
What is the size of the induction port (or expansion chamber) used for testing?	N/A	
Are ≤ 10 actuations used for cascade impactor study?	Yes (1 actuation)	
If >1 actuation, what is the # of actuations used?	N/A	
Are the testing methods acceptable?	INCOMPLETE	
If not, why?	Due to deficiencies in method validation and study information.	
STUDY RESULTS:		
Is drug deposition reported in mass units?	Yes	
Is the mass balance data reported?	Yes in the study report (pdf format) for individual units, but not in the summary table or SAS .xpt file.	
Results	Does Impactor Size Mass data pass PBE?	To be determined
	Does ISM data pass modified chi-square ratio test?	To be determined
	Do mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle dose (FPD) pass PBE?	To be determined
If not, why?	Pending the firm's additional information on repeat analysis.	

Comments:

The firm's pivotal APSD study for the 250/50 mcg strength is **incomplete**.

5.3.2.4.6 Deficiencies / Recommendations

Please see Section 4.10.

APPEARS THIS WAY ON
ORIGINAL

5.3.2.5 Single Actuation Content through Container Life – 500/50 mcg strength

5.3.2.5.1 Study Information

Study No.	057755-02-07 Protocol #: P21756.00
Study Site	(b) (4)
Principal Investigator	(b) (4)
Study Dates	9/22/2015 to 10/30/2015
SOP No.	MGR-METH-546070 (v. 7.0)
SOP Effective Date	12/22/2014
SOP Title	Determination of emitted dose of MGR001 (PF-04764793) from multidose powder inhalation devices using (b) (4) (b) (4)
Test Method Description	(b) (4) for Dry Powder Inhalers (DPIs) is used to determine the emitted dose (ED) of MGR001 (PF-04764793) in 100/50, 250/50 and 500/50 µg multidose dry powder inhalers containing 100, 250 or 500 µg Fluticasone propionate and 50 µg salmeterol as xinafoate salt respectively and for Advair® and Seretide® Accuhaler® Reference Listed Drug (RLD).
Testing Equipment Used (e.g., name, model, etc)	USP <601> Apparatus B with modified end caps
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	30, 60 or 90 L/min flow rate; 2 L volume. Testing carried out at ambient laboratory conditions.
Analytical Method Description	(b) (4)
Analytical Equipment Used (e.g., name, model, etc.)	(b) (4) LC (b) (4) UPLC

Comments:

Reviewer's note: The firm's study protocol (P21756.00) for the current study is similar to the study protocol (P20987.00) for the 100/50 mcg strength SAC study. The reviewer has the same comments regarding the study information as compared to the 100/50 mcg strength SAC study (please see reviewer's comments in Section 5.3.2.1.1) except the firm has different target emitted dose and the reviewer has different comment for raw data and chromatograms as detailed below.

- In the study protocol, the firm stated that the target emitted dose for both T and RLD product are FP = 465 mcg, and SA = 45 mcg. This is the target emitted dose specified in the USP monograph for Fluticasone and Salmeterol Inhalation

Powder¹⁶³ when tested at a flow rate of 60 L/min for 2 seconds. According to the RLD labeling, these values are also what RLD product delivers under standardized in vitro test conditions when tested at a flow rate of 60 L/min for 2 seconds. Please note that RLD labeling and USP monograph did not mention delivered dose or target emitted dose for flow rate at 30 L/min and 90 L/min.

- The firm provided raw analytical data and 33% chromatograms for SAC and APSD studies.

Similar to comments in Section 5.3.2.1.1, the firm's raw data is too granular, and thus will be asked to compile the raw data of each run. The raw data should include all samples (including blank/diluent, standards, etc.) in a run in run sequence order.

In addition, the firm's chromatograms show that SA retention time ranges from ~1.5 min (9/22/2016 submission, Module 3.2.P.2\Attachment 3-4..., p. 1568 of 4892) to ~2.2 min (p. 3865 of the aforementioned document), which is wide with lower end deviated from expected SA retention time (approximate retention time: 2.00 min for SAC study and 1.8 to 2.2 min for APSD study according to the study methods). As mentioned in Section 5.3.2.1.1, the firm will be asked to explain for this wide range and deviation from SA retention time.

5.3.2.5.2 Analytical Method Validation for UPLC

Same as SAC study for the 100/50 mcg strength (please see Section 5.3.2.1.2).

5.3.2.5.3 Calibration of Manual and/or Automated Spray Pump Actuator (For the Single Actuation Content Study)

Same as SAC study for the 100/50 mcg strength (please see Section 5.3.2.1.3).

¹⁶³ USP Monograph for Fluticasone and Salmeterol Inhalation Powder:
http://www.uspnf.com/uspnf/pdf/download?usp=39&nf=34&s=1&q=usp39nf34s1_m3467.pdf&officialOn=August%201,%202016&target=oldwindow&time=1472465975258, p. 5 of 7. Last accessed: 8/28/2016.

5.3.2.5.4 Results Summary

Firm's results

Flow Rate (L/min)	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
30	FP	BoL	458.99	104.24	4.40	18.06	162.57	0.11
		EoL	470.36	481.88	0.98	19.97	55.44	0.36
		MoL	452.55	445.30	1.02	20.27	76.15	0.27
	Sal	BoL	46.20	10.40	4.44	1.47	16.02	0.09
		EoL	47.38	47.41	1.00	1.72	5.38	0.32
		MoL	45.55	43.75	1.04	1.68	7.42	0.23
60	FP	BoL	474.46	445.78	1.06	20.66	16.31	1.27
		EoL	478.71	497.77	0.96	19.08	12.20	1.56
		MoL	468.53	479.82	0.98	22.19	15.37	1.44
	Sal	BoL	47.37	44.04	1.08	1.80	1.67	1.07
		EoL	48.16	48.92	0.98	1.96	1.22	1.60
		MoL	46.65	47.13	0.99	1.90	1.48	1.29
90	FP	BoL	481.70	451.22	1.07	21.78	11.25	1.94
		EoL	487.98	498.22	0.98	18.97	13.51	1.40
		MoL	476.63	477.05	1.00	20.90	15.82	1.32
	Sal	BoL	47.97	44.53	1.08	1.84	1.12	1.64
		EoL	48.89	48.88	1.00	1.70	1.28	1.33
		MoL	47.55	47.01	1.01	1.76	1.53	1.15

Reviewer's Comments:

- The firm did not provide actual actuation numbers (or dose counter numbers) in the SAS .xpt dataset, thus the reviewer is unable to verify whether the actuation used was at the beginning, middle and end lifestages of the device. Therefore, same as the SAC study for the 100/50 mcg strength, the firm will be asked to add a column for dose counter number in their SAC SAS .xpt dataset. In addition, for those samples that were lost and “next dose” of the same device was measured, the firm will be asked to provide detailed cause of sample loss as well as supporting documents (e.g. investigational report) for these sample loss.
- It is also noted that the firm repeated 2 samples using new devices, and each of these 2 samples were repeated for both FP and SA. Please note that beginning, middle and end lifestages should be from the same device. Nevertheless, given the multiple incidences of alternative actuation/alternative devices throughout the in vitro BE studies, the firm will be asked to explain and provide supporting documents for them (please see details below), and explain why there are multiple incidences of alternative actuation/replacement device, and the impact of it on the in vitro BE studies.

The firm provided the reason for their original sample rejections below. The firm also stated that these samples did not have the original data generated due to analysis being stopped prior to data generation.

Sample	Product	Batch number	Original inhaler number	Replacement inhaler number	Flow rate (L/min)	Reason for replacement
1	Advair	4ZP5917	40	111	60	Leak in sample collection tube, analysis halted.
2	Advair	4ZP7022	53	112	90	

For the 2 samples above, the reviewer considers the firm's reason for original sample rejection (leak in sample collection tube, analysis halted) acceptable. However, it should be noted that the firm only repeated the sample at the end lifestage in the replacement device.

- Due to aforementioned missing information, the reviewer could not verify the firm's results summary at this time.
- The firm did not provide % of label claim in their SAS dataset, and thus will be asked to add a column for this in the SAS .xpt file.

(b) (4)

5.3.2.5.5 In Vitro PBE Analysis

As detailed above, analysis will be carried out pending the firm's additional information on actual dose counter numbers, % of label claim, and lost samples.

5.3.2.5.6 Conclusions

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE		
REVIEW OF TESTING METHODS:		
Is the testing method validated?	Yes, but with deficiencies	
Is the Quantitative Analytical Method Validated? (e.g., HPLC)	Yes, but with deficiencies	
Is the method sufficiently sensitive?	Yes	
Is testing performed as per RLD labeling?	To be determined	
Are data measured at both beginning, middle & end lifestages?	Yes	
Is testing a single actuation per determination?	Yes	
If yes, what is the actuation number tested?	Study protocol states that dose counter #s 60 (beginning), 30 (middle) and 1 (end) were to be used. The firm did not provide actual dose counter number, and thus will be asked to provide so.	
Are the testing methods acceptable?	INCOMPLETE	
If not, why?	Due to deficiencies in method validation and study information.	
STUDY RESULTS:		
Are data expressed as actual amount and % of label claim?	No	
Is the geo-mean of the test product (% of label claim) within 95-105%?	Beginning	To be determined
	Middle	To be determined
	End	To be determined
Are the PBE results acceptable?	To be determined	
If not, why?	Pending additional information about actual dose counter numbers, % of label claim, and repeat analysis.	

Comments:

The firm's pivotal SAC study for the 500/50 mcg strength is **incomplete**.

5.3.2.5.7 Deficiencies / Recommendations

Please see Section 4.10.

5.3.2.6 Aerodynamic Particle Size Distribution (APSD) – 500/50 mcg strength

5.3.2.6.1 Study Information

Study No.	057755-02-07 Protocol #: P21756.00
Study site	(b) (4)
Principal Investigator	(b) (4)
Study dates	9/22/2015 to 10/30/2015
SOP No.	MGR-METH-546069 (v. 6.0)
SOP Effective Date	12/22/2014
SOP Title	Determination of aerodynamic particle size distribution of MGR001 (PF-04764793) dry powder inhaler products at 60 l per minute using a (b) (4) Impactor (b) (4) by UPLC.
Testing Method Description	(b) (4) Impactor (b) (4) is used to determine the aerodynamic particle size distribution (APSD) of PF-04764793 in 100/50, 250/50 and 500/50 µg MGR001 dry powder inhaler products containing 50 µg salmeterol as xinafoate salt and 100, 250 or 500 µg fluticasone propionate respectively and for Advair® and Seretide® Accuhaler®.
Testing Equipment Used (e.g., name, model, etc)	USP <601> Apparatus 5
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	30, 60 or 90 L/min flow rate; 4 L volume. Testing carried out at ambient laboratory conditions.
Analytical Method Description	(b) (4)
Analytical Equipment Used (e.g., name, model, etc)	(b) (4) LC (b) (4) UPLC

Comments:

Reviewer's note: The firm's study protocol (P21756.00) for the current study is similar to the study protocol (P20987.00) for the 100/50 mcg strength APSD study. The reviewer has the same comments regarding to study information as compared to the 100/50 mcg strength APSD study (please see reviewer's comments in Section 5.3.2.2.1), except that the firm has different definition for mass balance as detailed below.

- Mass Balance (MB): calculated as % "TDD". TDD values are taken from patient information for Advair® Diskus® (45 mcg for SA and 465 mcg for FP).

Please note that according to the RLD labeling³⁰, under standardized in vitro test conditions, RLD delivers 465 mcg of FP and 45 mcg of SA per blister from Advair Diskus 500/50, when tested at a flow rate of 60 L/min for 2 seconds. This

is also the target emitted dose in USP monograph for Fluticasone Propionate and Salmeterol Inhalation Powder. Please note that RLD labeling and USP monograph did not mention delivered dose or target emitted dose for flow rate at 30 L/min and 90 L/min.

According to guidance-generating review¹⁶⁴, the total mass of drug collected on all stages¹⁶⁵ and accessories should be between 85 and 115%¹⁶⁶ of label claim on a per actuation basis¹⁶⁷.

5.3.2.6.2 Validation Summary Table for Aerodynamic Particle Size Distribution

5.3.2.6.2.1 Analytical Method Validation for UPLC

Same as APSD study for the 100/50 mcg strength (please see Section 5.3.2.2.2.1).

5.3.2.6.2.2 Validation Table for Cascade Impaction

Same as APSD study for the 100/50 mcg strength (please see Section 5.3.2.2.2.2).

5.3.2.6.3 Results Summary – Aerodynamic Particle Size Distribution

Firm’s results - ISM

Flow Rate (L/min)	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
30	FP	BoL	(b) (4)					
		EoL						
	Sal	BoL						
		EoL						
60	FP	BoL						
		EoL						
	Sal	BoL						
		EoL						
90	FP	BoL						
		EoL						
	Sal	BoL						
		EoL						

¹⁶⁴ V:\Science Group\Master Files BE Posting\Fluticasone Propionate_Salmeterol Xinafoate_021077\Fluticasone Propionate_Salmeterol Xinafoate_21077_RC09-13.doc, p. 14 of 62.

¹⁶⁵ Footnote as in the guidance-generating review: “Total mass of drug includes drug deposition on each individual site, to include the mouthpiece adapter, throat, preseparator, and each stage of the impactor including the filter, is requested.”

¹⁶⁶ Footnote as in the guidance-generating review: “<http://www.fda.gov/downloads/Drugs/Guidances/ucm070573.pdf>”

¹⁶⁷ Footnote as in the guidance-generating review: “As determined by USP <601> apparatus B.”

Reviewer's Comments:

- According to study protocol, the APSD study should be performed at dose counter #59 for beginning lifestage and #2 for end lifestage. Same to the 100/50 mcg strength in vitro BE study, if a sample is lost due to an assignable cause (e.g., (b) (4) tube leakage, dropped (b) (4) plate, etc) during sample preparation in beginning or middle lifestage, further collection/recovery of the lost sample will be ceased, and a new sample will be prepared from the next dose(s) (may be performed within ± 3 doses of those stated) of the same device per the test method.

The reviewer checked the firm's SAS dataset, and noticed that the following samples had dose counter number other than #59 and #2, thus the original samples were likely lost. The firm will be asked to explain the detailed reason of their corresponding sample loss and provide supporting document as well as corrective action taken. The firm will also be asked to provide the same information for any additional "next dose" repeat they identified in the study.

¹⁶⁸ Please note that for each of reference and test product at 60 L/min, n=119. This is because the firm stated that 1 sample in each of the reference batch 5ZP8689 and the test batch 631-006 at 60 L/min flow rate had "no acceptable data will be reported for FP and SA" (please see details in the reviewer's comment below).

Flow Rate	Product	Batch	Unit	Stage	Dose Counter Number
30	REF	4ZP7022	9	BOL	58
30	TEST	631-006	111	EOL	1
60	TEST	631-005	32	BOL	58
90	REF	5ZP8689	50	BOL	58

- It is also noted that the firm repeated 2 samples using new devices, and each of these 2 samples were repeated for both FP and SA. Please note that beginning, middle and end lifestages should be from the same device. Nevertheless, given the multiple incidences of alternative actuation/alternative devices throughout the in vitro BE studies, the firm will be asked to explain and provide supporting documents for them (please see details below), and explain why there are multiple incidences of alternative actuation/replacement device, and the impact of it on the in vitro BE studies.

The firm provided the reason for their original sample rejections below. The firm also stated that these samples did not have the original data generated due to analysis being stopped prior to data generation.

Sample	Product	Batch number	Original inhaler number	Replacement inhaler number	Flow rate (L/min)	Reason for replacement
1	Advair	4ZP7022	7	111	30	Leak occurred while recovering preseparator, analysis halted.
2	MGR001	631-006	9	111	30	Collection cup insufficiently dry, analysis halted.

For the 2 samples above, the reviewer considers the firm's reason for original sample rejection (please see details in the table above) acceptable. According to the study report, these are end of lifestages samples. The reviewer checked the dose counter number provided in the SAS dataset, and noticed that the firm did not report original sample dose counter numbers. However, since rejecting the original samples happened during sample processing, and by that time, the suitable "next dose" has already been used for SAC test as per protocol, the reviewer considers the firm's usage of a replacement device acceptable. However, it should be noted that the firm only repeated the sample at the end lifestage in the replacement devices.

- According to the study report MGR-REP-2015-097 (version 1.0, p. 13 of 178), the firm stated that *"for units 180 and 221 EOL 60 L/min, no acceptable data will be reported for FP and SA"*. The firm will be asked to provide the data obtained

as well as supporting document for why this data was not acceptable. The firm will also be asked to provide SOP that pre-defined data acceptance criteria.

- Due to aforementioned missing information, the reviewer could not verify the firm's results summary at this time.
- Based on the firm's results, it is noted that RLD product had high variability for ISM of FP at beginning lifestage at 30 L/min flow rate. The reviewer checked study data for each individual unit, and found that RLD batches had multiple samples that had low ISM for FP, and some these samples had low FP content in each stage, MT and preseparator (PS) of the (b) (4).

Additionally, based on reviewer's calculation of mass balance (% of label claim) using the firm's mass balance (mcg) data, it is noted that RLD product had mass balance (% of label claim) as low as 18.1% for FP and 17.9% for SA at 30 L/min. The reviewer checked the individual study results and found that RLD batches had a few samples that had low % recovery for each stage, MT and PS of the (b) (4) this observation is consistent with the observation above about high ISM variability under the same testing condition.

5.3.2.6.4 In Vitro PBE Analysis

As detailed above, analysis will be carried out pending the firm's additional information lost samples and unacceptable data.

5.3.2.6.5 Conclusions

AERODYNAMIC PARTICLE SIZE DISTRIBUTION		
REVIEW OF TESTING METHODS:		
Is the testing method for CI test validated?	Yes, but with deficiencies	
Is the analytical method (e.g. HPLC) validated?	Yes, but with deficiencies	
Is the analytical method sufficiently sensitive?	Yes	
Is testing conducted as per RLD labeling?	To be determined	
What is the size of the induction port (or expansion chamber) used for testing?	N/A	
Are ≤ 10 actuations used for cascade impactor study?	Yes (1 actuation)	
If >1 actuation, what is the # of actuations used?	N/A	
Are the testing methods acceptable?	INCOMPLETE	
If not, why?	Due to deficiencies in method validation and study information.	
STUDY RESULTS:		
Is drug deposition reported in mass units?	Yes	
Is the mass balance data reported?	Yes in the study report (pdf format) for individual units, but not in the summary table or SAS .xpt file.	
Results	Does Impactor Size Mass data pass PBE?	To be determined
	Does ISM data pass modified chi-square ratio test?	To be determined
	Do mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle dose (FPD) pass PBE?	To be determined
If not, why?	Pending the firm's additional information on repeat analysis.	

Comments:

The firm's pivotal APSD study for the 500/50 mcg strength is **incomplete**.

5.3.2.6.6 Deficiencies / Recommendations

Please see Section 4.10.

5.3.3 Individual In Vitro-Test Reviews – Studies with 4 kPa Fixed Pressure Drop

Reviewer’s note: Please note that this study is considered unacceptable due to insufficient number of units used in the study. Other deficiencies identified in this section will be communicated to the firm for them to take consideration for their repeat study.

5.3.3.1 Single Actuation Content through Container Life – 4 kPa Fixed Pressure Drop (100/50 mcg strength)

5.3.3.1.1 Study Information

Study No.	Study Report #: MGR-REP-2015-092 Protocol #: P20877.00 (b) (4) study number 057755-02-06
Study Site	(b) (4)
Principal Investigator	(b) (4)
Study Dates	8/24/2015-8/31/2015
SOP No.	MGR-METH-546070 (v. 7.0)
SOP Effective Date	12/22/2014
SOP Title	Determination of emitted dose of MGR001 (PF-04764793) from multidose powder inhalation devices using (b) (4)
Test Method Description	(b) (4) for Dry Powder Inhalers (DPIs) is used to determine the emitted dose (ED) of MGR001 (PF-04764793) in 100/50, 250/50 and 500/50 µg multidose dry powder inhalers containing 100, 250 or 500 µg Fluticasone propionate and 50 µg salmeterol as xinafoate salt respectively and for Advair and Seretide® Accuhaler® Reference Listed Drug (RLD).
Testing Equipment Used (e.g., name, model, etc)	USP <601> Apparatus B with modified end caps
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	Flow rates were used through each device to achieve a 4 kPa pressure drop (approximately 60 L/min and 75 L/min, for the MGR001 and RLD products, respectively); 2 L volume. Testing carried out at ambient laboratory conditions.
Analytical Method Description	(b) (4)
Analytical Equipment Used (e.g., name, model, etc.)	(b) (4) LC (b) (4) UPLC

Comments:

Reviewer’s note: The firm conducted SAC and APSD tests on the same device. Therefore, some of the comments below are common to both SAC and APSD study design. For reviewer’s comments specific for SAC study, please see “Comments for SAC” below.

General Comments

- According to CC13-0422¹⁶⁹, the CC reviewer provided the following reasoning of recommending the 4 kPa fixed pressure drop study to the firm: “[i]n literature, it has been reported that patients produce around 4 kPa pressure drop across the inhaler when inhale against resistances typical for the marketed DPIs. Comparable emitted dose and fine particle mass measured at 4kPa pressure drop for both the devices can provide additional confirmation that resistance difference between the RLD and MGR001 is acceptable.”
- According to the study protocol and pharmaceutical development report (p. 657 of 676), the test and RLD batches and analytical procedures used in this study were the same as those used in pivotal in-vitro equivalence studies.
- The test was conducted on 3 lots of test and 3 lots of RLD product. For each lot, 3 test and 3 RLD devices were tested, with 3 replicates of SAC (beginning, middle, and end), and 2 replicates of APSD (beginning and end) collected from each device. The firm then conducted statistical comparison of geometric mean ratios at 4 kPa vs. 60 L/min. The firm will be asked to repeat the study with 10 test and 10 RLD devices per lot, using 3 lots of test and 3 lots of RLD product. SAC study should be tested at beginning, middle and end lifestages, while APSD studies should be tested at beginning and end lifestages. The firm will be asked to conduct statistical comparison of T vs. R at 4 kPa pressure drop using PBE analysis. The firm will be referred to Draft Guidance on Budesonide Inhalation Suspension for step-wise procedure of the PBE analysis.
- According to the study protocol, the following are the actuation #s used for SAC and APSD testing. Please note that device-specific optimal flow was determined on each sample device. In addition, the firm conducted SAC (ED) and APSD ^{(b) (4)} test on the same device.

¹⁶⁹ <\\cdsnas\OGDS6\CONTROLS\2013-docs\13-0422.pdf> p. 21 of 28.

Test Sequence Dose counter number	Procedure	Testing to be Performed	Test Day
60	Waste/Optimal Flow	Optimal Flow Determination	1
59	ED Beginning	Emitted Dose	
58	(b) (4) Beginning	(b) (4)	
57-33	Waste	Wasting at ED optimal flow	
Leave device to rest at least overnight			
32-31	Waste	Wasting at ED optimal flow	2
30	ED Middle	Emitted Dose	
29-5	Waste	Wasting at ED optimal flow	
Leave device to rest at least overnight			
4-3	Waste	Wasting ED optimal flow	3
2	(b) (4) End	(b) (4)	
1	ED End	Emitted Dose	

NA = Not Applicable

- According to the pharmaceutical development report (p. 657 of 676), the flow rates used through each device to achieve a 4 kPa pressure drop were approximately 60 L/min and 75 L/min, for the test and RLD product, respectively (please see the firm’s table below).

Table 73. Flow Rates Used During Comparative Testing at 4 kPa Fixed Pressure Drop



(b) (4)

- As mentioned in Section 5.3.2.1.1, the firm will be asked explain for sealing non-functional holes in the test device, and provide picture(s) to illustrate how test and RLD devices were set up with the testing apparatus in SAC and APSD studies.
- The firm did not submit study results in SAS .xpt format for SAC and APSD studies at 4 kPa fixed pressure drop. Therefore, the firm will be asked to provide so. This SAS dataset should include % of label claim for the SAC study, mass balance (% of label claim) for the APSD study, and dose counter number for both SAC and APSD studies.
- The firm provided raw analytical data and chromatograms for SAC and APSD studies.

Similar to comments in Section 5.3.2.1.1, the firm's raw data is too granular, and thus will be asked to compile the raw data of each run. The raw data should include all samples (including blank/diluent, standards, etc.) in a run in run sequence order.

(b) (4)

As mentioned in Section 5.3.2.1.1, the firm will be asked to explain for this deviation from SA retention time.

Comments for SAC

- (b) (4)
- In the study protocol, the firm also stated that the target emitted dose for both T and RLD product are FP = 93 mcg, and SA = 45 mcg. This is the target emitted dose specified in the USP monograph for Fluticasone and Salmeterol Inhalation Powder¹⁷⁰ when tested at a flow rate of 60 L/min for 2 seconds. According to the RLD labeling, these values are also what RLD product delivers under standardized in vitro test conditions when tested at a flow rate of 60 L/min for 2 seconds. Please note that RLD labeling and USP monograph did not mention delivered dose or target emitted dose for flow rate at 30 L/min and 90 L/min.

5.3.3.1.2 Analytical Method Validation for UPLC

Same as the pivotal SAC study for the 100/50 mcg strength (please see Section 5.3.2.1.2).

5.3.3.1.3 Calibration of Manual and/or Automated Spray Pump Actuator (For the Single Actuation Content Study)

Same as the pivotal SAC study for the 100/50 mcg strength (please see Section 5.3.2.1.2).

¹⁷⁰ USP Monograph for Fluticasone and Salmeterol Inhalation Powder:
http://www.uspnf.com/uspnf/pdf/download?usp=39&nf=34&s=1&q=usp39nf34s1_m3467.pdf&officialOn=August%201.%202016&target=oldwindow&time=1472465975258, p. 5 of 7. Last accessed: 8/28/2016.

5.3.3.1.4 Results Summary

Firm's results

Pressure Drop	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
4 kPa	FP	BoL	100.25	94.36	1.06	2.78	2.55	1.09
		EoL	97.94	101.74	0.96	4.20	1.37	3.06
		MoL	99.13	97.99	1.01	5.44	2.35	2.32
	Sal	BoL	50.47	46.33	1.09	1.03	1.44	0.71
		EoL	49.26	50.01	0.98	2.30	0.62	3.68
		MoL	49.76	48.06	1.04	2.70	0.95	2.86

Reviewer's Comments:

- The firm did not provide study data in SAS .xpt file. In addition, the firm did not provide actual dose counter number for the study, thus it is unclear if the firm lost any sample and measured the “next dose” of the same device. Therefore, the firm will be asked to provide SAS dataset with dose counter number included. In addition, for each sample that was lost and “next dose” of the same device was measured, the firm will be asked to provide detailed cause of sample loss as well as supporting documents (e.g. investigational report) for these sample loss. The reviewer’s SAC summary results will be calculated upon receipt of this information.
- The firm stated that no replacement inhalers were used in this study.
- The firm did not provide % of label claim, and thus will be asked to provide so in their SAS .xpt file.

5.3.3.1.5 In Vitro PBE Analysis

As detailed above, analysis will be carried out pending the firm’s submission of SAS dataset and additional information on lost samples.

5.3.3.1.6 Conclusions

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE		
REVIEW OF TESTING METHODS:		
Is the testing method validated?	Yes, but with deficiencies	
Is the Quantitative Analytical Method Validated? (e.g., HPLC)	Yes, but with deficiencies	
Is the method sufficiently sensitive?	Yes	
Is testing performed as per RLD labeling?	To be determined	
Are data measured at both beginning, middle & end lifestages?	Yes	
Is testing a single actuation per determination?	Yes	
If yes, what is the actuation number tested?	Study protocol states that dose counter #s 60 (beginning), 30 (middle) and 1 (end) were to be used. The firm did not provide actual dose counter number, and thus will be asked to provide so.	
Are the testing methods acceptable?	INCOMPLETE	
If not, why?	Due to deficiencies in method validation and study information.	
STUDY RESULTS:		
Are data expressed as actual amount and % of label claim?	No	
Is the geo-mean of the test product (% of label claim) within 95-105%?	Beginning	To be determined
	Middle	To be determined
	End	To be determined
Are the PBE results acceptable?	INCOMPLETE	
If not, why?	Pending firm's submission of SAS .xpt dataset and additional information on repeat analysis.	

Comments:

The firm's SAC study at 4 kPa fixed pressure drop for the 100/50 mcg strength is incomplete.

5.3.3.1.7 Deficiencies / Recommendations

Please see Section 4.10.

5.3.3.2 Aerodynamic Particle Size Distribution (APSD) – 4 kPa Fixed Pressure Drop (100/50 mcg strength)

5.3.3.2.1 Study Information

Study No.	Study Report #: MGR-REP-2015-092 Protocol #: P20877.00
Study site	(b) (4)
Principal Investigator	(b) (4)
Study dates	8/24/2015-8/31/2015
SOP No.	MGR-METH-546069 (v. 6.0)
SOP Effective Date	12/22/2014
SOP Title	Determination of aerodynamic particle size distribution of MGR001 (PF-04764793) dry powder inhaler products at 60 l per minute using a (b) (4) Impactor (b) (4) by UPLC.
Testing Method Description	(b) (4) Impactor (b) (4) is used to determine the aerodynamic particle size distribution (APSD) of PF-04764793 in 100/50, 250/50 and 500/50 µg MGR001 dry powder inhaler products containing 50 µg salmeterol as xinafoate salt and 100, 250 or 500 µg fluticasone propionate respectively and for Advair® Diskus® and Seretide® Accuhaler®.
Testing Equipment Used (e.g., name, model, etc)	USP <601> Apparatus 5
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	Flow rates were used through each device to achieve a 4 kPa pressure drop (approximately 60 L/min and 75 L/min, for the MGR001 and RLD products, respectively); 4 L volume. Testing carried out at ambient laboratory conditions.
Analytical Method Description	(b) (4)
Analytical Equipment Used (e.g., name, model, etc)	(b) (4) LC (b) (4) UPLC

Comments:

Reviewer's note: The firm conducted SAC and APSD tests on the same device. Therefore, some of the comments are common to both SAC and APSD study design (please refer to reviewer's general comments in Section 5.3.3.1.1). For reviewer's comments specific for APSD study, please see below.

Comments for APSD

- According to the study protocol, actuation (solenoid) times for testing were to be determined as follows:

$$T = \frac{L}{Q} \times 60 \text{ seconds}$$

Where:

T = time required to draw 4.0 L of air through the device at the measured flow rate

L = is the amount of air to be pulled through device, which is 4L for APSD (b) (4) study

Q = determined optimal flow rate, in “L/min”

- The firm had the same definition for total recovery, ISM and mass balance as detailed in Section 5.3.2.2.1. And the firm has the same issue on the definition of FPM, MMAD and GSD as detailed in the aforementioned section.

5.3.3.2.2 Validation Summary Table for Aerodynamic Particle Size Distribution

5.3.3.2.2.1 Analytical Method Validation for UPLC

Same as the pivotal APSD study for the 100/50 mcg strength (please see Section 5.3.2.2.2.1).

5.3.3.2.2.2 Validation Table for Cascade Impaction

Same as the pivotal APSD study for the 100/50 mcg strength (please see Section 5.3.2.2.2.2).

5.3.3.2.3 Results Summary – Aerodynamic Particle Size Distribution

Firm’s results - ISM

Pressure Drop	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
4 kPa	FP	BoL	(b) (4)					
		EoL						
	Sal	BoL						
		EoL						

Reviewer's Comments:

- Similar to the SAC study, the firm did not provide study data in SAS .xpt file. In addition, the firm did not provide actual dose counter number for the study, thus it is unclear if the firm lost any sample and measured the “next dose” of the same device. Therefore, the firm will be asked to provide SAS dataset with dose counter number included. In addition, for each sample that was lost and “next dose” of the same device was measured, the firm will be asked to provide detailed cause of sample loss as well as supporting documents (e.g. investigational report) for these sample loss. The reviewer’s APSD results will be calculated upon receipt of this information.
- The firm stated that no replacement inhalers were used in this study.
- The firm did not provide mass balance (% of label claim), and thus will be asked to provide so in their SAS .xpt file.

5.3.3.2.4 In Vitro PBE Analysis

As detailed above, analysis will be carried out pending the firm’s submission of SAS dataset and additional information on lost samples.

5.3.3.2.5 Conclusions

AERODYNAMIC PARTICLE SIZE DISTRIBUTION		
REVIEW OF TESTING METHODS:		
Is the testing method for CI test validated?	Yes, but with deficiencies	
Is the analytical method (e.g. HPLC) validated?	Yes, but with deficiencies	
Is the analytical method sufficiently sensitive?	Yes	
Is testing conducted as per RLD labeling?	To be determined	
What is the size of the induction port (or expansion chamber) used for testing?	N/A	
Are ≤ 10 actuations used for cascade impactor study?	Yes (1 actuation)	
If >1 actuation, what is the # of actuations used?	N/A	
Are the testing methods acceptable?	INCOMPLETE	
If not, why?	Due to deficiencies in method validation and study information.	
STUDY RESULTS:		
Is drug deposition reported in mass units?	Yes	
Is the mass balance data reported?	Yes in the study report (pdf format) for individual units, but not in the summary table or SAS .xpt file.	
Results	Does Impactor Size Mass data pass PBE?	To be determined
	Does ISM data pass modified chi-square ratio test?	To be determined
	Do mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle dose (FPD) pass PBE?	To be determined
If not, why?	Pending firm's submission of SAS .xpt dataset and additional information on repeat analysis.	

Comments:

The firm's APSD study at 4 kPa fixed pressure drop for the 100/50 mcg strength is **incomplete**.

5.3.3.2.6 Deficiencies / Recommendations

Please see Section 4.10.

5.3.3.3 Single Actuation Content through Container Life – 4 kPa Fixed Pressure Drop (250/50 mcg strength)

5.3.3.3.1 Study Information

Study No.	Study Report #: MGR-PRO-REP-2015-103 Protocol #: MGR-PRO-2015-103
Study Site	Mylan Global Respiratory Group IPC008, Discovery Park House, Floor 3 Sandwich, Kent. CT13 9ND. UK
Principal Investigator	Elizabeth Clift Karen Weaver
Study Dates	10/29/2015-11/3/2015
SOP No.	MGR-METH-546070 (v. 7.0)
SOP Effective Date	12/22/2014
SOP Title	Determination of emitted dose of MGR001 (PF-04764793) from multidose powder inhalation devices using (b) (4)
Test Method Description	(b) (4) for Dry Powder Inhalers (DPIs) is used to determine the emitted dose (ED) of MGR001 (PF-04764793) in 100/50, 250/50 and 500/50 µg multidose dry powder inhalers containing 100, 250 or 500 µg Fluticasone propionate and 50 µg salmeterol as xinafoate salt respectively and for Advair and Seretide® Accuhaler® Reference Listed Drug (RLD).
Testing Equipment Used (e.g., name, model, etc)	USP <601> Apparatus B with modified end caps
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	Flow rates were used through each device to achieve a 4 kPa pressure drop (approximately 60 L/min and 75 L/min, for the MGR001 and RLD products, respectively); 2 L volume. Testing carried out at ambient laboratory conditions.
Analytical Method Description	(b) (4)
Analytical Equipment Used (e.g., name, model, etc.)	(b) (4) UPLC

Comments:

Reviewer's note: The firm's study protocol (MGR-PRO-2015-103) for the current study is similar to the study protocol (P20877.00) for the 100/50 mcg strength SAC study. The reviewer has the same comments regarding to study information as compared to the 100/50 mcg strength SAC study (please see reviewer's comments in Section 5.3.3.1.1) except the firm did not specify target emitted dose and the reviewer has different comments for raw data and chromatograms as detailed below. The reviewer also has an additional comment about extra solenoid activation as detailed below.

- The firm provided raw analytical data and chromatograms for SAC and APSD studies.

Similar to comments in Section 5.3.2.3.1, the firm did not submit 100% raw data, as there are many instances that the result IDs in the run are not consecutive. Therefore, as mentioned in the aforementioned section, the firm will be asked to provide 100% raw data.

In addition, based on chromatograms provided for the APSD study, it is noted that some runs had run time of 6.5 min while others had 3.5 min (9/22/2016 submission, Module 3.2.P.2\Attachment 3-7..., p. 131 of 238). Therefore, the firm will be asked to explain why different run times were used.

- In the study protocol, the firm stated that to clear the test device of any potentially extraneous powder, an extra solenoid activation is recommended after a final waste shot, just prior to an SAC or APSD collection.

5.3.3.3.2 Analytical Method Validation for UPLC

Same as the pivotal SAC study for the 250/50 mcg strength (please note that this study was conducted at a different site as compared to studies for the other 2 strengths. Please see details in Section 5.3.2.3.2).

5.3.3.3.3 Calibration of Manual and/or Automated Spray Pump Actuator (For the Single Actuation Content Study)

Same as the pivotal SAC study for the 250/50 mcg strength (please note that this study was conducted at a different site as compared to studies for the other 2 strengths. Please see details in Section 5.3.2.3.3).

5.3.3.3.4 Results Summary

Firm's results

Pressure Drop	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
4 kPa	FP	BoL	235.08	236.16	1.00	6.02	6.12	0.98
		EoL	241.86	241.06	1.00	9.41	10.63	0.89
		MoL	243.82	239.04	1.02	7.72	7.44	1.04
	Sal	BoL	47.57	46.59	1.02	0.80	1.19	0.67
		EoL	48.19	47.99	1.00	1.44	1.60	0.90
		MoL	48.45	47.65	1.02	1.81	1.59	1.14

Reviewer's Comments:

- Similar to the 4 kPa pressure drop study on the 100/50 mcg strength, the firm did not provide study data in SAS .xpt file. In addition, the firm did not provide actual dose counter number for the study, thus it is unclear if the firm lost any sample and measured the "next dose" of the same device. Therefore, the firm will be

asked to provide SAS dataset with dose counter number included. In addition, for each sample that was lost and “next dose” of the same device was measured, the firm will be asked to provide detailed cause of sample loss as well as supporting documents (e.g. investigational report) for these sample loss. The reviewer’s SAC summary results will be calculated upon receipt of this information.

- The firm stated that no replacement inhalers were used in this study.
- The firm did not provide % of label claim, and thus will be asked to provide so in their SAS .xpt file.

5.3.3.3.5 In Vitro PBE Analysis

As detailed above, analysis will be carried out pending the firm’s submission of SAS dataset and additional information on lost samples.

5.3.3.3.6 Conclusions

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE		
REVIEW OF TESTING METHODS:		
Is the testing method validated?	Yes, but with deficiencies	
Is the Quantitative Analytical Method Validated? (e.g., HPLC)	Yes, but with deficiencies	
Is the method sufficiently sensitive?	Yes	
Is testing performed as per RLD labeling?	To be determined	
Are data measured at both beginning, middle & end lifestages?	Yes	
Is testing a single actuation per determination?	Yes	
If yes, what is the actuation number tested?	Study protocol states that dose counter #s 60 (beginning), 30 (middle) and 1 (end) were to be used. The firm did not provide actual dose counter number, and thus will be asked to provide so.	
Are the testing methods acceptable?	INCOMPLETE	
If not, why?	Due to deficiencies in method validation and study information.	
STUDY RESULTS:		
Are data expressed as actual amount and % of label claim?	No	
Is the geo-mean of the test product (% of label claim) within 95-105%?	Beginning	To be determined
	Middle	To be determined
	End	To be determined
Are the PBE results acceptable?	INCOMPLETE	
If not, why?	Pending firm's submission of SAS .xpt dataset and additional information on repeat analysis.	

Comments:

The firm's SAC study at 4 kPa fixed pressure drop for the 250/50 mcg strength is **incomplete**.

5.3.3.3.7 Deficiencies / Recommendations

Please see Section 4.10.

5.3.3.4 Aerodynamic Particle Size Distribution (APSD) – 4 kPa Fixed Pressure Drop (250/50 mcg strength)

5.3.3.4.1 Study Information

Study No.	Study Report #: MGR-PRO-REP-2015-103 Protocol #: MGR-PRO-2015-103
Study site	Mylan Global Respiratory Group IPC008, Discovery Park House, Floor 3 Sandwich, Kent. CT13 9ND. UK
Principal Investigator	Elizabeth Clift Karen Weaver
Study dates	10/29/2015-11/3/2015
SOP No.	MGR-METH-546069 (v. 6.0)
SOP Effective Date	12/22/2014
SOP Title	Determination of aerodynamic particle size distribution of MGR001 (PF-04764793) dry powder inhaler products at 60 l per minute using a (b) (4) Impactor (b) (4) by UPLC.
Testing Method Description	(b) (4) Impactor (b) (4) is used to determine the aerodynamic particle size distribution (APSD) of PF-04764793 in 100/50, 250/50 and 500/50 µg MGR001 dry powder inhaler products containing 50 µg salmeterol as xinafoate salt and 100, 250 or 500 µg fluticasone propionate respectively and for Advair® Diskus® and Seretide® Accuhaler®.
Testing Equipment Used (e.g., name, model, etc)	USP <601> Apparatus 5
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	Flow rates were used through each device to achieve a 4 kPa pressure drop (approximately 60 L/min and 75 L/min, for the MGR001 and RLD products, respectively); 4 L volume. Testing carried out at ambient laboratory conditions.
Analytical Method Description	(b) (4)
Analytical Equipment Used (e.g., name, model, etc)	(b) (4) UPLC

Comments:

Reviewer's note: The firm's study protocol (MGR-PRO-2015-103) for the current study is similar to the study protocol (P20877.00) for the 100/50 mcg strength APSD study. The reviewer has the same comments regarding to study information as compared to the 100/50 mcg strength APSD study (please see reviewer's comments in Section 5.3.3.2.1) except the firm has different definition for mass balance (please see below). The reviewer also has an additional comment on extra solenoid activation as detailed below.

- **Mass Balance (MB):** calculated as % TDD. TDD values taken from patient information for Advair® Diskus® (45 mcg for SA and 233 mcg for FP).

Please note that according to the RLD labeling³⁰, under standardized in vitro test conditions, RLD delivers 233 mcg of FP and 45 mcg of SA per blister from Advair Diskus 250/50, when tested at a flow rate of 60 L/min for 2 seconds. This is also the target emitted dose in USP monograph for Fluticasone Propionate and Salmeterol Inhalation Powder. Please note that RLD labeling and USP monograph did not mention delivered dose or target emitted dose for flow rate at 30 L/min and 90 L/min.

According to guidance-generating review¹⁷¹, the total mass of drug collected on all stages¹⁷² and accessories should be between 85 and 115%¹⁷³ of label claim on a per actuation basis¹⁷⁴.

- In the study protocol, the firm stated that to clear the test device of any potentially extraneous powder, an extra solenoid activation is recommended after a final waste shot, just prior to an SAC or APSD collection.

5.3.3.4.2 Validation Summary Table for Aerodynamic Particle Size Distribution

5.3.3.4.2.1 Analytical Method Validation for UPLC

Same as the pivotal APSD study for the 250/50 mcg strength (please note that this study was conducted at a different site as compared to studies for the other 2 strengths. Please see details in Section 5.3.2.4.2.1).

5.3.3.4.2.2 Validation Table for Cascade Impaction

Same as the pivotal APSD study for the 250/50 mcg strength (please note that this study was conducted at a different site as compared to studies for the other 2 strengths. Please see details in Section 5.3.2.4.2.2).

5.3.3.4.3 Results Summary – Aerodynamic Particle Size Distribution

Firm's results - ISM

¹⁷¹ V:\Science Group\Master Files BE Posting\Fluticasone Propionate_Salmeterol Xinafoate_021077\Fluticasone Propionate_Salmeterol Xinafoate_21077_RC09-13.doc, p. 14 of 62.

¹⁷² Footnote as in the guidance-generating review: "Total mass of drug includes drug deposition on each individual site, to include the mouthpiece adapter, throat, preseparator, and each stage of the impactor including the filter, is requested."

¹⁷³ Footnote as in the guidance-generating review: "<http://www.fda.gov/downloads/Drugs/Guidances/ucm070573.pdf>"

¹⁷⁴ Footnote as in the guidance-generating review: "As determined by USP <601> apparatus B."

Pressure Drop	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
4 kPa	FP	BoL	(b) (4)					
		EoL						
	Sal	BoL						
		EoL						



Reviewer’s Comments:

- Similar to the 4 kPa pressure drop study on the 100/50 mcg strength, the firm did not provide study data in SAS .xpt file. In addition, the firm did not provide actual dose counter number for the study, thus it is unclear if the firm lost any sample and measured the “next dose” of the same device. Therefore, the firm will be asked to provide SAS dataset with dose counter number included. In addition, for each sample that was lost and “next dose” of the same device was measured, the firm will be asked to provide detailed cause of sample loss as well as supporting documents (e.g. investigational report) for these sample loss. The reviewer’s APSD results will be calculated upon receipt of this information.
- The firm stated that no replacement inhalers were used in this study.
- The firm did not provide mass balance (% of label claim), and thus will be asked to provide so in their SAS .xpt file.

5.3.3.4.4 In Vitro PBE Analysis

As detailed above, analysis will be carried out pending the firm’s submission of SAS dataset and additional information on lost samples.

5.3.3.4.5 Conclusions

AERODYNAMIC PARTICLE SIZE DISTRIBUTION		
REVIEW OF TESTING METHODS:		
Is the testing method for CI test validated?	Yes, but with deficiencies	
Is the analytical method (e.g. HPLC) validated?	Yes, but with deficiencies	
Is the analytical method sufficiently sensitive?	Yes	
Is testing conducted as per RLD labeling?	To be determined	
What is the size of the induction port (or expansion chamber) used for testing?	N/A	
Are ≤ 10 actuations used for cascade impactor study?	Yes (1 actuation)	
If >1 actuation, what is the # of actuations used?	N/A	
Are the testing methods acceptable?	INCOMPLETE	
If not, why?	Due to deficiencies in method validation and study information.	
STUDY RESULTS:		
Is drug deposition reported in mass units?	Yes	
Is the mass balance data reported?	Yes in the study report (pdf format) for individual units, but not in the summary table or SAS .xpt file.	
Results	Does Impactor Size Mass data pass PBE?	To be determined
	Does ISM data pass modified chi-square ratio test?	To be determined
	Do mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle dose (FPD) pass PBE?	To be determined
If not, why?	Pending firm's submission of SAS .xpt dataset and additional information on repeat analysis.	

Comments:

The firm's APSD study at 4 kPa fixed pressure drop for the 250/50 mcg strength is **incomplete**.

5.3.3.4.6 Deficiencies / Recommendations

Please see Section 4.10.

5.3.3.5 Single Actuation Content through Container Life – 4 kPa Fixed Pressure Drop (500/50 mcg strength)

5.3.3.5.1 Study Information

Study No.	057755-02-08 Protocol #: P21164.00 (b) (4) study number 057755-02-08
Study Site	(b) (4)
Principal Investigator	(b) (4)
Study Dates	9/30/2015-10/16/2015
SOP No.	MGR-METH-546070 (v. 7.0)
SOP Effective Date	12/22/2014
SOP Title	Determination of emitted dose of MGR001 (PF-04764793) from multidose powder inhalation devices using (b) (4) (b) (4)
Test Method Description	(b) (4) for Dry Powder Inhalers (DPIs) is used to determine the emitted dose (ED) of MGR001 (PF-04764793) in 100/50, 250/50 and 500/50 µg multidose dry powder inhalers containing 100, 250 or 500 µg Fluticasone propionate and 50 µg salmeterol as xinafoate salt respectively and for Advair® and Seretide® Accuhaler® Reference Listed Drug (RLD).
Testing Equipment Used (e.g., name, model, etc)	USP <601> Apparatus B with modified end caps
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	Flow rates were used through each device to achieve a 4 kPa pressure drop (approximately 60 L/min and 75 L/min, for the MGR001 and RLD products, respectively); 2 L volume. Testing carried out at ambient laboratory conditions.
Analytical Method Description	(b) (4)
Analytical Equipment Used (e.g., name, model, etc.)	(b) (4) LC (b) (4) UPLC

Comments:

Reviewer's note: The firm's study protocol (MGR-PRO-2015-103) for the current study is similar to the study protocol (P20877.00) for the 100/50 mcg strength SAC study. The reviewer has the same comments regarding to study information as compared to the 100/50 mcg strength SAC study (please see reviewer's comments in Section 5.3.3.1.1) except the firm had different target emitted dose and the reviewer has different comments for raw data and chromatograms as detailed below. The reviewer also has an additional comment about extra solenoid activation as detailed below.

- In the study protocol, the firm stated that the target emitted dose for both T and RLD product are FP = 465 mcg, and SA = 45 mcg. This is the target emitted dose

specified in the USP monograph for Fluticasone and Salmeterol Inhalation Powder¹⁷⁵ when tested at a flow rate of 60 L/min for 2 seconds. According to the RLD labeling, these values are also what RLD product delivers under standardized in vitro test conditions when tested at a flow rate of 60 L/min for 2 seconds. Please note that RLD labeling and USP monograph did not mention delivered dose or target emitted dose for flow rate at 30 L/min and 90 L/min.

- The firm provided raw analytical data and chromatograms for SAC and APSD studies. Similar to comments in Section 5.3.3.1.1, the firm’s raw data is too granular, and thus will be asked to compile the raw data of each run.
- In the study protocol, the firm stated that to clear the test device of any potentially extraneous powder, an extra solenoid activation is recommended after a final waste shot, just prior to an SAC or APSD collection.

5.3.3.5.2 Analytical Method Validation for UPLC

Same as the pivotal SAC study for the 100/50 mcg strength (please see Section 5.3.2.1.2).

5.3.3.5.3 Calibration of Manual and/or Automated Spray Pump Actuator (For the Single Actuation Content Study)

Same as the pivotal SAC study for the 100/50 mcg strength (please see Section 5.3.2.1.3).

5.3.3.5.4 Results Summary

Firm’s results

Pressure Drop	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
4 kPa	FP	BoL	469.81	460.87	1.02	21.45	8.07	2.66
		EoL	484.52	496.93	0.98	20.94	21.12	0.99
		MoL	469.69	485.83	0.97	23.92	12.49	1.92
	Sal	BoL	47.07	45.61	1.03	1.21	0.94	1.29
		EoL	48.48	48.95	0.99	1.66	2.11	0.78
		MoL	47.35	47.86	0.99	2.16	1.16	1.86

Reviewer’s Comments:

- Similar to the 4 kPa pressure drop study on the 100/50 mcg strength, the firm did not provide study data in SAS .xpt file. In addition, the firm did not provide actual dose counter number for the study, thus it is unclear if the firm lost any sample and measured the “next dose” of the same device. Therefore, the firm will be

¹⁷⁵ USP Monograph for Fluticasone and Salmeterol Inhalation Powder: http://www.uspnf.com/uspnf/pdf/download?usp=39&nf=34&s=1&q=usp39nf34s1_m3467.pdf&officialOn=August%201,%202016&target=oldwindow&time=1472465975258, p. 5 of 7. Last accessed: 8/28/2016.

asked to provide SAS dataset with dose counter number included. In addition, for each sample that was lost and “next dose” of the same device was measured, the firm will be asked to provide detailed cause of sample loss as well as supporting documents (e.g. investigational report) for these sample loss. The reviewer’s SAC summary results will be calculated upon receipt of this information.

- The firm stated that no replacement inhalers were used in this study.
- The firm did not provide % of label claim, and thus will be asked to provide so in their SAS .xpt file.
- As highlighted in table above, based on the firm’s results, test product has higher variability as compared to variability of other SAC studies at 4 kPa pressure drop.

5.3.3.5.5 In Vitro PBE Analysis

As detailed above, analysis will be carried out pending the firm’s submission of SAS dataset and additional information on lost samples.

5.3.3.5.6 Conclusions

SINGLE ACTUATION CONTENT THROUGH CONTAINER LIFE		
REVIEW OF TESTING METHODS:		
Is the testing method validated?	Yes, but with deficiencies	
Is the Quantitative Analytical Method Validated? (e.g., HPLC)	Yes, but with deficiencies	
Is the method sufficiently sensitive?	Yes	
Is testing performed as per RLD labeling?	To be determined	
Are data measured at both beginning, middle & end lifestages?	Yes	
Is testing a single actuation per determination?	Yes	
If yes, what is the actuation number tested?	Study protocol states that dose counter #s 60 (beginning), 30 (middle) and 1 (end) were to be used. The firm did not provide actual dose counter number , and thus will be asked to provide so.	
Are the testing methods acceptable?	INCOMPLETE	
If not, why?	Due to deficiencies in method validation and study information.	
STUDY RESULTS:		
Are data expressed as actual amount and % of label claim?	No	
Is the geo-mean of the test product (% of label claim) within 95-105%?	Beginning	To be determined
	Middle	To be determined
	End	To be determined
Are the PBE results acceptable?	INCOMPLETE	
If not, why?	Pending firm's submission of SAS .xpt dataset and additional information on repeat analysis.	

Comments:

The firm's SAC study at 4 kPa fixed pressure drop for the 500/50 mcg strength is **incomplete**.

5.3.3.5.7 Deficiencies / Recommendations

Please see Section 4.10.

5.3.3.6 Aerodynamic Particle Size Distribution (APSD) – 4 kPa Fixed Pressure Drop (500/50 mcg strength)

5.3.3.6.1 Study Information

Study No.	057755-02-08 Protocol #: P21164.00 (b) (4) study number 057755-02-08
Study site	(b) (4)
Principal Investigator	(b) (4)
Study dates	9/30/2015-10/16/2015
SOP No.	MGR-METH-546069 (v. 6.0)
SOP Effective Date	12/22/2014
SOP Title	Determination of aerodynamic particle size distribution of MGR001 (PF-04764793) dry powder inhaler products at 60 l per minute using a (b) (4) Impactor (b) (4) by UPLC.
Testing Method Description	(b) (4) Impactor (b) (4) is used to determine the aerodynamic particle size distribution (APSD) of PF-04764793 in 100/50, 250/50 and 500/50 µg MGR001 dry powder inhaler products containing 50 µg salmeterol as xinafoate salt and 100, 250 or 500 µg fluticasone propionate respectively and for Advair® Diskus® and Seretide® Accuhaler®.
Testing Equipment Used (e.g., name, model, etc)	USP <601> Apparatus 5
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	Flow rates were used through each device to achieve a 4 kPa pressure drop (approximately 60 L/min and 75 L/min, for the MGR001 and RLD products, respectively); 4 L volume. Testing carried out at ambient laboratory conditions.
Analytical Method Description	(b) (4)
Analytical Equipment Used (e.g., name, model, etc)	(b) (4) LC (b) (4) UPLC

Comments:

Reviewer's note: The firm's study protocol (P21164.00) for the current study is similar to the study protocol (P20877.00) for the 100/50 mcg strength APSD study. The reviewer has the same comments regarding to study information as compared to the 100/50 mcg strength APSD study (please see reviewer's comments in Section 5.3.3.2.1) except the firm has different definition for mass balance (please see below). The reviewer also has an additional comment on extra solenoid activation as detailed below.

- **Mass Balance (MB):** calculated as % TDD. TDD values taken from patient information for Advair® Diskus® (45 mcg for SA and 465 mcg for FP).

Please note that according to the RLD labeling³⁰, under standardized in vitro test conditions, RLD delivers 465 mcg of FP and 45 mcg of SA per blister from Advair Diskus 500/50, when tested at a flow rate of 60 L/min for 2 seconds. This is also the target emitted dose in USP monograph for Fluticasone Propionate and Salmeterol Inhalation Powder. Please note that RLD labeling and USP monograph did not mention delivered dose or target emitted dose for flow rate at 30 L/min and 90 L/min.

According to guidance-generating review¹⁷⁶, the total mass of drug collected on all stages¹⁷⁷ and accessories should be between 85 and 115%¹⁷⁸ of label claim on a per actuation basis¹⁷⁹.

- In the study protocol, the firm stated that to clear the test device of any potentially extraneous powder, an extra solenoid activation is recommended after a final waste shot, just prior to an SAC or APSD collection.

5.3.3.6.2 Validation Summary Table for Aerodynamic Particle Size Distribution

5.3.3.6.2.1 Analytical Method Validation for UPLC

Same as the pivotal APSD study for the 100/50 mcg strength (please see Section 5.3.2.2.2.1).

5.3.3.6.2.2 Validation Table for Cascade Impaction

Same as the pivotal APSD study for the 100/50 mcg strength (please see Section 5.3.2.2.2.2).

5.3.3.6.3 Results Summary – Aerodynamic Particle Size Distribution

Firm's results - ISM

Pressure Drop	Active	Life Stage	GM (T)	GM (R)	GMR (T/R)	SD (T)	SD (R)	SD ratio (T/R)
4 kPa	FP	BoL	(b) (4)					

¹⁷⁶ V:\Science Group\Master Files BE Posting\Fluticasone Propionate_Salmeterol Xinafoate_021077\Fluticasone Propionate_Salmeterol Xinafoate_21077_RC09-13.doc, p. 14 of 62.

¹⁷⁷ Footnote as in the guidance-generating review: "Total mass of drug includes drug deposition on each individual site, to include the mouthpiece adapter, throat, preseparator, and each stage of the impactor including the filter, is requested."

¹⁷⁸ Footnote as in the guidance-generating review:

“<http://www.fda.gov/downloads/Drugs/Guidances/ucm070573.pdf>”

¹⁷⁹ Footnote as in the guidance-generating review: "As determined by USP <601> apparatus B."

		EoL	(b) (4)
	Sal	BoL	
		EoL	



Reviewer’s Comments:

- Similar to the 4 kPa pressure drop study on the 100/50 mcg strength, the firm did not provide study data in SAS .xpt file. In addition, the firm did not provide actual dose counter number for the study, thus it is unclear if the firm lost any sample and measured the “next dose” of the same device. Therefore, the firm will be asked to provide SAS dataset with dose counter number included. In addition, for each sample that was lost and “next dose” of the same device was measured, the firm will be asked to provide detailed cause of sample loss as well as supporting documents (e.g. investigational report) for these sample loss. The reviewer’s APSD results will be calculated upon receipt of this information.
- The firm stated that no replacement inhalers were used in this study.
- The firm did not provide mass balance (% of label claim), and thus will be asked to provide so in their SAS .xpt file.

5.3.3.6.4 In Vitro PBE Analysis

As detailed above, analysis will be carried out pending the firm’s submission of SAS dataset and additional information on lost samples.

5.3.3.6.5 Conclusions

AERODYNAMIC PARTICLE SIZE DISTRIBUTION		
REVIEW OF TESTING METHODS:		
Is the testing method for CI test validated?	Yes, but with deficiencies	
Is the analytical method (e.g. HPLC) validated?	Yes, but with deficiencies	
Is the analytical method sufficiently sensitive?	Yes	
Is testing conducted as per RLD labeling?	To be determined	
What is the size of the induction port (or expansion chamber) used for testing?	N/A	
Are ≤ 10 actuations used for cascade impactor study?	Yes (1 actuation)	
If >1 actuation, what is the # of actuations used?	N/A	
Are the testing methods acceptable?	INCOMPLETE	
If not, why?	Due to deficiencies in method validation and study information.	
STUDY RESULTS:		
Is drug deposition reported in mass units?	Yes	
Is the mass balance data reported?	Yes in the study report (pdf format) for individual units, but not in the summary table or SAS .xpt file.	
Results	Does Impactor Size Mass data pass PBE?	To be determined
	Does ISM data pass modified chi-square ratio test?	To be determined
	Do mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle dose (FPD) pass PBE?	To be determined
If not, why?	Pending firm's submission of SAS .xpt dataset and additional information on repeat analysis.	

Comments:

The firm's APSD study at 4 kPa fixed pressure drop for the 500/50 mcg strength is **incomplete**.

5.3.3.6.6 Deficiencies / Recommendations

Please see Section 4.10.

5.4 Clinical Endpoint Study

5.4.1 Study Information

Study Number	MGR001-3001
Study Title	A Randomized, Double-Blind, Double-Dummy, Parallel Group Study to Determine the Local Equivalence of Multiple Doses of MGR001 to Advair® Diskus® Administered Via Oral Inhalation in Adult Asthma Patients
Clinical Site (Name & Address)	Please see table in Section 5.10.1
Principal Investigator	Please see table Section 5.10.1
Study Period	10/22/2014 (First subject first visit) to 7/10/2015 (Last subject last visit)

5.4.2 Product Information

Product	Test	Reference	Placebo
Product Name	MGR001 100/50	Advair® Diskus® 100/50	(A) Placebo for CRC749 (B) Placebo for Diskus®
Manufacturer	MGR Dublin	GSK	(A) MGR Dublin (b) (4)
Batch/Lot No.	Batch 1: lot 631-001 Batch 2: lot 631-002	Lot 4ZP4083	(A): lot 605-039 (B): lot E113247-0003I002
Manufacture Date	Batch 1: 08May2014 Batch 2: 25Jun2014	Not available	(A) 20Dec2013 (B) 19Jul2013
Expiration Date	Batch 1: 07Nov2015 Batch 2: 24Dec2015	30Sep2015	(A): 19Dec2015 (B): 19Jul2016
Strength	100/50 mcg	100/50 mcg	Placebo (lactose only)
Bio-batch Size	(b) (4)	--	--
Production Batch Size	(b) (4)	--	--
Dosage Form	Powder	Powder	Powder
Potency, %	FP Batch 1: 99% Batch 2: 98%	Not provided	--
	SX Batch 1: 99.5% Batch 2: 97.1%	Not provided	
Content Uniformity (Mean, %CV)	FP Batch 1: 99% (93-107%) Batch 2: 104% (96-112%)	Not provided	--
	SX Batch 1: 104% (99-111%) Batch 2: 108% (101-114%)	Not provided	

Dose administered	100 mcg fluticasone propionate/50 mcg salmeterol	100 mcg fluticasone propionate/50 mcg salmeterol	Placebo (lactose only)
Dosing regimen (e.g., BID, QD)	BID	BID	BID
Route of Administration	Oral inhalation	Oral inhalation	Oral inhalation

Reviewer’s Comments:

1. It is noted that the firm used 2 lots of test product in the clinical endpoint study.
2. All lots (test, RLD and placebo) used in the study were unexpired at the time of the study.
3. Same as in fasting studies MGR001-1006 and MGR001-1007, the firm stated that the test device used for the clinical endpoint study (clinical device: (b) (4) is different from the proposed commercial device (b) (4).

As mentioned in Section 5.1.1.1, the firm will be asked to conduct bridging study between the clinical device and the commercial device.
4. As mentioned in Section 5.3.1.1, the firm did not provide COA for the RLD lot (Lot 4ZP4083) used in the clinical endpoint study. Therefore, the firm will be asked to provide this information.

The study information is **incomplete**.

5.4.3 Study Design

Number of Subjects	Enrolled:1871 Randomized: 1128 Dosed:1127 Completed:1097 Firm’s Full Analysis Set: 1122 Firms’ Per Protocol Set: 1105
No. of Periods	2 (1 placebo run-in period, followed by 1 treatment period)
No. of Treatments	3 treatments in the treatment period Treatment 1: one inhalation each from the placebo (RLD device) and test product

¹⁸⁰ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.7\Container Closure System, p. 66-67 of 229).

¹⁸¹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 2.5\Clinical Review, p. 12 of 21).

	Treatment 2: one inhalation each from the placebo (test device) and RLD product Treatment 3: one inhalation from each of the placebo (test device and RLD device)
No. of Sites	101 sites, of which 97 sites screened and enrolled subjects, 3 sites screened but did not enroll any subjects, and 1 site neither screened nor enrolled any subjects but received investigational product.
Placebo Run-In Period	Original Protocol (dated 11/25/2013): 28 days ($\pm$ 2 days) Protocol Amendment (dated 1/26/2015): 28 days (+7/-2 days) This placebo run-in period started after a screening visit (Visit 1), it also incorporates a run-in visit (Visit 2) 3 to 7 days prior to randomization (Please see the firm's study procedures below).
Randomization Scheme (Sequence of T and R)	Please see table below
Inclusion Criteria	1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study. 2. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and all other study procedures. 3. Male or female subjects aged ≥ 18 years. Females may be of either childbearing or non childbearing potential. All females of childbearing potential must be either abstinent from sexual intercourse or using adequate contraception and must also have a negative urine pregnancy test. Pregnant or nursing females or females intending to become pregnant during the course of the study must be excluded from the study. 4. A physician diagnosed history of asthma for at least 12 weeks prior to screening in accordance with National Asthma Education and Prevention Program Expert Panel Report 3 (NAEPP EPR-3). 5. Screening visit (Visit 1) pre-bronchodilator FEV1 50-85% (55-95% for subjects taking ICS or LABA prior to screening) AND run-in visit (Visit 2) pre-bronchodilator FEV1 AND the mean of the pre dose Visit 3 (Day 1) FEV1 measures must be 50-85% of predicted values according to age, height, race and sex using The National Health and Nutrition Examination Survey (NHANES) III predicted values, following abstinence from short-acting beta-agonists for a minimum of 6 hours and withholding restricted medications prior to the visits. Measurement and reproducibility should conform to current American Thoracic Society (ATS) guidelines. 6. Post-bronchodilator reversibility $\geq 12\%$ (within 30 minutes following 360 mcg albuterol (from a pressurized metered dose inhaler [pMDI] and spacer) at either the screening or run-in visit. This may be assessed at the screening visit (Visit 1) or, if necessary (i.e. if not assessed at screening or if assessed and reversibility $< 12\%$) at the run-in visit (Visit 2). 7. Study run in medication compliance of 75-125% of per protocol compliance as assessed from subject diaries and inhaler dose counters. The inhaler dose counter will be the primary method of assessing compliance. 8. Non-smokers and prior smokers with no history of smoking

	within the past 12 months prior to screening and a total smoking history of ≤ 10 pack-years; formula for pack-years: (Average number of cigarettes per day/20) x (years of smoking) Or (Ounces of tobacco per week) x (2/7) x (years of smoking) 9. Where necessary, able to discontinue asthma medications for the duration of the study and be maintained using albuterol prn (as required) during the study. 10. A body mass index between 18-45 kg/m², inclusive. 11. Subjects must be able to use the inhalation devices as assessed at Visit 1 (according to the Instructions for Use).
Exclusion Criteria	1. The presence or recent history, based on complete medical history, full physical examination, 12-lead ECG, or clinical laboratory test results, of any other active, severe, progressive, and/or uncontrolled clinical disease (e.g., renal, hepatic, gastrointestinal, metabolic, endocrine, cardiac, pulmonary, or neurological), other than asthma, such as: • Poorly controlled Type 1 or Type 2 diabetes. • Seizure disorder or epilepsy. • Cerebrovascular accident. • Significant cardiac conduction abnormalities. Subjects with seasonal or perennial allergic rhinitis (i.e., to common aeroallergens) may be included provided they are either asymptomatic (and expect to remain so throughout the study) or are willing to be maintained throughout the study using a regular dose of intranasal corticosteroids and/or oral/intranasal anti-histamines only and the allergy is known not to cause a worsening of asthma symptoms. Stable, well-controlled conditions such as controlled hypertension [but excluding those on beta blockers], thyroid disease, controlled Type 1 and Type 2 diabetes, hypercholesterolemia and gastroesophageal reflux are acceptable provided the symptoms and medication would not be predicted to compromise safety or interfere with the tests and interpretation of the study would be allowed. 2. Evidence of respiratory conditions other than asthma and allergic rhinitis, including but not limited to: severe nasal polyposis or chronic rhinosinusitis, chronic obstructive pulmonary disease, bronchiectasis, Churg-Strauss Disease, lung resection, pulmonary fibrosis (primary or secondary), pulmonary hypertension, cystic fibrosis, sarcoidosis. 3. Significant (as determined by the Investigator) disease instability/uncontrolled asthma, necessitating exclusion from the study following Investigator review. 4. History of life-threatening asthma, defined as a history of asthma episode(s) requiring intubation, and/or associated with hypercapnoea; respiratory arrest or hypoxic seizures, asthma related syncopal episode(s). 5. In patient hospitalization (not including ER visits) for an asthma exacerbation within the past year or during the run in period. 6. An asthma exacerbation in the 3 months prior to screening (defined as worsening asthma symptoms requiring a change in regular asthma maintenance medication or short course of systemic [oral or IV] corticosteroid therapy). 7. A history of seasonally unstable asthma where the season will

	coincide with the subject's participation in the study. 8. Viral or bacterial, upper or lower respiratory tract infection or sinus or middle ear infection within 4 weeks prior to the screening visit or during the run-in period. 9. Use of any of the following excluded respiratory medications within the indicated time frame prior to screening (Visit 1) and throughout the study (subjects may sign consent and washout of medications under the supervision of the Investigator where appropriate): a. Anti-IgE antibody (eg, Xolair®) - 6 months b. Systemic (I.V., I.M., oral) corticosteroids - 3 months c. Orally inhaled corticosteroids - Stop at screening d. Leukotriene receptor antagonists - Stop at screening e. Long-acting anti-muscarinics (e.g., tiotropium, aclidinium) - 48 hours f. Short acting anti-muscarinics (e.g., ipratropium) - 24 hours g. Methylxanthines (e.g., theophylline) - Stop at screening h. Sodium cromoglycate/nedocromil - Stop at screening i. LABA (e.g., salmeterol, formoterol, indacaterol) - 12 hours j. Oral β2-adrenergic agonists - 2 weeks k. Over-the-counter bronchodilators - 2 weeks l. Herbal remedies - 4 weeks 10. Use of prescription or non-prescription drugs as follows: Medication contraindicated in the Advair® Diskus® or albuterol product labels or with the potential to affect the course of asthma or interact with sympathomimetic amines are excluded within 28 days of the first dose of study treatment and throughout the study: • Potent cytochrome P450 3A4 inhibitors (e.g., ritonavir and ketoconazole). • β blockers. • Tricyclic anti-depressants (regardless of the indication). • Oral decongestants. • Benzodiazepines. • Digitalis. • Phenothiazines, e.g. chlorpromazine. • Polycyclic antidepressants. • Monoamine oxidase inhibitors. 11. Suspected hypersensitivity to any sympathomimetic drug (e.g., salmeterol or albuterol) or any orally inhaled, intranasal, or systemic corticosteroid therapy or ingredients of the study drug (including lactose) or severe milk protein allergy. 12. Subjects in whom Advair® Diskus® or albuterol are contraindicated. 13. 12-lead ECG demonstrating QTcF >480 msec or a QRS interval >120 msec at screening. If QTcF exceeds 480 msec, or QRS exceeds 120 msec, the ECG should be repeated two more times and the average of the three QTcF or QRS values should be used to determine the subject's eligibility. 14. Evidence (as assessed by the Investigator using good clinical judgment) of alcohol or drug abuse or dependency at the time of screening, for the 6 months prior to screening. 15. Treatment with an investigational drug within 1 month or at least 5 half-lives (whichever is longer) preceding the first dose of trial medication. 16. Inability to perform required study procedures e.g. to use the

	spirometer correctly (for any reason) or comply with study visits and Lifestyle guidelines. 17. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study.
Randomization Criteria	Subjects were randomly assigned to double-blind treatment provided they had satisfied all subject selection criteria, including predose FEV1 assessments on Day 1 (Visit 3) (inclusion criterion 5). On the day of randomization (Day 1), 2 PFTs (after having withheld albuterol for at least 6 hours) were performed 30 minutes apart, prior to randomization. Under Protocol Amendment 1 (dated 26 Jan 2015), the mean value of the 2 measures of FEV1 must have been 50% to 85% of predicted value to be eligible for the study. The visit could have been rescheduled once if FEV1 criteria were not met, after which the subject was excluded.
IRB Approval (Y/N, Date)	Not clear (the firm will be asked to clarify)
Informed Consent (Y/N, Date)	Not clear (the firm will be asked to clarify)
Subject Screening	At the screening visit (Visit 1), subjects were assessed for entry into the placebo run-in period of the study including evaluation of medical history (including asthma history), concomitant medication use, physical examination, supine or seated blood pressure and pulse rate, 12-lead ECG, laboratory safety data, pregnancy testing (if required), and pulmonary function tests (PFT) that included FEV1 and bronchodilator reversibility. Under the Original Protocol (dated 25 November 2013), subjects were eligible to enter the placebo run-in period if they had a screening visit FEV1 of 60% to 85% of predicted values according to age, height, race, and sex using the Third National Health and Nutrition Examination Survey (NHANES III) (or 60% to 95% of predicted if previously maintained on LABA and/or ICS). Following Protocol Amendment 1 (dated 26 January 2015), the lower end of the FEV1 range was reduced to 50% of predicted (or 55% predicted if previously maintained on LABA and/or ICS).
Length of Confinement	During Visit 3 (Day 1 of double-blinded treatment period), subjects will remain resident in the clinic until after 12 hr post dose pulmonary function tests are completed.
Safety Monitoring	Throughout the study, subjects were instructed to monitor their lung function at home using a peak flow meter to measure peak expiratory flow rate [PEFR]. If, during the study, the subject's PEFR decreased by 20% or more from their mean PEFR (assessed in the last week of the placebo run-in period) on 2 consecutive days, or they had a persistent worsening of their asthma symptoms or found their asthma symptoms unacceptable, subjects were instructed to call the investigative site, where the Investigator (or medically-qualified designee) was to speak with and assess the subject. If required (ie, for subjects with worsening asthma control), the site arranged for the subject to be evaluated by the Investigator in the clinic as soon as possible, if possible before any change in therapy was instituted. Adverse events (AEs) were collected from the signing of the ICF to

	30 days after the last dose of double-blind study medication. Subjects were routinely queried for AEs using open-ended questions. Spontaneously reported AEs were also recorded. The investigator evaluated safety using the following assessments: laboratory values, vital signs, physical exams, or ECG parameters; any clinically significant changes were recorded as AEs. The Investigator was responsible for assessing seriousness, intensity, and relationship of AEs to the study drug (eg, causality assessment). An AE was defined as any untoward medical occurrence in a subject or clinical trial subject administered a medicinal product and which did not necessarily have to have a causal relationship with treatment. An AE could therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An SAE required immediate notification to Mylan Product Safety and Risk Management. "Immediate" was defined as within 24 hours of the Investigator's or site staff's knowledge of the event.

Table 74. Study Procedure (based on original protocol dated 11/25/2013)

	Visit 1 Screening Visit 1 -28 (-2) Days	Visit 2 Run-in Visit (-3 to -7 Days)	Visit 3 Day 1											Visit 4 Day 15 (±2)	Visit 5 Day 29 (±2) End of treatment and follow-up		
			-30 min	0h	0.5h	1h	2h	3h	4h	6h	8h	10h	12h		-30 min	0h	Post Spirometry
Informed Consent	X																
IVRS/IWRS Registration/Entry	X			X													
Medical History (including asthma/atopy) and demographics	X																
Full physical examination (inc. height and weight at Screening)	X																X
Inclusion/exclusion criteria	X	X	X														
Confirm no SABA for 6 hours and other background medications that day	X	X	X											X	X		X
Spirometry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FEV ₁ reversibility	X	X ²															
12-lead ECG/BP/PR	X																X
Lab safety tests (blood and urine) including FSH ¹	X																X
Urine pregnancy test (if applicable)	X		X														X
Inhaler training	X		X														
Dispense PEFr meter and diary & rescue medication	X																
PEFR and complete daily diary	X																X
Diary data review		X	X											X	X		
Concomitant medication	X	X	X											X	X		
Placebo run in	X		X														
Compliance/accountability		X	X											X	X		
Randomization				X													
Administer study drug in clinic				X										X			
Device Questionnaire															X		
Review adverse events		X	X										X	X	X		X

¹ Screening only. ² only if not assessed or <12% reversible at screening visit

Table 75. Study Procedure (based on protocol amendment dated 1/26/2015) (differences from the original study procedure highlighted in red by the reviewer)

	Visit 1 Screening Visit 1 28 (-7/+2) Days pre-Visit 3	Visit 2 Run-in Visit (3 to 7 Days pre-Visit 3)	Visit 3 Day 1											Visit 4 Day 15 (±2)	Visit 5 Day 29 (±2) End of treatment and follow-up		
			-30 min	0h	0.5h	1h	2h	3h	4h	6h	8h	10h	12h		-30 min	0h	Post Spirometry
Informed Consent	X																
IVRS/TWRS Registration/Entry	X			X													X
Medical History (including asthma/atopy) and demographics	X																
Concomitant medication	X	X	X										X	X			
Full physical examination (inc. height and weight at Screening)	X															X	
Inclusion/exclusion criteria	X	X	X														
Confirm no SABA for 6 hours and other background medications that day	X	X	X										X	X		X	
12-lead ECG/BP/PR	X															X	
Spirometry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
FEV ₁ reversibility	X	X ²															
Lab safety tests (blood and urine) including FSH ¹	X															X	
Urine pregnancy test (if applicable)	X		X													X	
Inhaler training	X		X														
Dispense PEFR meter and diary & rescue medication	X																
PEFR and complete daily diary	X-----X																
Diary data review		X	X											X	X		
Placebo run in	X-----X																
Compliance/accountability		X	X											X	X		
Randomization				X													
Administer study drug in clinic	X	X		X									X ³	X			
Device Questionnaire															X		
Review adverse events		X	X-----X											X	X	X	

¹ Screening only. ² only if not assessed or <12% reversible at screening visit. ³ Evening dose may be administered in clinic after completion of 12h spirometry

Comments on Study Design:

1. It is noticed that the firm also submitted the synopsis of this clinical endpoint study in their IND 118769 11/25/2015 annual report.¹⁸² The firm stated that this synopsis is extracted from the full clinical study reports that would be presented in the upcoming ANDA submission (which is the current application).¹⁸³ This annual report may not have been reviewed as the review of this annual report could not be located in DARRTS¹⁸⁴ or in GDRP¹⁸⁵. Therefore, this will be the first review of the firm's clinical endpoint study.
2. For the study design, the current product-specific guidance recommends a randomized, multiple-dose, placebo-controlled, parallel group design consisting of a 2 week run-in period followed by a 4-week treatment period of the placebo, T or R product. The firm conducted randomized, *double-blind, double-dummy*, placebo-controlled, parallel group design consisting of a 4 week run-in period followed by a 4-week treatment period. To maintain the blind, subjects were required to take one inhalation from each of 2 inhalers, one Diskus[®] and once CRC749 (each containing either active or matched placebo treatment) morning and evening. This difference in study design (i.e. double-blind, double-dummy, and 4 week run-in period) was found acceptable in CC #13-0422.¹⁸⁶
3. The firm did not provide formulation table for the placebo. However, they stated that the placebo contained lactose only and was supplied in placebo inhalers that matched the CRC749 inhaler (test placebo) or Diskus[®] inhaler (RLD placebo). It should be noted that for both test and RLD product, lactose (in monohydrate form) is the only excipient. Therefore, the reviewer will not pursue this issue further.

Protocol

4. The firm's original protocol (dated 11/25/2013) was amended (dated 1/26/2015) during the study [10/22/2014 (first subject first visit) to 7/10/2015 (last subject last visit)] "*[f]ollowing review of screen failure subjects and discussions with [i]nvestigators*"¹⁸⁷. The reviewer could not locate IRB approval information of the original protocol and its amendment. Therefore, the firm will be asked to provide such information.
5. The firm did not specify starting when, how many and which subjects were recruited under the protocol amendment. In addition, although the firm stated that subjects had different criteria for screening visit FEV1 %predicted depending on

¹⁸² GS Review: IND 118769, New/Annual Report, 11/25/2015 (Module 5.3.5.1\MGR001-3001 Synopsis.pdf).

¹⁸³ GS Review: IND 118769, New/Annual Report, 11/25/2015 (Module 1.2\Cover Letter – 0021 – Annual Report – 20151125, p. 2 of 3).

¹⁸⁴ DARRTS: IND 118769, View Application. Last accessed: 7/7/2016.

¹⁸⁵ GDRP: search term: 118769. Last accessed: 12/6/2016.

¹⁸⁶ [\cdsnas\OGDS6\CONTROLS\2013-docs\13-0422.pdf](#) p. 11-13 of 28.

¹⁸⁷ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.5.1\Protocol or Amendment, p. 119 of 149).

the protocol they were enrolled under¹⁸⁸, it is unclear whether subjects also had different criteria for rest of the protocol (e.g. criteria for FEV1 %predicted during Visits 2 and 3; whether rescheduling during placebo run-in period for failed %predicted FEV1 and reversibility were allowed; and acceptable days of placebo run-in period) depending on the protocol they were enrolled under. Since DCR will make PPP recommendation, this issue will be deferred to DCR. Please note that DCR has issued a deficiency on this issue.¹⁸⁹

6. Major changes made in the protocol amendment are listed below in comparison to the original protocol and product-specific guidance. Please note that both the original and amendment protocol had a few inclusion criteria that are different from the product-specific guidance. Reviewer's comments of these differences is listed in the table below or below the table (depending on the length of the comments).

¹⁸⁸ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.5.1\Study Report Body\MGR001-3001 Study Report, p. 37-38 of 811).

¹⁸⁹ GDRP: ANDA 208891, Clinical Primary Review, A208891N000DCR_ANDAconsult.docx, 1/23/2017.

a) Pre-bronchodilator FEV1 of the predicted value

According to the product-specific guidance, pre-bronchodilator FEV1 is recommended to be 40-85% of the predicted value during the screening visit and on the first day of treatment. And one of the inclusion criteria is that subject should be able to discontinue their asthma medications (ICS and LABA) during the run-in period and for remainder of the study.

Firm's criterion for FEV1 of predicted

In the **original protocol**, the firm's criterion for FEV1 of predicted is 60-85% for screening visit (Visit 1), run-in visit (Visit 2) and treatment Day 1 (Visit 3). This 60-85% criterion was found acceptable in CC 13-0422. In addition, the product-specific guidance does not require Visit 2, thus the firm's criterion in Visit 2 is considered as an additional criterion as compared to the guidance. Therefore, the reviewer considers it acceptable.

In the **protocol amendment**, the firm broadened the FEV1 criterion to 50-85% of predicted for Visits 1-3. Although this is still within the guidance recommendation of 40-85%, the change of criterion happened during the course of the study. During the 10/17/2016 internal meeting with DCR, ORS, and OTS, DCR stated that 505 subjects (out of the 2726 subjects who were screened and enrolled) had pre-bronchodilator FEV1 of 50% to 59.9% at visit 1, 2 or 3. Among these 505 subjects, 145 subjects were randomized into the test treatment group, 146 in the reference treatment group, 31 in the placebo treatment group, and 183 subjects not randomized into the treatment phase. DCR states that since the subjects falling under 50% to 59.9% pre-bronchodilator FEV1 are balanced among 3 groups (T, R and placebo), this broaden of FEV1 criterion is considered acceptable.

Firm's criterion for FEV1 of predicted for subjects who previously maintained on LABA and/or ICS

In both of the **original and amendment protocols**, the firm also had FEV1 criteria of 60-95% (original protocol) or 55-95% (protocol amendment) of predicted at screening Visit 1 for "*subjects taking ICS or LABA prior to screening*".¹⁹⁰ This upper limit of 95% is higher than what is recommended in the product-specific guidance (40-85%). In addition, although the guidance did not specify whether the recommended 40-85% is also applicable for subjects who take ICS or LABA prior to screening, one of the inclusion criteria is that subject should be able to discontinue asthma medications (ICS and LABA) during the run-in period and for remainder of the study.

¹⁹⁰ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.5.1\Protocol or Amendment\Protocol and Amendments, p. 18 and 80 of 149).

It should be noticed that in the firm's submission for CC 13-0422, the firm also proposed to have FEV1 of 60-90% predicted for subjects taking ICS prior to screening visit (please note that this range is narrower than the ranges in the current protocols, and did not include a situation for subjects who took LABA). However, CC reviewer did not comment on whether this is acceptable or not.

According to the protocol¹⁹¹, at screening Visit 1, “[s]ubjects taking a LABA should stop taking the LABA (combination therapy containing a LABA should also be stopped) at least 12 hours prior to the assessment of the screening pulmonary function tests; this may require an additional visit in order to obtain informed consent prior to stopping LABA or LABA containing combination therapy.” Additionally, subjects should stop ICS at screening. This is in line with the product-specific guidance. Therefore, it is unclear how the firm defines “subjects taking ICS or LABA prior to screening” (e.g. how long prior to screening), how the firm came up with the 60-95% and 55-95% criteria, and how many and which subjects fell under this category. Since DCR will make PPP recommendation, this issue will be deferred to DCR. Please note that DCR has issued a deficiency on this issue.¹⁸⁹

b) Rescheduling

In both the original and amendment protocols, the firm allowed for rescheduled visit for subjects who do not meet the FEV1 criteria in Visit 3 and reversibility criteria in Visit 1. The protocol amendment additionally allows for rescheduled visit for subjects who do not meet the FEV1 criteria in Visits 1-2. This is considered acceptable according to internal meeting between DBI, DCR, ORS and OTS.¹⁹²

c) Duration of placebo run-in period

The firm changed their duration of placebo run-in period of 28±2 days in the original protocol to 28-7/+2 days in the protocol amendment. Since both duration meets the duration recommended in the product-specific guidance (2 weeks), and having variable duration of run-in period may introduce more variation into the study, which makes the study more difficult to pass, the reviewer considers this change of run-in period duration acceptable. Please note that this change is also considered acceptable according to the aforementioned internal meeting.¹⁹²

¹⁹¹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.5.1\Protocol or Amendment\Protocol and Amendments, p. 30 and 93 of 149).

¹⁹² V:\DIVISION\BIO\BIO1\Meeting Minutes\DBI non-Bio Management Meeting\2016\ 08292016-09082016 ANDA 208891_ (b) (4) Fluticasone_salmeterol DPI.doc

d) Upper limit of BMI

In the protocol amendment, the firm increased its upper limit of BMI from 40 kg/m² to 45 kg/m². It should be noticed that the product-specific guidance does not have recommendation for BMI. In addition, in the 1128 subjects that were randomized into the study, 3.7% of them (42 subjects) had BMI between 40 and 45 kg/m². The ratio of these subjects among different treatment group (RLD: 16 subjects, test: 22 subjects, placebo: 4 subjects) is also comparable to the ratio of all randomized subjects (RLD:test:placebo of 5:5:1). Therefore, the reviewer considers this change acceptable. Please note that this change is also considered acceptable according to the aforementioned internal meeting.¹⁹²

e) Spirometry Data Quality

In the **original protocol**, the firm stated that the spirometry data quality needs to meet ATS guideline criteria. This criteria still hold true for visit 1 (or the rescheduled visit) in the protocol amendment. However, according to this protocol amendment, for other visits, subjects with “borderline acceptable” (technically acceptable but the repeatability criterion is not met) data will be allowed. According to the aforementioned internal meeting¹⁹², this “borderline acceptable” is not a term in the ATS guideline. Additional information is needed for subjects with “borderline acceptable” (e.g. which subjects had “borderline acceptable” data, and how the firm decide which FEV1 value to report for these subjects). Since DCR will make PPP recommendation, this issue will be deferred to DCR. Please note that DCR has issued a deficiency on this issue.¹⁸⁹

7. According to the product-specific guidance, subjects should be able to withhold the different forms of theophylline for *12-36 hrs* (depending on the specific form of theophylline) *prior* to each clinic visit. It is noticed that both of the original and amendment protocols stated that subjects should be stopped from theophylline *at screening*. However, since no subjects that were enrolled in the study had theophylline as their prior or concomitant medication, this difference does not impact the study outcome. Therefore, the reviewer will not pursue this issue further.
8. According to the study report, during the placebo run-in period, compliance was to have been 75% to 125%, inclusive, of per-protocol dosing for subjects to be eligible to enter the double-blind treatment period of the study. The primary assessment of compliance was the dose counter on inhalers.

For the double-blind treatment period, which used a double dummy dosing technique, overall compliance for each test and RLD treatment group was derived from the corresponding *active* inhaler component. For the Placebo treatment group, overall compliance was based on the compliance from the placebo inhaler

component with the highest absolute deviation from 100%. If both placebo inhaler compliances had the same absolute deviation from 100% then the lower compliance was reported. A subject was considered compliant if their overall study drug compliance was between 75% to 125%, inclusive, of per-protocol dosing. This is in line with the product-specific guidance. Therefore, the reviewer considers the firm's definition of compliant subject acceptable.

9. Per study report, baseline for trough FEV1 on Day 29 was calculated by taking the mean of [prebronchodilator FEV1 measured at run-in (Visit 2) and the mean of the 2 predose FEV1 measures taken at Day 1 (Visit 3)]. In addition, baseline for FEV1 AUEC0-12 endpoint was the mean of the 2 predose FEV1 measures (30 minutes and 0 hr predose). Please note that the baseline for each of the two clinical endpoints (i.e. for FEV1 AUEC0-12 and trough FEV1) is different.

According to the product-specific guidance, a FEV1 baseline is defined as the average of pre-dose FEV1 values of at least two time points measured in the morning of the first day of a 4 week treatment period. This baseline definition is consistent with the one used for RLD approval. In general, RLD's study design, which is also how the guidance is generated, will be referenced.¹⁹³ However, since the firm's baseline selection was found acceptable in CC 13-0422,¹⁹⁴ the reviewer will not pursue this issue further.

The firm's study design is **incomplete**.

¹⁹³ Based on internal discussion with ORS.

¹⁹⁴ <\\cdsnas\OGDS6\CONTROLS\2013-docs\13-0422.pdf> p. 14 and 24 of 28.

5.4.4 Demographic Profile of Subjects (Safety Population, Full Analysis Set, and Per-Protocol Population)

Demographic (Safety Population)		Test (N)	Reference (N)	Placebo (N)	p value
Age (years)	Mean ± SD	42.6 ± 14.08	42.5 ± 14.21	43.5 ± 13.85	N/A
	Range	18-84	18-81	18-77	
Gender (N and %)	Female	306 (59.8%)	309 (60.4%)	64 (62.1%)	N/A
	Male	206 (40.2%)	203 (39.6%)	39 (37.9%)	
Ethnicity (N and %)	Hispanic/Latino	102 (19.9%)	92 (18.0%)	24 (23.3%)	N/A
	Not Hispanic/Latino	410 (80.1%)	420 (82.0%)	79 (76.7%)	
Race (N and %)	White	378 (73.8%)	372 (72.7%)	73 (70.9%)	N/A
	Black/African American	92 (18.0%)	98 (19.1%)	22 (21.4%)	
	Native Hawaiian/Other Pacific Islander	1 (0.2%)	0 (0%)	1 (1.0%)	
	Asian	11 (2.1%)	11 (2.1%)	1 (1.0%)	
	American Indian/Alaska Native	0 (%)	0 (0%)	0 (0%)	
	Other	30 (5.9%)	31 (6.1%)	6 (5.8%)	

Demographic (MITT Population)*		Test (N)	Reference (N)	Placebo (N)	p value
Age (years)	Mean ± SD	42.6 ± 14.09	42.5 ± 14.23	43.5 ± 13.92	N/A
	Range	18-84	18-81	18-77	
Gender (N and %)	Female	305 (59.9%)	308 (60.3%)	64 (62.7%)	N/A
	Male	204 (40.1%)	203 (39.7%)	38 (37.3%)	
Ethnicity (N and %)	Hispanic/Latino	101 (19.8%)	92 (18.0%)	24 (23.5%)	N/A
	Not Hispanic/Latino	408 (80.2%)	419 (82.0%)	78 (76.5%)	
Race (N and %)	White	377 (74.1%)	371 (72.6%)	73 (71.6%)	N/A
	Black/African American	91 (17.9%)	98 (19.2%)	21 (20.6%)	
	Native Hawaiian/Other Pacific Islander	1 (0.2%)	0	1 (1.0%)	
	Asian	10 (2.0%)	11 (2.2%)	1 (1.0%)	
	American Indian/Alaska Native	0	0	0	
	Other	30 (5.9%)	31 (6.1%)	6 (5.9%)	

* The firm stated that the term 'Full Analysis Set (FAS)' is used in place of 'mITT' in the MGR001-3001 clinical study report

Demographic (Per-Protocol Population)		Test (N)	Reference (N)	Placebo (N)	p value
Age (years)	Mean ± SD	42.7 ± 14.11	42.4 ± 14.23	43.5 ± 13.98	N/A
	Range	18-84	18-81	18-77	
Gender (N and %)	Female	301 (60.0%)	302 (60.2%)	63 (62.4%)	N/A
	Male	201 (40.0%)	200 (39.8%)	38 (37.6%)	
Ethnicity (N and %)	Hispanic/Latino	98 (19.5%)	92 (18.3%)	23 (22.8%)	N/A
	Not Hispanic/Latino	404 (80.5%)	410 (81.7%)	78 (77.2%)	
Race (N and %)	White	373 (74.3%)	367 (73.1%)	72 (71.3%)	N/A
	Black/African American	88 (17.5%)	95 (18.9%)	21 (20.8%)	
	Native Hawaiian/Other Pacific Islander	1 (0.2%)	0	1 (1.0%)	
	Asian	10 (2.0%)	10 (2.0%)	1 (1.0%)	
	American Indian/Alaska Native	0	0	0	
	Other	30 (6.0%)	30 (6.0%)	6 (5.9%)	

Reviewer comments:

1. According to the study report, the randomization ratio is 5:5:1 for test:RLD:placebo. Demographic characteristics are consistent with this ratio, and are consistent between safety, full analysis and per-protocol (PP) population.
2. The product-specific guidance recommends male and female subjects (≥ 12 years of age) of non-child bearing potential or of child bearing potential committing to consistent and correct use of an acceptable method of birth control. The firm recruited subjects that were ≥ 18 years of age. As mentioned in Reviewer's Comment #6 in Section 5.4.3, this was considered acceptable in CC 13-0433.
3. According to the biostatistics consult response¹⁹⁵, the demographic and baseline characteristics such as age, gender, race, ethnicity, BMI, duration of asthma, geographical region, FEV1 at the screening visit, and FEV1 at the run-in visit in the FDA's modified intent-to-treat population (mITT population, which according to the biostatistics reviewer, is essentially the same as the firm's SS in this application) were similar across the 3 study groups.

The demographic profile of subjects is **acceptable**.

¹⁹⁵ GDRP: ANDA 208891, Documents, A208891_Statistical.doc, 8/12/2016.

5.4.5 Discontinued/Early Terminated Subjects

Reason for Discontinuation	Test	Reference	Placebo	Total
Adverse Events	4,	4,	4, (b) (6)	12
Insufficient Therapeutic Response/Treatment Failure	0	0	0	0
Lost to follow-up	3,	5,	1, (b) (6)	9
Restricted Medication	0	0	0	0
Withdrew Consent	6,	3, (b) (6)	0	9
Non-Compliance	0	0	0	0
Mis-randomization	0	1, (b) (6)	0	1

Detailed reason of discontinuation for each subject is listed below.¹⁹⁶

Study Treatment	Subject	Reason for Discontinuation	Adverse Event Preferred Term (If Applicable)
MGR001 100/50	(b) (6)	Adverse Event	Rhinitis allergic
		Other: Patient can't continue to Visit 5 because he has to move out of state due to family emergency	N/A
		Withdrawal by subject	N/A
		Other: Lost to follow up	N/A
		Adverse Event	Bronchitis
		Withdrawal by subject	N/A
		Withdrawal by subject	N/A
		Adverse Event	Pneumonia
		Withdrawal by subject	N/A
		Withdrawal by subject	N/A
		Other: Lost to follow up	N/A
		Withdrawal by subject	N/A
		Adverse Event	Asthma
		Advair®	Other: Lost to follow up
Diskus®	Other: Subject never returned to site for visits	N/A	

¹⁹⁶ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 2.7.4\Summary of Clinical Safety, p. 8 of 33).

100/50	(b) (6)	4 and 5	
		Other: Lost to follow up	N/A
		Adverse Event	Sinusitis
		Adverse Event	Anxiety and Insomnia
		Withdrawal by subject	N/A
		Adverse Event	Asthma
		Other: Leaving country for a few weeks, will not be able to do V5 within window	N/A
		Adverse Event	Pneumonia
		Other: Subject decision	N/A
		Other: Lost to follow up	N/A
		Withdrawal by subject	N/A
Placebo	(b) (6)	Adverse Event	Inguinal hernia
		Other: Lost to follow up	N/A
		Adverse Event	Bronchitis
		Adverse Event	Asthma
		Adverse Event	Asthma

Reviewer's Comments:

A total of 1128 subjects were randomized in the treatment period. One subject (b) (6) in the RLD group was not treated due to mis-randomization. Among 1127 subjects that were treated in the treatment period, 1097 subjects completed the study and 30 subjects discontinued from the study due to reasons listed above.

The impact of subject discontinuation/early termination on PPS selection will be evaluated by DCR.

5.4.6 Study Adverse Events

Description	Test N(%)	Reference N(%)	Placebo N(%)	Total N(%)
Patients Randomized	512	512*	103	
Patients with at least one AEs	72 (14.1%)	75 (14.6%)	15 (14.6%)	162 (14.4%)
Discontinued study drug due to above AE	4 (0.8%)	4 (0.8%)	4 (3.9%)	12 (1.1%)
AEs reported	92	99	18	209
Mild	57	62	10	129
Moderate	35	37	8	80
Severe	0	0	0	0
Definite Related	2	2	0	4
Probably Related	3	6	0	9
Possibly Related	9	7	2	18
Unlikely Related	12	11	4	27
Not Related	66	73	12	151
Death	0	0	0	0
Serious AE	0	0	0	0

*513 subjects were randomized but 512 received at least one dose of double-blind study drug.

Table 76. Overall Summary of Treatment-Emergent Adverse Events (TEAE) - Safety Set

Number of subjects with	MGR001 100/50		Advair® Diskus® 100/50		Placebo		Total	
	N = 512		N = 512		N = 103		N = 1127	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any TEAE	72 (14.1)	92	75 (14.6)	99	15 (14.6)	18	162 (14.4)	209
Any study drug-related TEAE	14 (2.7)	14	14 (2.7)	15	2 (1.9)	2	30 (2.7)	31
Any severe TEAE	0	0	0	0	0	0	0	0
Any severe study drug-related TEAE	0	0	0	0	0	0	0	0
Any treatment-emergent SAE	0	0	0	0	0	0	0	0
Any study drug-related treatment-emergent SAE	0	0	0	0	0	0	0	0
Any TEAE leading to treatment discontinuation	4 (0.8)	4	4 (0.8)	5	4 (3.9)	4	12 (1.1)	13
Any AE leading to death	0	0	0	0	0	0	0	0

Abbreviations: AE, adverse event; E, the number of events at each level of summarization; N, number of subjects in each treatment group for the analysis set; n, number of subjects at each level of summarization; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Note: Study drug-related TEAEs were AEs assessed as 'possible', 'probable' or 'definite', including AEs with unknown or missing relationship.

Table 77. Most Frequent TEAE by System Organ Class and by Preferred Term Occurring in at Least 3 Subjects across Treatment Groups - Safety Set

System Organ Class Preferred Term	MGR001 100/50	Advair® Diskus® 100/50	Placebo	Total
	N = 512	N = 512	N = 103	N = 1127
	n (%) [E]	n (%) [E]	n (%) [E]	n (%) [E]
Number of subjects with at least 1 TEAE^a	72 (14.1) [92]	75 (14.6) [99]	15 (14.6) [18]	162 (14.4) [209]
Infections and infestations	34 (6.6) [34]	38 (7.4) [39]	5 (4.9) [5]	77 (6.8) [78]
Upper respiratory tract infection	7 (1.4) [7]	11 (2.1) [11]	0	18 (1.6) [18]
Nasopharyngitis	3 (0.6) [3]	7 (1.4) [7]	2 (1.9) [2]	12 (1.1) [12]
Sinusitis	3 (0.6) [3]	3 (0.6) [3]	1 (1.0) [1]	7 (0.6) [7]
Oral candidiasis	4 (0.8) [4]	2 (0.4) [2]	0	6 (0.5) [6]
Urinary tract infection	2 (0.4) [2]	2 (0.4) [2]	0	4 (0.4) [4]
Viral upper respiratory tract	1 (0.2) [1]	3 (0.6) [3]	0	4 (0.4) [4]
Bronchitis	2 (0.4) [2]	0	1 (1.0) [1]	3 (0.3) [3]
Gastroenteritis	0	3 (0.6) [3]	0	3 (0.3) [3]
Viral infection	1 (0.2) [1]	2 (0.4) [2]	0	3 (0.3) [3]
Respiratory, thoracic and mediastinal disorders	15 (2.9) [20]	25 (4.9) [29]	7 (6.8) [7]	47 (4.2) [56]
Asthma	7 (1.4) [9]	10 (2.0) [13]	5 (4.9) [5]	22 (2.0) [27]
Oropharyngeal pain	3 (0.6) [3]	5 (1.0) [5]	1 (1.0) [1]	9 (0.8) [9]
Dysphonia	1 (0.2) [1]	3 (0.6) [3]	0	4 (0.4) [4]
Cough	1 (0.2) [1]	2 (0.4) [2]	0	3 (0.3) [3]
Gastrointestinal disorders	6 (1.2) [9]	5 (1.0) [6]	1 (1.0) [1]	12 (1.1) [16]
Dyspepsia	1 (0.2) [1]	2 (0.4) [2]	0	3 (0.3) [3]
Nervous system disorders	6 (1.2) [6]	6 (1.2) [6]	0	12 (1.1) [12]
Headache	3 (0.6) [3]	5 (1.0) [5]	0	8 (0.7) [8]
Musculoskeletal and connective tissue disorders	4 (0.8) [4]	4 (0.8) [4]	1 (1.0) [1]	9 (0.8) [9]
Injury, poisoning and procedural complications	2 (0.4) [2]	3 (0.6) [4]	1 (1.0) [1]	6 (0.5) [7]
Investigations	3 (0.6) [4]	2 (0.4) [2]	0	5 (0.4) [6]
Cardiac disorders	3 (0.6) [3]	0	1 (1.0) [1]	4 (0.4) [4]
General disorders and administration site conditions	2 (0.4) [3]	2 (0.4) [2]	0	4 (0.4) [5]
Skin and subcutaneous tissue disorders	2 (0.4) [2]	1 (0.2) [1]	0	3 (0.3) [3]

Abbreviations: AE, adverse event; E, the number of events at each level of summarization; N, number of subjects in each treatment group for the analysis set; n, number of subjects at each level of summarization; TEAE, treatment-emergent adverse event.

Note: Treatment-emergent adverse events were reported. The total number of AEs counts all TEAEs for subjects.

^a At each level of subject summarization, a subject was counted once if the subject reported one or more events. The preferred terms were presented by decreasing frequency of incidence for all treatment groups combined

5.4.6.1 Description of Adverse Events (per Applicant)

Overall, there were 162 subjects who experienced 209 treatment-emergent adverse events (TEAEs), with the percentage of subjects experiencing any TEAE being similar among the 3 treatment groups. The percentage of subjects experiencing any study drug-related

TEAE or TEAE leading to treatment discontinuation was comparable between the test and RLD treatment groups and both active treatments were lower compared to placebo treatment group. There were no incidences of treatment-emergent serious AEs (fatal, nonfatal, or drug-related) reported.

When evaluated by System Organ Class (Table 17), the most frequent categories; which represented almost two-thirds of the 209 TEAEs reported, were Infections and Infestations (78 events experienced by 77 subjects), and Respiratory, Thoracic and Mediastinal Disorders (56 events experienced by 47 subjects).

When evaluated by preferred term, there were no TEAEs that occurred in more than 5% of the subjects for any treatment group. The most common TEAEs across all 3 treatment groups (Table 17) were asthma (2.0%) and upper respiratory tract infection (1.6%); the percentage of subjects was similar between the 3 treatment groups, with the exception of asthma which was more frequently observed in the placebo group (4.9%) versus the active treatment groups (test: 1.4% and RLD: 2.0%).

Of the 209 TEAEs reported by 162 subjects (14.4%), there were 129 TEAEs of mild severity that were reported by 98 subjects and 80 TEAEs of moderate severity that were reported by 64 subjects. There were no severe TEAEs reported.

Most subjects experienced TEAEs that were considered not related or unlikely related to study drug. There were only 4 subjects (0.4%) that reported 4 TEAEs definitely related to study drug.

Overall, there were 12 subjects who experienced 13 TEAEs leading to discontinuation of treatment. In each treatment group, there were 4 subjects that experienced AEs that led to discontinuation of study drug.

Reviewer's Comments:

AE comparison between test and RLD treatment group

Overall, the test and the RLD products had comparable adverse events. There is no strong evidence suggesting that the test product caused substantially more serious AEs compared to the RLD product.

AE during the placebo run-in period

According to the study report¹⁹⁷, the firm stated that 6 subjects experienced non-treatment-emergent serious AEs during the *placebo run-in period*. All of these serious AEs were recovered/resolved except for 1 subject (b) (6) psychogenic non-epileptic spell, pattern: intermittent, severity: moderate) that was not recovered/not resolved.¹⁹⁸ Since these subjects were not yet treated with test or RLD product that time, these serious AEs are considered unrelated to the study drug.

¹⁹⁷ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.5.1\Study Report Body\MGR001-3001 Study Report, p. 160 of 811).

¹⁹⁸ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.5.1\Study Report Body\MGR001-3001 Study Report, p. 598-600 of 811).

The impact of AE on study endpoints and PPS selection will be evaluated by DCR.

5.4.7 Protocol Deviations

Reviewer's Note: Please note that the firm's table below only listed protocol deviations that were considered to be significant by the firm. For a complete list of protocol deviations (regardless of significant or not), please see Table 18 in reviewer's comments.

Protocol Deviation Type	Test	Reference	Placebo	Total
Randomized in error	0	1, (b) (6) ^ @ \$	0	1
Significant protocol deviations resulting in exclusion from Safety, mITT*, and/or Per Protocol Sets:				
History of other acute or chronic medical condition (exclusion #17)	2, (b) (6) ^	4, (b) (6) ^	0	6
Randomized into trial more than once	3, (b) (6) ^ @	1, (b) (6) ^ @	1, (b) (6) ^ @	5
Concomitant use of beta-blockers after randomization	1, (b) (6) ^	2, (b) (6) ^	0	3
Post-bronchodilator reversibility not $\geq 12\%$	2, (b) (6) ^	0	1, (b) (6) ^	3
History of symptomatic seasonal or perennial allergic rhinitis not controlled by medication	1, (b) (6) ^	1, (b) (6) ^	0	2
FEV ₁ at V1, V2 and pre-dose V3 not 60-85% of predicted	1, (b) (6) ^	0	0	1
Inadequate control of investigational product (dose dumping)	0	1, (b) (6) ^	0	1
Visit performed outside of protocol schedule (run-in period 10 days only)	0	1, (b) (6) ^	0	1
History of smoking within the past 12 months	0	1, (b) (6) ^	0	1
Did not take a single dose of study medication	0	1, (b) (6) ^	0	1
All significant protocol deviations, including those that did and did not result in exclusion from Safety, mITT*, or Per Protocol Sets:				
Non-Compliance	24	19	4	47
Lost To Follow Up	0	0	0	0
Outside Visit Window	9	15	2	26
Restricted Medication	4	8	2	14
Spirometry performed outside time window	85	89	19	193

Dosed prior to completion of pre-dose assessments at Visit 5 (Day 29)	4	2	0	6
Met at least one exclusion criterion	4	9	1	14
Did not meet at least one inclusion criterion	4	3	1	8
Randomized into trial more than once	3	1	1	5
Consumed caffeine prior to visit	1	0	0	1
Investigator subject medical care (spirometry data not evaluated by site in timely manner)	3	1	1	5
Incorrect treatment kit ID assigned/dispensed	0	1	1	2
Inadequate control of investigational product	0	1	0	1

* The term 'Full Analysis Set (FAS)' is used in place of 'mITT' in the MGR001-3001 clinical study report by the firm.

^ Excluded from PPS by the firm

@ Excluded from FAS by the firm.

§ Excluded from SS by the firm.

Comments on Protocol Deviations:

According to the study report¹⁹⁹, protocol deviations were documented on an ongoing basis and were reviewed prior to database lock and unblinding. According to the firm's protocol deviation dataset²⁰⁰, a total of 2034 protocol deviation occurrences in 793 subjects were identified prior to database lock and unblinding. Please note that the firm's table above only listed protocol deviations that were considered significant by the firm.

The firm also stated that they identified additional protocol deviations post database lock.²⁰¹ The firm's protocol deviations (identified pre-database lock and post-database lock) and their impact on SS, FAS and PPS are summarized in Table 78 below.

The firm's definition²⁰² of SS, FAS and PPS are below:

Safety Set (SS):

The Safety Set was defined as all randomly assigned subjects who had taken at least one dose of study drug and for whom postdose safety data were available. Subjects in this set were analyzed and summarized according to their actual treatment received.

Full Analysis Set (FAS):

¹⁹⁹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.5.1\Study Report Body\MGR001-3001 Study Report, p. 112 of 811).

²⁰⁰ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.5.1\Data Tabulation Data\Data Tabulation Dataset SDTM\dy).

²⁰¹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.5.1\Study Report Body\MGR001-3001 Study Report, p. 114-115 of 811).

²⁰² GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.5.1\Study Report Body\MGR001-3001 Study Report, p. 79 of 811).

The Full Analysis Set was defined as all randomly assigned subjects who had taken at least one dose of study drug and had provided data for either the FEV1 AUEC0-12 co-primary endpoint measured on Day 1 (Visit 3), the trough FEV1 measured on Day 15 (Visit 4), or the trough FEV1 co-primary endpoint measured on Day 29 (Visit 5), including a corresponding baseline FEV1 value. Subjects in this set were analyzed and summarized according to their assigned treatment at randomization.

Per Protocol Set (PPS):

The Per Protocol Set was defined as all subjects in the Full Analysis Set who had not violated, or deviated from, the protocol in such a way that could have affected the outcome of the FEV1 assessments for both primary endpoints.

It should be noted that the firm's PPS definition does not require a subject to meet all inclusion/exclusion criteria, or be compliant with the dosing schedule in the treatment period (between 75% and 125%). In addition, subjects will be remained in PPS if they had not violated, or deviated from, the protocol that could have affected the outcome for the FEV1 assessments for **both** primary endpoints.

According to internal meeting between DBI, DCR, ORS and OTS ¹⁹², PPS should meet all inclusion/exclusion criteria, and should meet the compliance criteria for the treatment period. In addition, PPS should exclude subjects that do not meet the criteria for **either** primary endpoints. For exploratory analyses, PPS will be selected for the AUEC0-12 endpoint (Day 1), and then a separate PPS will be selected for the trough FEV1 endpoint (Week 4).

The impact of protocol deviations on study endpoints and PPS selection will be reviewed by DCR.

5.4.8 Statistical Results

Table 79. Primary Endpoint Analysis Results (firm's results)

	Per Sponsor		
Primary Endpoint 1 (continuous endpoint)			
	Test	Reference	Placebo
PP Population	Endpoint: Change from baseline AUEC ₀₋₁₂ FEV ₁ on Day 1		
N	502	502	101
LS Mean	3.9734 (L hr)	3.5411 (L hr)	0.8400 (L hr)
90% CI for Test and Reference for Mean Response (e.g., test/reference or test-reference)	Ratio of LS means (test/reference): 1.120 90% CI: 1.016, 1.237		Not applicable
90% CI for Test and Reference for Median Response (e.g., test/reference or test-reference)	Not applicable		Not applicable
mITT* Population			
N	508	510	102
LS Mean	3.9534 (L hr)	3.4964 (L hr)	0.8191 (L hr)
(Test or Reference) vs. Placebo (p-value)	3.1343 (L hr) (p<0.0001)	2.6773 (L.hr) (p<0.0001)	Not applicable

* The term 'Full Analysis Set (FAS)' is used in place of 'mITT' in the MGR001-3001 Clinical Study Report.

	Per Sponsor		
Primary Endpoint 2 (continuous endpoint)			
	Test	Reference	Placebo
PP Population	Endpoint: Change from baseline Trough FEV₁ on Day 29 (± 2 days)		
N	498	497	99
LS Mean	0.2911 (L)	0.2728 (L)	0.0574 (L)
90% CI for Test and Reference for Mean Response (e.g., test/reference or test-reference)	Ratio of LS means (test/reference): 1.069 90% CI: 0.938, 1.220		Not applicable
90% CI for Test and Reference for Median Response (e.g., test/reference or test-reference)	Not applicable		Not applicable
mITT* Population			
N	504	505	100
LS Mean	0.2927 (L)	0.2720 (L)	0.0575 (L)
(Test or Reference) vs. Placebo (p-value)	0.2352 (L) (p<0.0001)	0.2145 (L) (p<0.0001)	Not applicable

* The term 'Full Analysis Set (FAS)' is used in place of 'mITT' in the MGR001-3001 Clinical Study Report.

Reviewer's Comments:

According to the study report (p. 96 of 811), the firm used actual time of collection to calculate FEV1 AUC0-12.

- On 6/6/2016, DBI sent a biostatistics consult to OTS/OB/DBVIII for a statistical evaluation of the clinical endpoint study data.¹⁸ Please note that the biostatistics consult response¹⁹ was based on the firm's PPS and DCR will recommend Agency's PPS to OTS. In general, the biostatistics reviewer was able to verify the firm's results using their ANCOVA model and Fieller's formula.

Blinded sample size re-estimation

- As per the study protocol, a blinded sample size re-estimation was conducted after 286 subjects completed Visit 5 and provided data for both the primary efficacy endpoints. The total sample size complete the study was revised from 836 to 990 subjects so that the study would have at least 81% power to show equivalence between the two active products for the trough FEV1 endpoint. The biostatistics reviewer considered that no adjustment on Type I error due to this interim analysis was needed since the plan was pre-specified.

Equivalence

- In the consult response, the biostatistics reviewer identified some minor statistical issues such as missing time point assessment handling for FEV1 AUEC0-12 calculation, etc. However, the biostatistics reviewer did not consider these issues have any major impact on the applicant's primary results since the biostatistics reviewer's sensitivity analyses showed similar findings.
- The biostatistics reviewer also noticed that when the firm excluded additional subjects with significant protocol deviations and/or adverse events solely related to the trough FEV1 on Day 29 endpoint from PPS in a sensitivity analysis, the equivalence finding of the test to RLD product for this endpoint was no longer observed. The biostatistics reviewer considers that the firm's primary results for the baseline-adjusted trough FEV1 on Day 29 endpoint were not robust enough to the analysis population used. Again this finding underscores the importance of PPS identification for this study.

Sensitivity

- According to the biostatistics consult response, the current practice of OTS for the firm's FAS population is to include all randomized subjects who have taken at least one study drug. This is referred to as FDA's mITT population. The biostatistics reviewer also noted that the FDA's mITT population is essentially the same as the firm's safety population.
- According to the biostatistics consult response, both active drugs were statistically superior to placebo with respect to the co-primary efficacy endpoints using the firm's FAS as well as the FDA's mITT population, and thus assay sensitivity was confirmed.

Please note that the above statistical comments are based on the firm's PPS, and are subject to change upon the identification of the Agency's PPS that will be recommended by DCR.

5.4.9 Device Questionnaire

Reviewer's note: As mentioned in the reviewer's comment for the study design, the device use in this clinical endpoint study (clinical device: (b) (4) is different from the proposed commercial device (b) (4). Therefore, subject experience with the commercial device might be different from the clinical device, and thus might not be reflected from this device questionnaire.

5.4.9.1 Questionnaire Information

Subjects were given a questionnaire at Day 29 (± 2 days; Visit 5) or early termination to complete in order to assess the ease of inhalation through the double-blind inhalers. The questionnaire contains the following questions:

For both CRC749 and Diskus[®]:

a. How easy or difficult did you find it to inhale (breathe in) through this inhaler?

1	2	3	4	5
Very Difficult	Difficult	Neutral	Easy	Very Easy

b. Based on how easy or difficult you found it to inhale through the device, would you use this device for your asthma medicine in the future if it were prescribed by your doctor or given to you by your pharmacist?

Yes	No

One (1) additional question for Diskus[®] only:

c. Have you used the Diskus[®] inhaler before this study?

Yes	No

5.4.9.2 Results Summary

Table 80. Summary of Device Usability Questionnaire by Inhaler Type and Treatment Group - Safety Set

	MGR001 100/50	Advair® Diskus® 100/50	Placebo	Total
	N = 512	N = 512	N = 103	N = 1127
	n (%)	n (%)	n (%)	n (%)
Total number of subjects who filled out the Device Usability Questionnaire				
	504 (98.4)	504 (98.4)	101 (98.1)	1109 (98.4)
Responses for the MGR001 inhaler				
How easy or difficult did you find it to inhale (breathe in) through this inhaler?				
Very difficult	1 (0.2)	3 (0.6)	0	4 (0.4)
Difficult	17 (3.4)	11 (2.2)	4 (4.0)	32 (2.9)
Neutral	35 (6.9)	36 (7.1)	7 (6.9)	78 (7.0)
Easy	125 (24.8)	149 (29.6)	25 (24.8)	299 (27.0)
Very Easy	326 (64.7)	305 (60.5)	65 (64.4)	696 (62.8)
Mean Score	4.5	4.5	4.5	4.5
Based on how easy or difficult you found it to inhale through the device, would you use this device for your asthma medicine in the future if it were prescribed by your doctor or given to you by your pharmacist?				
Yes	474 (94.0)	476 (94.4)	95 (94.1)	1045 (94.2)
No	30 (6.0)	28 (5.6)	6 (5.9)	64 (5.8)
Responses for the Diskus® inhaler				
How easy or difficult did you find it to inhale (breathe in) through this inhaler?				
Very difficult	1 (0.2)	0	2 (2.0)	3 (0.3)
Difficult	6 (1.2)	5 (1.0)	2 (2.0)	13 (1.2)
Neutral	25 (5.0)	24 (4.8)	6 (5.9)	55 (5.0)
Easy	126 (25.0)	134 (26.6)	28 (27.7)	288 (26.0)
Very Easy	346 (68.7)	341 (67.7)	63 (62.4)	750 (67.6)
Mean Score	4.6	4.6	4.5	4.6
Based on how easy or difficult you found it to inhale through the device, would you use this device for your asthma medicine in the future if it were prescribed by your doctor or given to you by your pharmacist?				
Yes	488 (96.8)	484 (96.0)	97 (96.0)	1069 (96.4)
No	16 (3.2)	20 (4.0)	4 (4.0)	40 (3.6)

Note: Percentages for each questionnaire response is calculated based on the total number of subjects (n) who filled out the Device Usability Questionnaire. All other percentages are calculated based on the number of subjects in each treatment group in the Safety Set.

Reviewer's Comments:

The device questionnaire is not mentioned in the product-specific guidance, but was recommended by the agency to the firm in CC13-0422²⁰⁶ to “evaluate/capture patients’ experience with the use of MGR001” in order to “provide justification that the airflow

²⁰⁶ <\\cdsnas\OGDS6\CONTROLS\2013-docs\13-0422.pdf> p. 28 of 28.

resistance difference between MGR001 and the RLD does not impact the usability” of the test product.

According to the study report, a total of 1109 (98.4%) subjects in the Safety Set filled out the device usability questionnaire with 69.1% of the subjects having previously used Diskus[®] inhaler.

Overall, as summarized in the table above, %subjects that found the CRC749 inhaler easy or very easy to use (89.8%) was comparable to %subjects that found the Diskus[®] inhaler easy or very easy to use (93.6%). And %subjects that would use the CRC749 inhaler again (94.2%), if prescribed, was comparable to the percentage of subjects that would use the Diskus[®] inhaler again (96.4%), if prescribed. The results were comparable across the treatment groups (test, RLD, and placebo).

The firm also summarized questionnaire response for the subset of subjects who completed the study, and similar results were observed.²⁰⁷

The firm also stratified the questionnaire response by subjects’ previous Advair[®] Diskus[®] experience prior to the study²⁰⁸ (please see the reviewer-summarized table below). It is noticed that for subject that were naïve to Advair[®] Diskus[®], %subjects that found the CRC 749 inhaler easy or very easy to use is numerically higher than %subjects that found the Diskus[®] easy or very easy to use, whereas it is the opposite for Advair[®] Diskus[®] experienced subjects. However, these numbers are still comparable. The results were comparable across the treatment groups (test, RLD, and placebo), and similar findings were observed for the subset of subjects who completed the study²⁰⁹.

	Overall		Advair [®] Diskus [®] Naive		Advair [®] Diskus [®] Experienced	
	CRC749	Diskus [®]	CRC749	Diskus [®]	CRC749	Diskus [®]
% subjects that found the inhaler easy or very easy to use	89.8%	93.6%	93.2%	91.8%	88.3%	94.3%
% subjects that would use the inhaler again	94.2%	96.4%	95.3%	95.0%	93.7%	97.0%

As mentioned above, since the device use in the clinical endpoint study (clinical device: (b) (4) is different from the proposed commercial device (b) (4) (b) (4) subject experience with the commercial device might be different and thus might not be reflected from this device questionnaire.

²⁰⁷ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.5.1\Study Report Body\MGR001-3001 Study Report, p. 458-459 of 811).

²⁰⁸ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.5.1\Study Report Body\MGR001-3001 Study Report, p. 460-463 of 811).

²⁰⁹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.5.1\Study Report Body\MGR001-3001 Study Report, p. 464-467 of 811).

5.5 Flow Profiling Study

Reviewer's note: Please note that this study is considered unacceptable due to the use of non-US RLD. Other deficiencies identified in this section will be communicated to the firm for them to take consideration for their repeat study.

5.5.1 Study Information

Study Number	MGR000-1003		
Study Title	An open study to measure the inhaled flow rates generated by healthy volunteers and patients inhaling through the CRC749 and Accuhaler™/Diskus® dry powder inhalers		
Clinical Site (Name & Address)	Site	Principal Investigator	Address
	1	Dominik Kappeler	Inamed Clinical Unit, 82131 Gauting, Germany
	2	Isabelle Schenkenberger	Clinical Research Berlin GbR; 10787 Berlin, Germany
	3	Prof. Dr. med. Walter Dorsch	Practice for Child and Adolescent Medicine, Allergy, Pediatric Pulmonology, Naturopathic, 81379 Munich, Germany
	4	Dr. med. Manfred Praun	Practice for Child and Adolescent Medicine Dr. Praun & Dr. Stiebing, 82205 Gilching, Germany
	5 (not activated)	Prof. Dr. med. Stefan Zielen	University Hospital Johann Wolfgang Goethe-Universität Frankfurt/Main, Centre for children and adolescents, Departement of paediatric pneumology, allergology and cystic fibrosis, 60590 Frankfurt/Main, Germany
Principal Investigator	Please see table above		

Study Period	Date of first signed ICF: 8/20/2013 Date of last follow-up: 12/18/2013

5.5.2 Product Information

Product	Test	Reference
Product Name	CRC749 (DPI), empty inhaler, contained within an inhaler connecting box	Accuhaler™/Diskus® (DPI), empty inhaler, contained within an inhaler connecting box
Manufacturer	Not provided	Not provided
Batch/Lot No.	547-047	547-046
Manufacture Date	Not provided	Not provided
Expiration Date	Not provided	Not provided
Strength	N/A (empty inhaler)	N/A (empty inhaler)
Bio-batch Size	--	--
Production Batch Size	--	--
Dosage Form	Empty inhaler	Empty inhaler
Potency, %	N/A (empty inhaler)	N/A (empty inhaler)
Content Uniformity (Mean, %CV)	N/A (empty inhaler)	N/A (empty inhaler)
Dose administered	N/A (empty inhaler)	N/A (empty inhaler)
Dosing regimen (e.g., BID, QD)	3 sequential oral inhalations	3 sequential oral inhalations
Route of Administration	Oral inhalation	Oral inhalation

5.5.3 Study Design

Number of Subjects	Screened and Signed ICF: 93 Randomized: 80 Dosed: 80 Completed: 80 Firm's Inhalation Analysis Set: 78
No. of Groups	5 <u>Group 1:</u> Healthy subjects aged 18-60 years, inclusive: N = 10 <u>Group 2:</u> Children with asthma aged 4 -7 years: N =20 (children aged 4 years: N = 4, children aged 5 years: N= 5, children aged 6 years: N= 6, children aged 7 years: N= 5) <u>Group 3:</u> Children with asthma aged 8 - 11 years: N = 20

	<u>Group 4</u>: Adult subjects with severe asthma aged 18 to 80 years: N = 14 <u>Group 5</u>: Adult subjects with severe COPD aged 40 to 80 years: N = 14
No. of Sequences	2
No. of Periods	<u>Visit 1</u>: screening <u>Visit 2</u>: inhalation profile generation for T and R devices (Group 1-3: 0-21 days after Visit 1; Groups 4 and 5: 1-14 days after Visit 1) <u>Visit 3</u>: telephone follow-up (1-7 days after Visit 2)
No. of Treatments	No treatment (empty inhaler). However, each subject was asked to generate 3 inhalation profiles through one device then 3 inhalation profiles through the other device. Both of these procedures were performed at Visit 2. There was an interval of 5-10 mins rest between the inhalation profile measurements with the first and the second DPI.
Randomization Scheme (Sequence of T and R)	Please see table below
Inclusion Criteria	<i>Inclusion criteria: All subjects:</i> • Subjects who were willing and able to comply with scheduled visits and study procedures. <i>Inclusion criteria: Group 1: Healthy volunteers</i> • Male and female healthy adult subjects. (Healthy was defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement). • Age 18-60 years inclusive. • Evidence of a signed and dated informed consent. • Body Mass Index (BMI): of 18 to 30.5 kg/m² inclusive; and a total body weight ≥ 45 kg (99 lbs). • Forced expiratory volume in the 1st second (FEV1) and forced vital capacity (FVC) ≥ 80% of predicted for age, height, sex and race for a subject to be eligible for the study. • Female patients of childbearing potential had to use an acceptable method of contraception starting from Screening (Visit 1) through to completion of all study procedures. • Non-smoker or ex-smoker for at least six months with a smoking pack history of ≤ 10 pack years.(pack years = (average number of cigarettes per day /20) x years of smoking cigarettes prior to Screening (Visit 1). • No history of chronic airway disease, no current evidence of upper or lower respiratory tract infection. <i>Inclusion criteria: Group 2: Children with asthma (controlled and partly controlled acc. to GINA, 2012)</i> • Male and female children. • Age from 4 to 7 years, inclusive (with at least N= 2 aged 4 years, at least N=5 aged 5 years, at least N= 5 aged 6 years

and at least N= 5 aged 7 years).

- Established diagnosis of asthma for a minimum of six months, diagnosed by an appropriately skilled physician.
- Lung function of either:
 - FEV1 (after abstaining from the restricted medicines²) of $\geq 60\%$ of predicted for age, height, sex and race for subjects aged 4, 5, 6 & 7, *or*
 - Morning Peak Expiratory Flow (PEF) (after abstaining from the restricted medicines of $\geq 60\%$ of predicted for age, height, sex and race for subjects aged 4 and 5 only.
- Subjects either:
 - Regularly use asthma medication for maintenance therapy for a minimum of three months prior to Screening (Visit 1). Maintenance therapy included treatment with inhaled corticosteroids (ICS), combinations of ICS and long acting β 2-agonists (LABA), leukotriene antagonists (LTA), *or*
 - Demonstrated reversibility, defined as an increase in FEV1 (or a morning PEF for 4 & 5 year olds) of $\geq 10\%$ (within 15-45 minutes following inhalation of 200 μ g salbutamol, administered from an MDI with a spacer) as measured during Screening (Visit 1). Documented reversibility meeting the above criteria within the last 12 months of Screening (Visit 1) was acceptable.
- For children and parents or legal representatives: Understanding of the study and agreement to give written informed consent by parents or legal representatives and written informed assent by each child.
- Able and willing to participate in the study.

Inclusion criteria: Group 3: Children with asthma (controlled and partly controlled acc. to GINA, 2012)

- Male and female children.
- Age from 8 to 11 years inclusive.
- Established diagnosis of asthma for a minimum of six months, diagnosed by an appropriately skilled physician.
- Lung function: FEV1 $\geq 60\%$ of predicted for age, height, sex and race after abstaining from the restricted medicines
- Subjects either:
 - Regularly use asthma medication for maintenance therapy for a minimum of three months prior to Screening (Visit 1). Maintenance therapy included treatment with inhaled corticosteroids (ICS), combinations of ICS and long acting β 2-agonists (LABA), leukotriene antagonists (LTA), *or*
 - Demonstrated reversibility, defined as an increase in FEV1 of $\geq 10\%$ (within 15-45 minutes following intake of 200 μ g salbutamol, administered from an MDI with a spacer) as measured during Screening (Visit 1).

Documented reversibility meeting the above criteria within the last 12 months of Screening (Visit 1) was acceptable.

- Female subjects had to be premenarchal.
- For children and parents or legal representatives: Understanding of the study and agreement to give written informed consent by parents or legal representatives and written informed assent by each child.
- Able and willing to participate in the study.

Inclusion criteria: Group 4: Adult subjects with severe asthma (acc. to GINA 2008, controlled and partly controlled acc. to GINA, 2012)

- Male and female subjects aged 18 to 80 years, inclusive.
- Evidence of a signed and dated informed consent.
- Established diagnosis of severe asthma diagnosed by an appropriately skilled physician (acc. to GINA 2008, controlled and partly controlled acc. to GINA, 2012) for at least six months prior to Screening (Visit 1) and who meet the following criterion:
 - Pre-bronchodilator FEV1 of $\leq 60\%$ of predicted for age, height, sex and race after abstaining from the restricted medicines
 - Reversibility, defined as an increase in FEV1 of $\geq 12\%$ and ≥ 200 mL (within 15-45 minutes following intake of 400 μ g salbutamol, administered from an MDI with a spacer) as measured during Screening (Visit 1).
- Regular treatment with inhaled asthma medication at a constant dosage during the last 4 weeks prior to Screening (Visit 1).
- Female subjects of childbearing potential had to use an acceptable method of contraception starting from Screening (visit 1) through to completion of all study procedures.
- If subject was an ex-smoker or current smoker they had to have a smoking pack history of ≤ 10 pack years (pack years = average number of cigarettes per day /20) x years of smoking cigarettes prior to Screening (Visit 1).

Inclusion criteria Group 5: Subjects with severe COPD (GOLD Stage III, 2011)

- Male and female subjects aged 40 to 80 years, inclusive.
- Evidence of a signed and dated informed consent.
- Established diagnosis of COPD diagnosed by an appropriately skilled physician (according to GOLD, 2011 update) for at least six months prior to Screening (Visit 1) who after abstaining from using short acting β -agonists (SABA) for a minimum of 6 hours and short acting anticholinergics for a minimum of 8 hours and following administration of 400 μ g of salbutamol administered from an MDI with a spacer at clinic, met the following criterion:
 - Severe COPD (GOLD III) - Post-bronchodilator FEV1/FVC ratio of <0.7 and a postbronchodilator FEV1 of $\geq 30\%$ and $< 50\%$ of predicted for age, height, sex and race.

	• Regular treatment with any COPD medication at a constant dosage during the last 4 weeks prior to Screening (Visit 1). • Female subjects of childbearing potential had to use an acceptable method of contraception starting from Screening (visit 1) through to completion of all study procedures. • Subject's had to be a smoker or ex-smoker with a smoking pack history of ≥ 10 pack years (pack years = average number of cigarettes per day /20) x years of smoking cigarettes prior to Screening (Visit 1).
Exclusion Criteria	• Acute exacerbation of bronchial asthma or COPD or hospitalisation/emergency room visits due to asthma/COPD exacerbation within the last 2 months prior to study participation. • History of life-threatening asthma episodes (e.g. emergency treatment requiring intubation, etc.). • Salbutamol intolerance or contraindication to salbutamol. • Requirement for oral/injectable steroid therapy due to respiratory disease within the last three months prior to Screening (Visit 1). • Significant lung/lower respiratory tract diseases other than the asthma or COPD diagnosis for each of the subject populations. • Surgery of the lower respiratory tract/lung or significant deformity (e.g. lung, conducting airways, thorax or vertebral column deformities) that may cause persistent airflow limitation or altered lung volumes. • Significant acute or chronic viral, bacterial or fungal airway infections. Point of recovery from lower respiratory tract infections should be 30 days or more prior to Screening (Visit 1). • Other chronic or clinically relevant acute infections. • Neurological diseases affecting the neuro-muscular function or performance of respiratory muscles, e.g. such as Myasthenia Gravis or Amyotrophic Lateral Sclerosis. • Drug or alcohol abuse which would interfere with the subject's compliance. • Exposure to an investigational agent or participation in another medical device study within the last 4 weeks or 5 half-lives (whichever was longer in the case of an investigational agent) prior to Screening (Visit 1) and during the study. • Employee of study site. • Vulnerable subjects (e.g. person kept in detention). • Anticipated non-availability for study visits/procedures. • Obvious mental or physical incapacity to follow study procedures and investigator instructions adequately. • Pregnant or lactating subjects. Any concomitant disease or condition, or use of concomitant medication which in the opinion of the Investigator could have an impact on the study participation or subject safety.
Randomization Criteria	Subjects were randomized into the study provided they had satisfied all selection criteria. In addition, each subject visiting the clinic on

	separate occasions for Visits 1 and 2 had to have the largest FEV1 value at Visit 2 within 15% of the largest FEV1 recorded at Visit 1. Each group was randomized to either receive the CRC749 first followed by the Accuhaler™/Diskus® or receive the Accuhaler™/Diskus® first followed by the CRC749.
IRB Approval (Y/N, Date)	7/26/2013
Informed Consent (Y/N, Date)	3/5/2013 (English version), 3/22/2013 (German version)
Subject Screening	Each prospective subject (or parents/legal representatives as appropriate) had to agree to participate in screening procedures by signing the Informed Consent Form (ICF) before any screening procedure was initiated. In addition children had to sign the assent form before any screening procedures were initiated. The Principal Investigator (PI) or Investigator reviewed the inclusion and exclusion criteria to confirm and document eligibility of each subject prior to enrolment. Subjects were to be screened within 0-21 days (Groups 1, 2, 3) or 1-14 days (Groups 4 and 5) prior to Visit 2, to confirm they met the subject selection criteria for the study. Visit 2 testing had to be conducted $\pm$ 2 hours of Screening (Visit 1). For Groups 4 and 5, Screening (Visit 1) and Visit 2 had to be conducted between 07:00 and 11:00 hours on the assessment day. The following procedures were performed: • Informed consent procedure. • Documentation of demography. • Documentation of medical history (during the last six months). • Physical examination including height and weight. • Measurement of vital signs. • Review of prior medication. • Medication restriction: Subjects with asthma or COPD had to abstain from the restricted medicines prior to spirometry at Visit 1. • Spirometry (FEV1, FVC & IC). • Test of reversibility for asthmatic subjects (all subjects from Group 4 and subjects from Groups 2 and 3 as required) and post-bronchodilator spirometry for COPD subjects (Group 5). • Review of inclusion/exclusion criteria.
Length of Confinement	During study visits
Safety Monitoring	All AEs were listed by individual subject and tabulated by subject group and device whether or not the AE was related to the use of the device. Concomitant medication was listed by individual subject (categorized by subject group and device) and summarized by subject group and device.

Randomization Scheme

Group=Group 1: Healthy subjects, aged 18-60 years

Treatment A = CRC749, Treatment B = ACCUHALER/DISKUS

Block	Random No.	Subject ID	Sequence	Period 1	Treatment	Period 2
1		(b) (6)	BA	B		A
			AB	A		B
2			AB	A		B
			BA	B		A
3			BA	B		A
			AB	A		B
4			BA	B		A
			AB	A		B
5	AB	A		B		
	BA	B		A		
6	AB	A		B		
	BA	B		A		
7	BA	B		A		
	AB	A		B		
8	BA	B		A		
	AB	A		B		

Group=Group 2a: Children with asthma aged 4 years

Treatment A = CRC749, Treatment B = ACCUHALER/DISKUS

Block	Random No.	Subject ID	Sequence	Period 1	Treatment	Period 2
1		(b) (6)	AB	A		B
			BA	B		A
2			BA	B		A
			AB	A		B
3			AB	A		B
			BA	B		A

Group=Group 2b: Children with asthma aged 5 years

Treatment A = CRC749, Treatment B = ACCUHALER/DISKUS

Block	Random No.	Subject ID	Sequence	Period 1	Treatment	Period 2
1	[REDACTED]	(b) (6)	A B	A		B
			B A	B		A
2			A B	A		B
			B A	B		A
3			B A	B		A
			A B	A		B
4			B A	B		A
			A B	A		B
5			B A	B		A
			A B	A		B

Group=Group 2c: Children with asthma aged 6 years

Treatment A = CRC749, Treatment B = ACCUHALER/DISKUS

Block	Random No.	Subject ID	Sequence	Period 1	Treatment	Period 2
1	[REDACTED]	(b) (6)	A B	A		B
			B A	B		A
2			B A	B		A
			A B	A		B
3			B A	B		A
			A B	A		B
4			B A	B		A
			A B	A		B
5			A B	A		B
			B A	B		A

Group=Group 2d: Children with asthma aged 7 years

Treatment A = CRC749, Treatment B = ACCUHALER/DISKUS

Block	Random No.	Subject ID	Sequence	Period 1	Treatment	Period 2
1	[REDACTED]	(b) (6)	A B	A		B
			B A	B		A
2			B A	B		A
			A B	A		B
3			A B	A		B
			B A	B		A
4			A B	A		B
			B A	B		A
5			B A	B		A
			A B	A		B

Group=Group 3: Children with asthma aged 8-11 years

Treatment A = CRC749, Treatment B = ACCUHALER/DISKUS

Block	Random No.	Subject ID	Sequence	Period 1	Treatment	Period 2
1		(b) (6)	BA AB	B A		A B
2			AB BA	A B		B A
3			BA AB	B A		A B
4			BA AB	B A		A B
5			BA AB	B A		A B
6			BA AB	B A		A B
7			BA AB	B A		A B
8			AB BA	A B		B A
9			BA AB	B A		A B
10			AB BA	A B		B A
11			AB BA	A B		B A
12			BA AB	B A		A B
13			AB BA	A B		B A

Group=Group 4: Adult subjects with asthma, aged 18 to 80 years

Treatment A = CRC749, Treatment B = ACCUHALER/DISKUS

Block	Random No.	Subject ID	Sequence	Period 1	Treatment	Period 2
1		(b) (6)	B A A B	B A		A B
2			B A A B	B A		A B
3			B A A B	B A		A B
4			B A A B	B A		A B
5			B A A B	B A		A B
6			A B B A	A B		B A
7			B A A B	B A		A B
8			B A A B	B A		A B
9			B A A B	B A		A B

Group=Group 5: Adults subjects with severe COPD, aged 40-80 years

Treatment A = CRC749, Treatment B = ACCUHALER/DISKUS

Block	Random No.	Subject ID	Sequence	Period 1	Treatment	Period 2
1		(b) (6)	A B	A		B
			B A	B		A
2			B A	B		A
			A B	A		B
3			B A	B		A
			A B	A		B
4			A B	A		B
			B A	B		A
5			A B	A		B
			B A	B		A
6			A B	A		B
			B A	B		A
7			B A	B		A
			A B	A		B
8			A B	A		B
			B A	B		A
9			B A	B		A
			A B	A		B

Study Flow Chart

Visit Number	1	2	3 ³
	Screening (Visit 1)	0-21 days after Visit 1 (Group 1, 2, 3) 1-14 days after Visit 1 (Group 4 and 5)	1-7 days after Visit 2
Informed consent	X		
Inclusion/Exclusion criteria	X		
Demography	X		
Medical history ⁴	X		
Prior / Concomitant medication	X ⁵	X	
Physical examination (including height and weight)	X	X ⁶	
Vital signs ⁷	X		
Medication restriction, if applicable	X	X	
Spirometry (FEV ₁ , FVC, FEV ₁ /FVC, IC)	X	X ⁸	
Post-bronchodilator spirometry (only COPD subjects, Group 5)	X		
Reversibility test (Groups 2, 3 & 4 as required)	X		
Training with test devices under the guidance of study staff		X	
Randomisation		X	
Measurement of inspiratory profiles		X	
AEs	X	X	X

³ Phone Call

⁴ During last six months

⁵ 4 weeks preceding Visit 1.

⁶ Shortened physical examination (including only respiratory examination, prior to and post measurement of inspiratory profiles. If Visit 1 and Visit 2 were on the same day, the physical examination at Visit 1 was to be used as prior to flow profiling measurement at Visit 2.

⁷ Blood pressure and pulse rate after 5 min rest in seated position.

⁸ Performed prior to measurement of inspiratory profiles. If Visit 1 and Visit 2 were on the same day, the spirometry data from Visit 1 were to be used.

Reviewer's Comments:

1. The firm stated in the clinical overview that the aim of the study was to determine inhalation profile parameters through empty CRC749 inhalers, in particular peak inhaled flow rate (PIF) data. The firm stated that this study was conducted to 1) ensure that all patients groups could achieve a PIF above the lower limit of the range of flow rates which in vitro BE is determined (i.e. ≥ 30 L/min), and 2) to provide flow profile parameters which may be included in the labeling, as required.

Regarding the firm's aim 2) above, according to *Draft Guidance for Industry – Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products – Chemistry, Manufacturing, and Controls Documentation* (posted on Oct 1998):

“A statement should be included that the amount of drug delivered to the lung will depend on patient factors such as inspiratory flow and peak inspiratory flow (PIF) through the device, which may vary for different asthma and COPD patient populations. The labeling should include typical PIF values for patients within a

range of pulmonary function. The details provided on these values should relate the findings of in vivo flow rate studies and describe the relationship of these flow rates to demographics (i.e., adult vs. pediatric and any gender effect) and to the degree of airflow obstruction (i.e., the PIF obtained in subjects with a particular level of FEV1 decrement). The flow rates given should include the mean rate for any given group and, in parentheses following the mean, the range found in that group.”

As mentioned in the table above, the current study was conducted in 5 groups of subjects:

- i) healthy adult subjects,
- ii) children with asthma (aged 4-7 years),
- iii) children with asthma (aged 8-11 years),
- iv) subject with severe asthma,
- v) subjects with severe COPD.

The firm stated in their study report that these study populations were selected as they covered the extremes of the range of subjects in whom the devices will be used either during their development (i.e. BE studies are conducted in healthy adult subjects) or in clinical use.

Please note that this study population is similar, but not the same as the study population described in the RLD labeling:

- i) adolescent (aged 12 to 17 years) and adult (aged 18 to 50 years) subjects with asthma,
 - ii) pediatric subjects with asthma (aged 4 years),
 - iii) pediatric subjects with asthma (aged 8 years),
 - iv) adult subjects with obstructive lung disease and severely compromised lung function (mean FEV1 20% to 30% of predicted).
2. It is noted that the firm used GINA instead of NAEPP, which was the guideline listed in the product-specific guidance for the clinical endpoint study, for asthma diagnosis and patient screening. Similar issue was previously found in (b) (4) and was consulted to ORS. In the consult response, ORS stated that “GINA/ATS guidance has been used in efficacy studies submitted to and accepted by the Agency in the past. From a clinical perspective, the two guidelines are similar, and ensure that the patient populations are comparable. Both organizations provide comprehensive guidance to diagnosis and management of asthma. (b) (4)
- ” Therefore, the use of GINA guidance is deemed acceptable.

3. According to the study report, the CRC749 and Accuhaler™/Diskus® inhalers used in this study did not contain any drug substance or any powder excipients. Subjects did not inhale any powder particles.
4. It is noticed that although the firm stated the reference devices used are Accuhaler™/Diskus® inhalers, on p. 40 of 321 of their study report, they stated that the reference batch (batch # 547-046) is **Accuhaler** [reviewer's note: Accuhaler™ is sold in countries such as the European Union (EU), and the US is marketed with Diskus®].

Since the firm used non-US version of the RLD for the study, based on 1/18/2017-1/19/2017 meeting with OB management¹²⁷, the current study is for information only and the firm will be asked to repeat the flow profiling study using US RLD product.

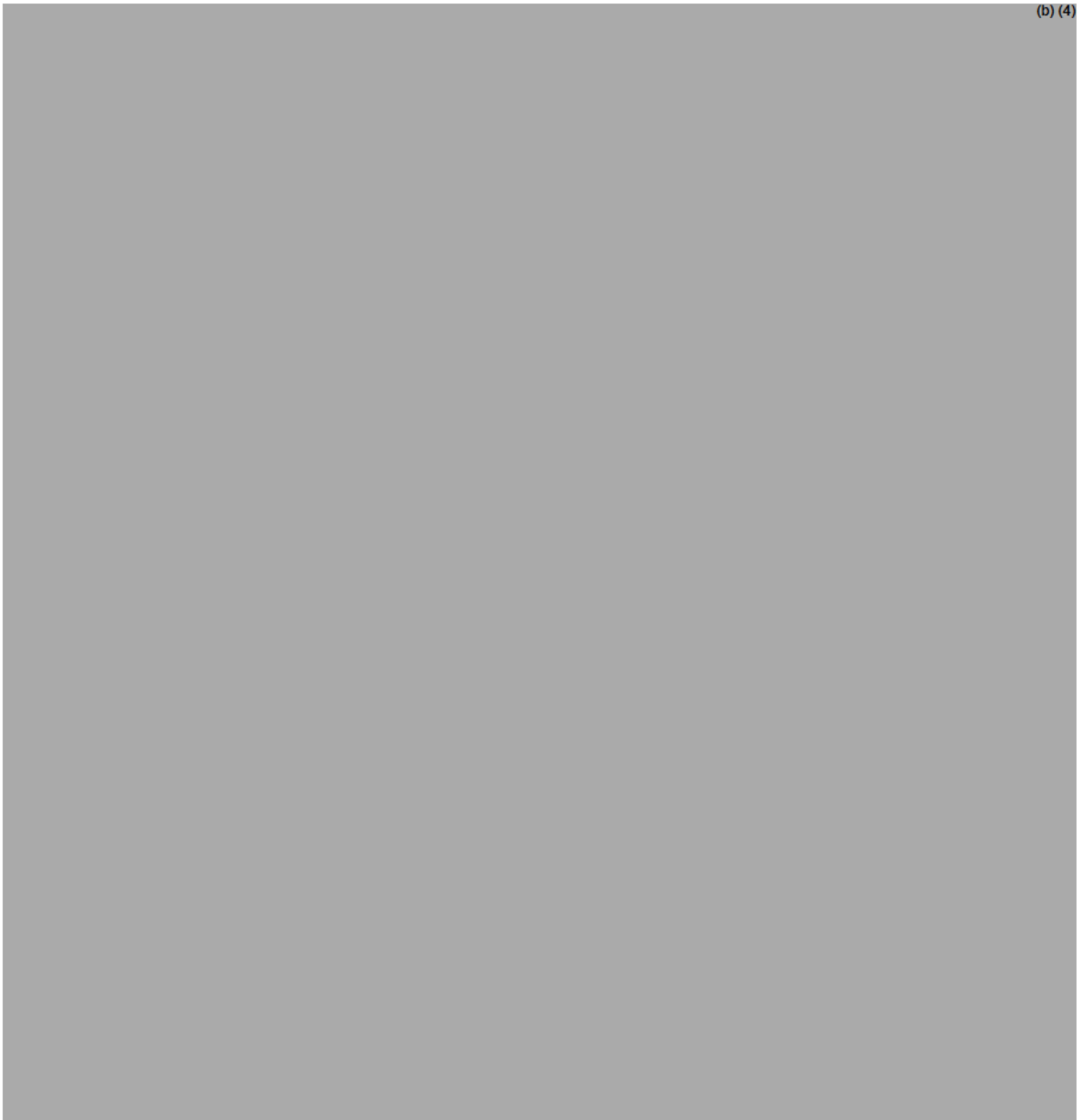
5. According to the clinical overview, “[t]he CRC749 device used in this study was identical in terms of the airway geometry (and therefore airflow paths and device resistance) and the drug-containing discs (and therefore the pharmaceutical performance) remained the same the CRC749 Clinical device used in the pivotal clinical endpoint BE study and PK BE studies with the 100/50 and 500/50 product strengths, and the Commercial device which was included in the pivotal PK BE studies with the 250/50 product strength.”²¹¹ Based on the firm’s statement, it appears that the firm was using a device other than clinical device (b) (4) and commercial device (b) (4). Since the firm will be asked to repeat the flow profiling study, the firm will be asked to use commercial device as the test device.
6. The firm used (b) (4) to both measure and graphically represent the inhalation profile (please see Figure 5 below). According to the study report, (b) (4) is a computer driven system designed to drive and record the inhalation profile (inspiratory flow rate and pressure drop as a function of time) that a subject generates when inhaling through a DPI. The test and reference empty inhalers were contained within an inhaler connecting box (ICB) in order to connect the inhaler with the inhalation profile recorder. Subjects inhaled through the DPI within the connecting box via a disposable microbiological filter attached to the ICB (please see Figure 6 below) to generate an inhalation profile. The disposable microbiological filter attached to the ICB was used to avoid potential contamination of devices between subjects.

²¹¹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 2.5\Clinical Overview, p. 7 of 21).

According to the Information for Study Participants and Informed Consent Form (12/29/2015 submission, Module 5.3.4.1\IEC IRB Consent Form List, p. 26-27 of 95), the inside of ICB for T (Figure 7) and R (Figure 8) devices are below. It should be noted that both T and R devices were placed in the ICB in the horizontal orientation. The firm will be asked to specify how patients hold ICB for each device (e.g. which orientation). If same orientation was held between T and R devices, the firm will be asked to justify the impact of device orientation on subject's flow profile.

It should also be noted that both the R and T devices were in an “open” position (please note that mouthpiece cover of the T device was removed). The lever for both R and T

devices were slid away from the mouthpiece, and both appear to be slid as far as it can go and thus mimicked the external operating procedures of (1) open (2) push down/click²¹², which is right before the (3) inhale and (4) close procedures.



7.  this was a key step in ensuring suitability of the enclosed DPI and the results were recorded in the batch records for the

²¹² Please note that according to product-specific guidance, external operating procedures of the test product should consist of (1) open, (2) click, (3) inhale, and (4) close.

ICBs containing the inhalers. The firm will be asked to provide these results. In addition, the firm will be asked to provide details of this study (e.g. study protocol/SOP and study report). In addition, as mentioned above, according to Figure 7, the firm removed mouthpiece cover of the T device. The firm will also be asked to justify its impact on device resistance.

8. At Visit 2, the (b) (4) was used to train subjects how to inhale rapidly and deeply through both the test and reference inhalers. After training, subjects were then instructed to inhale rapidly and deeply through both devices to generate 3 inhalation profiles from each device.

According to the study report, with both DPI devices, 3 technically acceptable inhalation manoeuvres (as judged by the investigator) were performed for each adult subject; whereas *up to* 3 technically acceptable inhalation manoeuvres (as judged by the investigator) were performed for each pediatric patient.

9. According to the study report, subjects had to wear a nose clip during the inhalation procedure.

The study design is **unacceptable**.

5.5.4 Demographic Profile of Subjects (Safety Population)

		<i>Healthy adult subject (N=10)</i>	<i>Children with asthma (4-7 years) (N=21)</i>	<i>Children with asthma (8-11 years) (N=21)</i>	<i>Adults with asthma (N=14)</i>	<i>Adults with severe COPD (N=14)</i>
Sex	Male	6 (60.0%)	14 (66.7%)	16 (76.2%)	5 (35.7%)	9 (64.3%)
	Female	4 (40.0%)	7 (33.3%)	5 (23.8%)	9 (64.3%)	5 (35.7%)
Age [Years]	n	10	21	21	14	14
	Mean	33.1	5.6	9.7	55.9	64.4
	SD	9.36	1.07	1.15	7.10	7.29
	Median	31.5	6.0	10.0	57.0	65.0
	Min	20.0	4.0	8.0	40.0	51.0
	Max	49.0	7.0	11.0	64.0	78.0
Race	Caucasian	10 (100.0%)	21 (100.0%)	21 (100.0%)	14 (100.0%)	14 (100.0%)
Weight [kg]	n	10	21	21	14	14
	Mean	72.3	22.2	39.1	89.6	74.2
	SD	14.37	3.71	14.13	23.73	11.71
	Median	68.4	21.0	34.1	85.2	74.1
	Min	55.5	16.0	23.1	50.0	52.4

Height [cm]	Max	96.3	29.4	83.1	132.0	95.1
	n	10	21	21	14	14
	Mean	173.7	118.8	144.3	167.6	168.4
	SD	8.73	7.69	11.97	9.68	8.74
	Median	176.0	117.0	143.0	163.0	168.0
	Min	162.0	101.0	128.0	157.0	152.0
BMI [kg/m ²]	Max	186.0	131.0	176.0	186.0	186.0
	n	10	21	21	14	14
	Mean	23.8	15.6	18.2	31.9	26.3
	SD	3.31	1.28	3.15	8.34	5.25
	Median	23.7	15.7	17.2	30.2	24.8
	Min	19.7	12.9	13.9	20.3	19.5
Smoking History	Max	30.4	18.5	26.8	51.6	41.2
	Non-smoker	8 (80.0%)	21 (100.0%)	21 (100.0%)	9 (64.3%)	0 (0.0%)
	Ex-smoker	2 (20.0%)	0 (0.0%)	0 (0.0%)	4 (28.6%)	9 (64.3%)
Number of pack years [cigarettes per day * smoking years/20]	Currently smoker	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	5 (35.7%)
	n	2	0	0	5	14
	Mean	4.8	-	-	4.6	42.6
	SD	5.30	-	-	3.36	21.48
	Median	4.8	-	-	4.0	37.5
	Min	1.0	-	-	1.0	15.0
Alcohol intake	Max	8.5	-	-	9.0	88.0
	Abstinent	3 (30.0%)	21 (100.0%)	21 (100.0%)	4 (28.6%)	5 (35.7%)
	Light	6 (60.0%)	0 (0.0%)	0 (0.0%)	7 (50.0%)	5 (35.7%)
Drug use	Moderate	1 (10.0%)	0 (0.0%)	0 (0.0%)	3 (21.4%)	4 (28.6%)
	No	10 (100.0%)	21 (100.0%)	21 (100.0%)	14 (100.0%)	14 (100.0%)

5.5.5 Discontinued/Early Terminated Subjects

None

5.5.6 Study Adverse Events

<i>SOC/PT</i>	<i>Healthy adult subject (N=10)</i>	<i>Children with asthma (4-7 years) (N=21)</i>	<i>Children with asthma (8-11 years) (N=21)</i>	<i>Adults with asthma (N=14)</i>	<i>Adults with severe COPD (N=14)</i>
Musculoskeletal and connective tissue disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
Back pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)

Reviewer’s Comment:

One (1) adverse event (AE) was reported for one (1/7.1%) adult subject (b) (6) with severe COPD. This AE (back pain) was recorded by the firm as not related to the devices or study-related procedures and was assessed as mild, non-serious and not significant.

The firm reported that there were no deaths or other serious adverse events reported during the study.

5.5.7 Protocol Deviations

The firm’s definition of safety analysis set (SS) and inhalation analysis set (IAS) are below:

Safety Analysis Set (SS):

All randomized subjects who attempted to inhale through either device at least once.

Inhalation Analysis Set (IAS):

All subjects who have been randomized and had at least one inhalation parameter derived (for at least one of the devices).

According to the study protocol, criteria for removal of a subject from the study include:

- Inclusion and exclusion criteria being violated,
- Non-compliance to protocol requirement

The firm reported 2 major protocol deviations and 5 minor protocol deviations as detailed below.

1. The firm reported the following 2 major protocol deviations, and excluded both subjects from the IAS population.

For both Subjects (b) (6), the firm stated that the subjects were not regularly using asthma medication during three months prior to screening. Therefore, inclusion criterion #5 were not met for both subjects. Subject (b) (6) also did not meet inclusion criterion #7.

The reviewer checked the firm's concomitant medication dataset for verification. However, it is noted that the SAS .xpt dataset contained drug trade names but not generic names. In addition, route of administration (CM1_ROUT) and frequency was indicated by numbers (e.g. 3, 7, 17 for CM1_ROUT and 1, 5, 9 for CM1_FREQ), and it is unclear what these numbers stand for. Moreover, for start and end time of concomitant medications, the firm stated in their data definition file that their data format is DDMMYY10. However, values (e.g. 19029, 19640, 4565) listed in the SAS .xpt file does not match this format. It is also unclear what those numbers in CM1_STA2, CM1_STO2, CM1_ONGO (e.g. 0, 1, 2) stand for. Therefore, the firm will be asked to clarify so. In addition, the firm will be asked to list out the washout/withhold period between the concomitant medications and study procedures for each subject visit.

2. The firm reported the following 5 minor protocol deviations, and resulted in incomplete measurements of IC, FEV1 and FVC. It should be noted that these are secondary parameters evaluated by the firm.

Subject	Subject group	Protocol deviation/comment
Subject (b) (6)	Adults with severe COPD	Lung function measurements V1 (pre Salbutamol): Parameter IC measured twice instead of three (3) times.
Subject (b) (6)	Adults with severe COPD	Lung function measurements V1 (post Salbutamol): FEV ₁ and FVC could only be measured twice instead of three (3) times due to cough.
Subject (b) (6)	Adults with severe asthma	Lung function measurements V2: Parameter IC measured twice instead of three (3) times.
Subject (b) (6)	Adults with severe COPD	Lung function measurements V1, V2: Parameter IC not measured.
Subject (b) (6)	Adults with severe asthma	Lung function measurements: Parameter IC measured twice instead of three (3) times.

COPD = chronic obstructive pulmonary disease, FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity, IC = inspiratory capacity

3. For pressure drop acceleration rate (kPa/sec), the firm excluded the following values from the summary statistics:
 - a) Subject (b) (4) (healthy adult subject) / device: Accuhaler™/Diskus® / manoeuver 8:

Regression R-squared did not meet pre-specified criterion of $R^2 > 0.995$ ($R^2 = 0.987$) and value is artefact (very high and not representative of other inhalations) – therefore the value (105.3 [kPa/sec]) was excluded from analysis.

b) Subject (b) (6) (healthy adult subject) / device: CRC749 / manoeuvre 1:

Regression R-squared did not meet pre-specified criterion of $R^2 > 0.995$ ($R^2 = 0.990$) and value was an artefact (very high and not representative of other inhalations) – therefore the value (104.3 [kPa/sec]) was excluded from analysis.

c) Subject (b) (6) (adult with severe COPD) / device: CRC749 / manoeuvre 4:

Value (120.3 [kPa/sec]) was an artefact (very high and not representative of other inhalations) – therefore the value was excluded from analysis.

d) Subject (b) (6) (child with asthma, 9 years) / device: AccuhalerTM/Diskus® / manoeuvres 2, 3 and 6 and device: CRC749 / manoeuvres 3, 4 and 5:

All 6 inhalation profiles show a clear 2 phase inhalation: a very quick early phase and a slightly longer and slower later phase. There is a marked difference in the PDAR values depending upon which phase is assessed. Both phases occur within the time frame of relevance (~ first 250ms - the time frame over which the powder leaves the device) so one phase cannot be discounted over the other.



The firm will be asked to provide their pre-specified acceptance criteria (e.g. in an SOP) for pressure drop acceleration rate data at the time of this study. Exclusion of the aforementioned data will be evaluated upon receipt of this information.

4. It is noted that although the use of rescue medicine is not mentioned in the study protocol or study report, the firm provided a SAS .xpt dataset “RESCUE”, which, according to the data definition file, is about “*Salbutamol Intake (Rescue Medication)*”. According to this dataset, multiple subjects took rescue medication. For each of these subjects, the firm will be asked to list out the washout period between the rescue medication and study procedures for each visit. The firm will also be asked to justify the impact of rescue medication usage on inhalation profile of these subjects.

The firm’s protocol deviation information is **incomplete**.



6. The firm stated that as a general observation, the values generated by older pediatric patients and the adult patients were comparable and slightly higher than those generated by the patients with COPD. The test device exhibited the same pattern of performance across the groups, albeit that the magnitude of the parameters were different in certain cases.

The firm also stated that in the context of conducting PK studies in healthy subjects to assess BE by T and R inhalers, the observation that both devices exhibit the same pattern of performance across the group studied (healthy subjects to pediatrics to patients with severe respiratory diseases) is reassuring as demonstrating equivalence in one group helps support and expectation that the products will be equivalent in other groups.

7. Since the in vitro studies and the current flow rate study is pending firm's response to deficiencies, whether drug delivery from both T and R devices is similar and relatively insensitive to change in flow rate will be determined upon receipt of firm's deficiency response.

The firm's flow rate study is **unacceptable** due to the use of non-US RLD product.

APPEARS THIS WAY ON
ORIGINAL

5.6 Device Orientation Study

5.6.1 Study Information

Study Number	MGR000-1004
Study Title	A non-dosing inhaler development study to assess the use of the 4 key operational steps of CRC749 and the likelihood of orientation related errors by representative users including Advair® Diskus® patients.
Market Research Facilities*^	(b) (4)
Moderator^	(b) (4)
Study Period	3/16/2016-4/3/2016

* Firm's note: These sites provided the facility in which user handling sessions were conducted; these facilities provided no other function or resource in the user handling assessment

^ The firm stated that the assessment was conducted by an independent human factors moderator (b) (4) as one to one sessions (moderator: participant). These sessions were undertaken within the physical confines of a room within market research facilities in order to simulate a home use environment whilst enabling remote observation; there was no input from the facilities to any aspect of the study conduct.

5.6.2 Product Information

Product	Test
Product Name	CRC749 (commercial device design (b) (4) 214), empty inhaler
Manufacturer	Mylan Global Respiratory Group
Batch/Lot No.	Not provided
Manufacture Date	Not provided
Expiration Date	Not provided
Strength	N/A (empty inhaler)

²¹⁴ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 3.2.P.7\Container Closure System, p. 134 of 229).

Dosage Form	Empty inhaler
Dose administered	N/A (empty inhaler)
Dosing regimen (e.g., BID, QD)	3 sequential oral inhalations
Route of Administration	Oral inhalation



(b) (4)

Reviewer's Comments:

- As mentioned in Section 3.1, according to CC 12-0731, the Agency had concern regarding the difference in the orientation of use between the test and RLD device. At that time, the Agency believed that some patients may use MGR001 horizontal orientation (i.e., the orientation that patients use for Advair Diskus). Such an error may result in incomplete lip sealing around the mouthpiece and lead to different air flow pattern through the inhaler compared to when the test product is used correctly (i.e. vertically). The Agency recommends that the firm to demonstrate *one of the following*:
 - i) Low likelihood of the orientation-related errors when MGR001 is used by the patients including prior Advair Diskus users.
 - ii) Inhalation profiles through inhaler (i.e. peak inhalation flow rate (PIFR) and total inhalation volume through inhaler) when used by the patients and the device retention (i.e. amount of drug retains in the device and air channel following inhalation) are comparable at both the (vertical and horizontal) orientations.

The current study is pertaining to i) above to demonstrate that there is a low likelihood of orientation-related use errors, such that if the CRC749 inhaler is used in the horizontal orientation (i.e. the orientation that patients use for Advair[®] Diskus[®]) there is no impact on delivery of the therapeutic dose.

- The firm previously submitted their study protocol to the Agency for review (IND118769 and CC26230). The CC reviewer sent a consult to DMEPA to assess the protocol of this study, and provide response to specific questions submitted by the firm.²¹⁵ Upon receipt of DMEPA’s consult response, CC reviewer made additional comments and recommendations and sent the response back to the firm with these additional comments and recommendations incorporated.
- As mentioned in Section 3.2, DBI sent consult request to DMEPA for evaluation of the firm’s device orientation study. In the consult response, DMEPA stated that:

“FDA had previously raised concerns that patients may use the proposed product in a horizontal orientation, as they would with the RLD. Although we reviewed the device orientation study protocol, submitted on August 27, 2014 and made recommendations to the study design, we note that this study was not designed to assess the differences in use error rates between this ANDA product and the RLD.

When differences in design are identified between an ANDA product and RLD, our current approach is to recommend that the Applicant analyze and describe these user interface differences between the ANDA product and RLD. Based on the outcome of these comparative analyses, an Applicant may need to provide additional data, such as data from a comparative use human factors study to address whether the proposed product can be substituted for the RLD with the full expectation that it will produce the same clinical and safety profile as the RLD under the conditions specified in the labeling.²¹⁶

We note that the Applicant conducted a non-comparative HFS. The Applicant has not provided data, such as data from a comparative use human factors study that assesses the differences in use error rates between the proposed product and the RLD. Such data may be warranted to assess the acceptability of the differences in device and labeling resulting from these differences in user interface between the proposed product and the RLD and to help evaluate whether the proposed product can be substituted for the RLD with the full expectation that the proposed product will produce the same clinical effect and safety under the conditions specified in labeling.”

In the consult response, DMEPA made the following conclusion:

²¹⁵ GDRP: Correspondence #26230, Primary Review, DMEPA consult request.docx, 10/29/2014.

²¹⁶ Footnote in DMEPA’s consult response: For example, FDA recommends that sponsors consider designing a comparative use human factors study to provide sufficient data to confirm that the use error rate, for the critical task(s) as impacted by the differing external critical design attribute of the delivery device constituent part for the proposed generic combination product, is not worse than the corresponding use error rate for the RLD when used by patients and caregivers in representative use scenarios and use environments consistent with the labeled conditions of use. *See Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA (January 2017)* (available at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm536959.pdf>).

“The proposed Wixela Inhub device has a different device orientation when compared to the RLD, Advair Diskus. The Applicant has not submitted supporting data, such as data from a comparative use human factors study that assesses the differences in use error rates between this product and the RLD as a result of design differences between the two products.

Such data may be warranted to assess the acceptability of the differences in device and labeling resulting from differences in user interface between the proposed product and the RLD and to help evaluate whether the proposed product can be substituted for the RLD with the full expectation that the proposed product will produce the same clinical effect and safety under the conditions specified in labeling.”

Please note that the deficiency language to be communicated to the firm (please see the deficiency letter at the end of this review) has been cleared by DMEPA, OGD Policy and Office of Chief Counsel (OCC).

- DMEPA also reviewed the human factors data the firm submitted, although they note that it is not a comparative use human factors study and therefore generally does not provide sufficient data and information to evaluate the acceptability in an ANDA of the differences in the proposed product’s device as compared to the RLD. Please see below for DMEPA’s comments as summarized by the reviewer.
 - According to the DMEPA consult response, out of 110 subjects in the study, 10 subjects used the device horizontally at some point over the 3 tasks. Of the 10 subjects, 9 were Advair users and 1 was a DPI naïve user. However, per their inhalation profile, nine of these 10 participants received the target delivered dose. Specifically, the inhalation profile of these nine participants was assessed through a CRC749 inhaler, where their mean peak inhalation flow rate (PIFR) was >30 L/min and mean total inhaled volume (TIV) was >1 over three inhalations. One participant reported a low PIFR and TIV, which could potentially indicate an underdose, but this participant experienced challenges with the lung function test and did not achieve the required volumes when using the device correctly with a vertical orientation. Therefore, per the firm, this error is not considered a true device related use error. DMEPA and the clinical team agreed with the firm’s assessment.
 - DMEPA reviewer stated that per the analysis of the inhalation profiles among participants who used the test product in the wrong direction, it appears that the device may be used in the vertical or horizontal position.
 - DMEPA had concerns about a potential build-up of powder and other device-related issues if the device was used continually in the horizontal position. The firm submitted data to demonstrate that the mechanical function of the device is maintained regardless of the orientation of the device during use and that potential powder build-up would not impact mechanical function of the device through its

life.

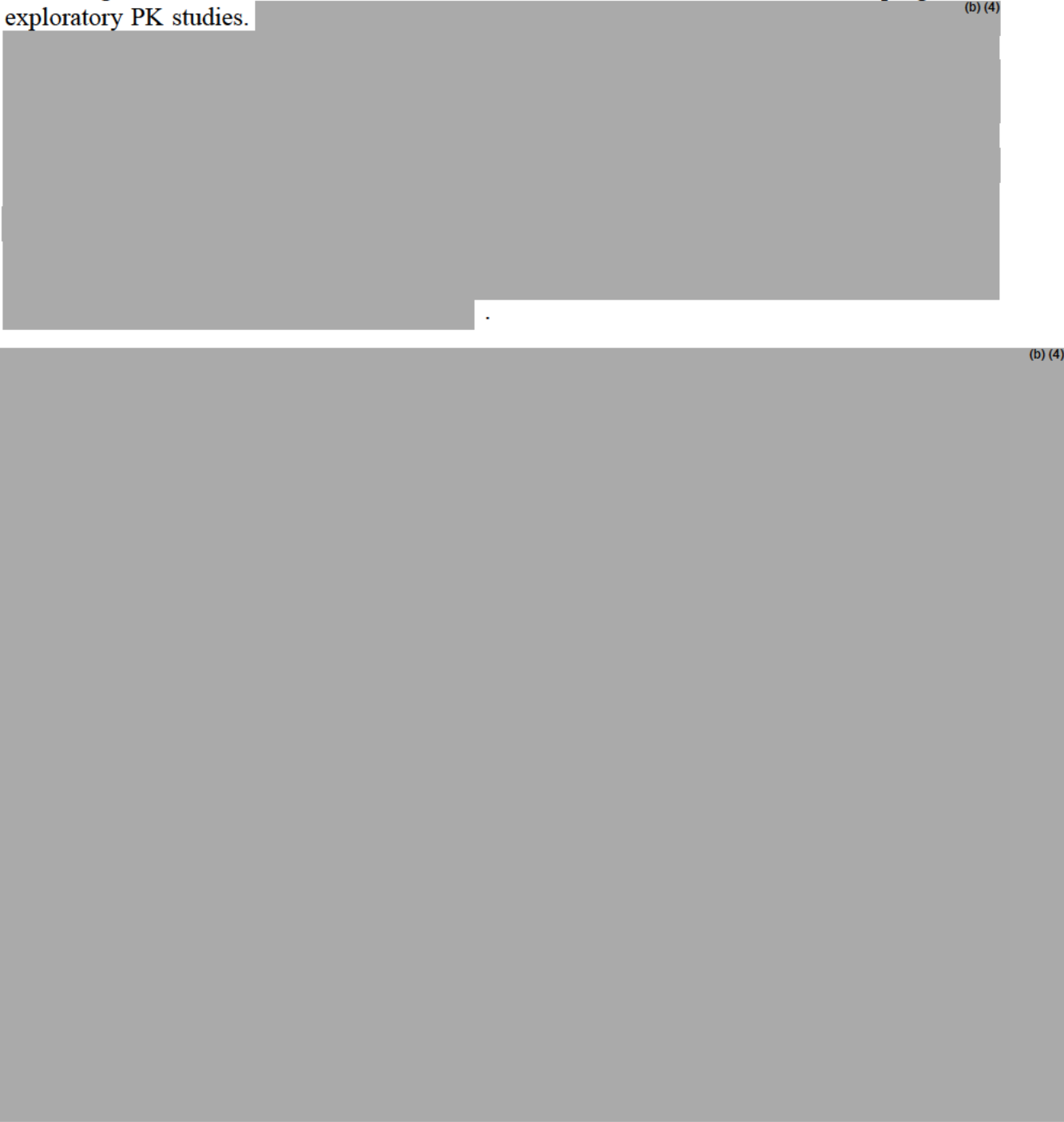
(b) (4)



The device orientation study is **unacceptable**.

5.7 Additional PK studies

According to the firm's Clinical Overview²¹⁷, the firm conducted an extensive program of exploratory PK studies. (b) (4)



²¹⁷ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 2.5\Clinical Overview, p. 6 of 21).

²¹⁸ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 2.3.P.2\Pharmaceutical Development, p. 268 of 676).

²¹⁹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 2.5\Clinical Overview, p. 11 of 21).

²²⁰ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.1.2. mgr001-1001...\MGR001-1001 Synopsis, p. 15 of 16).

5.8 OSIS Status

5.8.1 OSIS Inspection Report for PK BE Studies

5.8.1.1 Clinical Site (Worldwide Clinical Trials Early Phase Services, LLC, San Antonio, TX)

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the OSIS recommends accepting data without an on-site inspection.²²¹ The OSIS recently inspected the site and the inspectional outcome from the inspection was classified as No Action Indicated (NAI). Therefore, the OSIS inspection status is complete for the clinical site for PK BE studies.

5.8.1.2 Analytical Site (Mylan Pharmaceuticals Inc., Morgantown, WV)

This was a FY2016 GDUFA in vivo BE analytical site inspection. The OSIS conducted an inspection at Mylan Pharmaceuticals Inc., Morgantown, WV to audit the analytical portion of (b) (4) ANDAs (b) (4)²²². Per the inspection report dated 7/7/2016 from the OSIS, Form 483 was issued following the inspection at Mylan Pharmaceuticals Inc., Morgantown, WV (5/23/2016 to 5/27/2016). The firm's response to Form 483 was received on 6/20/2016. The OSIS outcome was voluntary action indicated (VAI) for the analytical portion of the study. The OSIS recommended that data from the audited studies to be accepted for further Agency review.

The current ANDA 208891 is one of the ANDAs that had the bioanalytical portion audited by the current OSIS inspection. Fasting BE studies MGR001-1006 (100/50 mcg strength), MGR001-1007 (500/50 mcg strength), and MGR001-1014 (250/50 mcg strength) of the current ANDA 208891 have been audited.

It is noted that the fasting study MGR001-1005 was not inspected. According to email communication with OSIS, when assessing all of the studies within the application to determine if they need to be covered during the inspection, OSIS also looked at study MGR001-1005 as part of their assessment. They noted that according to the sponsor, study MGR001-1005 failed to demonstrate BE. OSIS considered study MGR001-1014 as a re-dosing study that demonstrated BE (reviewer's note: as detailed in Section 5.1.4, this is actually a repeat study that failed BE, but the pooled analysis of this study and MGR001-1005, which is deemed unacceptable by the Agency, meets BE criteria.), so they focused on this particular study for the 250/50 mcg strength.

As mentioned above, this inspection report references (b) (4) ANDAs and the current ANDA 208891 is one of them. The current review will evaluate the impact of OSIS findings on the current ANDA (ANDA 208891) only. It should also be noted that the impact of OSIS findings on other parent ANDAs has been previously and separately evaluated.^{223,224}

²²¹ GDRP: ANDA 208891, Site: Worldwide Clinical Trials Early Phase Services, LLC, Decline to Inspect A208891_WCTClin.pdf, 3/3/2016.

²²² GDRP: ANDA 208891, Site: Mylan Pharmaceuticals Inc., EIR Review Memo for Mylan Morgantown WV 2016 final (2), 7/7/2016.

²²³ (b) (4)
²²⁴ (b) (4)

The OSIS provided the DBI with the following findings.

5.8.1.2.1 OSIS Comment #1

Not all aspects of method validation and study conduct were adequately documented. Specifically,

5.8.1.2.1.1 OSIS Comment #1a)

The storage location of stock and working solutions was not documented during method validation and sample analysis in the (b) (4) fluticasone/salmeterol, and (b) (4) studies.

Firm's Response to Form 483

Mylan generated additional stability data to determine whether the observation affected the inspected bioequivalence studies. Stock and working solutions of (b) (4) (b) (4) fluticasone/salmeterol, (b) (4) were prepared and stored for a specific period at room temperature or 4°C. Results showed that these 'stability' solutions were stable when compared to freshly prepared solutions. According to Mylan, stock and working solutions used in method validation and in studies were stable, even if analysts had consistently stored solutions at room temperature instead of 4°C (b) (4)

As a corrective action, Mylan plans to implement a mechanism to document the storage location of solutions for future bioanalytical projects starting on June 30, 2016.

OSIS Assessment

During the inspection, these investigators were concerned with the lack of documentation indicating where stock and working solutions were stored, (b) (4) (b) (4) Mylan has several refrigerators and freezers which made it difficult to verify whether the solutions were stored at the required temperature. Mylan's stability experiments and proposed corrective actions appear adequate.

5.8.1.2.1.1.1 DB Reviewer Comment #1a) for Current ANDA 208891:

The firm acknowledged the OSIS' observation and generated additional stability data to determine whether the observation affected the inspected BE studies. The data showed that the stability solutions were stable when compared to freshly prepared solution for at least 7 days for stock solution and 20 days for working solutions at room temperature for both FP and SA, which is the maximum intervals that the solutions had been used in MGR001-1006, MGR001-1007, and MGR001-1014 studies.

Therefore, the current reviewer agrees with the OSIS' evaluation that this finding does not affect the integrity of the study data in the current ANDA.

5.8.1.2.1.1.2 Parent ANDA Reviewer Comment #1a) for Related ANDAs:

Because this OSIS finding is related to the procedures used to conduct the BE studies, it is considered systemic. Reviewers of related ANDAs should evaluate the impact of this finding on his/her own respective ANDA.

Isolated

Systemic

5.8.1.2.1.2 OSIS Comment #1b)

(b) (4)

5.8.1.2.1.2.1 DB Reviewer Comment #1b) for Current ANDA 208891:

Please note that the above observation pertains to the (b) (4) studies and not the current ANDA 208891.

To further evaluate whether or not the OSIS inspectional finding above impact the current ANDA 208891, the reviewer checked its MV report (15-006). It is noted that the firm provided solution preparation document template without handwritten information about solution IDs. However, it should also be noted that the QC samples used in the pivotal PK studies are within the acceptable range.

Therefore, the current reviewer agrees with the OSIS' evaluation that this finding does not affect the integrity of the study data in the current ANDA.

5.8.1.2.1.2.2 Parent ANDA Reviewer Comment #1b) for Related ANDAs:

Because this OSIS finding is related to the procedures used to conduct the BE studies, it is considered systemic. Reviewers of related ANDAs should evaluate the impact of this finding on his/her own respective ANDA.

☐ Isolated	☒ Systemic

5.8.1.2.2 Overall Comments for OSIS Findings at the Analytical Site for PK BE Studies

None of the FDA-483 findings at the analytical site (Mylan Pharmaceuticals Inc., Morgantown, WV) would have impact on the outcome of the fasting BE studies MGR001-1006, MGR001-1007, and MGR001-1014 in the current ANDA 208891. Therefore, the OSIS inspection status is complete for the analytical site for PK BE studies.

5.8.2 OSIS Inspection Report for Clinical Endpoint Studies

5.8.2.1 Clinical Site

The inspected clinical endpoint study MGR001-3001 was a multi-center study conducted at 101 domestic sites, of which 97 sites screened and enrolled subjects, 3 sites screened but did not enroll subjects, and 1 site neither screened nor enrolled subjects but received investigational products. Out of the 97 active study sites, the OSIS selected 16 sites for inspection (please see site and inspection information in table below).²²⁵ Per the inspection report dated 10/28/2016 from the OSIS, Form 483 was issued to 7 of the 16 clinical sites following the inspection (please see highlights in table below). The OSIS outcome was VAI or NAI for the inspected sites (please see OSIS outcome for each site in table below). The OSIS recommended that data from the clinical endpoint study MGR001-3001 not be accepted for further Agency review.

²²⁵ GDRP: ANDA 208891, Clinical Endpoint Sites, EIR Cover Memo ANDA 208891, 10/28/2016.

	Clinical site#	Clinical site	Dates of Inspection	FDA FORM 483	OSIS Outcome
1	3001010	Prestige Clinical Research Center, Inc., Miami, FL	6/7-15/2016	Yes	VAI
2	3001033	Princeton Center for Clinical Research, Skillman, NJ	5/16-27/2016	Yes	VAI
3	3001019	The Clinical Research Center, LLC Saint Louis, MO	5/11-16/2016	No	NAI
4	3001046	Allergy and Asthma Consultants (of the Ozarks) - AKA Clinical Research of the Ozarks, Columbia, MO	5/23-25/2016	No	NAI
5	3001058	AAPRI Research Institute (FKA Kent Surgical Associates, Inc.)	6/28-30/2016	yes	VAI
6	3001004	The Asthma & Allergy Center, Bellevue, NE	7/19-22/2016	no	NAI
7	3001018	Timber Lane Allergy & Asthma Associates, South Burlington, VT	6/14-23/2016	yes	VAI
8	3001039	Pharmaceutical Research & Consulting, Inc., Dallas, TX (Part of the Dallas Allergy & Asthma Center)	07/12-19/2016	no	NAI
9	3001063	Allergy and Asthma Research Group, Eugene, OR	07/18-22/2016	yes	VAI
10	3001067	Providence Clinical Research, North Hollywood, CA	7/18-26/2016	yes	VAI
11	3001076	Pediatric Care Medical Group, Inc., Huntington Beach, CA	07/18-22/2016	no	NAI
12	3001120	Linfriz Research Center, Coral Gables, FL	7/18-22/2016	yes	VAI
13	3001022	Asthma and Allergy Center of Chicago River Forest, IL	5/11-18/2016	no	NAI
14	3001027	Northeast Medical Research Associates, North Dartmouth, MA	5/25-6/2/2016	no	NAI
15	3001090	Montgomery Medical, Smithfield, PA	8/1-5/2016	no	NAI
16	3001023	Analab Clinical Research, Inc. Lenexa, KS	7/18-22/2016	no	NAI

The OSIS provided the DBI with the following findings.

5.8.2.1.1 OSIS Comments That Are Common to Multiple Sites – Retention Samples

OSIS Comments, Firm’s Response to Form 483 (as summarized by OSIS) and OSIS Evaluation

Form FDA 483 at 6 of 7 sites (Clinical sites # 3001010; 3001058; 3001018; 3001063; 3001067 and 3001020) cited that the sites retained reserve samples from only the first shipment of drug products, and not from the later shipments of drug products used for dosing study subjects.

We acknowledge receipt of responses to Form FDA 483 from the 6 sites. The sites all stated that they were instructed to retain reserve samples from the first shipment by the SMO²²⁶ PPD on behalf of the sponsor. The sites also attached a portion of minutes from a meeting between the sponsor and OGD in support of their positions. Later OSIS located the OGD-finalized minutes at V:\FIRMSAM\MYLAN\CONTROL\13-0422.

²²⁶ Reviewer’s note: SMO stands for Site Management Organization.

The minutes of the September 2013 meeting between Mylan and OGD (Attachment 3) reveal that OGD provided guidance for quantities of reserve samples; however, we cannot ascertain whether there was a further discussion at the meeting on selecting reserves from only one shipment.

Inspection found that the reserve samples retained at the sites from the single shipment were sufficient in quantity and stored according to the FDA regulatory requirements. In addition, it was also found that there was no option in the Interactive Voice/Web Response System (IVRS/IWRS) for clinical sites to select reserve samples from subsequent shipments, including those used for dosing study subjects. In May 2015 (after the most of the study was completed) PPD provided each site with a sealed envelope containing the blinding code for the shipment of reserve samples. Note that the clinical sites had no access to blinding codes for the drug products used to dose subjects.

The study design and instructions from the sponsor and SMO did not call for clinical sites to retain reserve samples from each shipment. The sponsor (Mylan) (via SMO (PPD) and (b) (4)) should have arranged shipments to the clinical sites in a way to enable the sites to select reserve samples from each shipment.

This OSIS reviewer concludes that study MGR001-3001 violated 21 CFR 320.38 and 21 CFR 320.63 and their implementing final rule, because the study sites did not retain reserve samples representative of each shipment of drug product used in the BE study. However, the sites followed the directions of the sponsor and SMO, and retained reserve samples from the first shipment, to meet the quantity discussed during the sponsor-OGD meeting. Based on the information provided by SMO-PPD to the clinical sites, I conclude that failure to retain reserve samples from all drug shipments is likely to be common to all study sites. This OSIS reviewer defers this question to OGD for further evaluation.

5.8.2.1.1.1 DB Reviewer Comment for Current ANDA 208891:

According to Final Rule of 21 CFR Parts 312, 314 and 320 “Retention of Bioavailability and Bioequivalence Testing Samples”²²⁷, Section IIA3d:

“If the same batches of the test article and of the reference standard initially provided to the testing facility are used in performing more than one study, only one reserve sample of the test article and reference standard in sufficient quantity need be retained. The reserve samples must be identified as having come from the same batches as used in each specific study. **However, if additional supplies of the test article and of the reference standard are needed by a testing facility for performing additional studies, the testing facility must retain the required reserve samples from the subsequent shipment regardless of whether the shipment is from the same batch as that previously provided to**

²²⁷ <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm> Last accessed: 12/16/2016.

the testing facility.²²⁸ This is to ensure that the reserve samples are, in fact, representative of the batch provided by the study sponsor to the testing facility.”

In addition, according to Guidance for Industry - Handling and Retention of BA and BE Testing Samples (May 2004) states “if additional supplies of the test article and the reference standard will be used by a testing facility to perform the **same**²²⁹ study or additional studies, the testing facility should retain a sufficient quantity of reserve samples from the **subsequent**²³⁰ shipment.”

As mentioned by the OSIS reviewer, ORS previously provided guidance for quantities of reserve samples in meeting minutes of 9/2013 meeting between the firm and the Agency. According to CC13-0422²³¹, which contains meeting minutes for the aforementioned meeting, one of the firm’s retention sample proposal is that the initial consignment sent to the site should contain sufficient investigational product to support sampling on receipt. However, the rest of the review/meeting minutes does not mention about shipment/consignment.

According to the meeting minutes of the aforementioned meeting in CC13-0422, the following response was provided to the firm:

“The Agency does not agree with the firm’s proposal for retention of IP from study MGR001-3001. The agency recommends that at least 50 units for each batch of test and reference products, including placebos, with no less than 10 units per each batch per site, be retained for the BE studies. Please refer to Section 4 (B) of Drug Specific Guidance: BE Recommendation for Budesonide Inhalation Suspension Drug Product for further guidance.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf>”

The reviewer also checked the Section 4 (B) of the Budesonide Inhalation Suspension Guidance as mentioned in the above ORS response. It is noted that this guidance does not mention about retaining samples from multiple shipments.

The reviewer had an email communication with ORS about their previous response to the firm regarding reserve samples. According to ORS²³², their previous response was based on *Draft Guidance for Industry – Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (posted Apr 2003) (nasal BA/BE guidance) and product specific guidance for budesonide inhalation suspension; they focused only on the number of samples to retain per batch and per site. In addition, in the meeting package, Mylan did not explicitly say that they will not retain samples from subsequent consignment(s). ORS also do not recall any discussion on the consignment issue during the internal meeting or during the meeting with the

²²⁸ Emphasized by the reviewer.

²²⁹ Emphasized by the reviewer.

²³⁰ Emphasized by the reviewer/

²³¹ [\\cdsnas\OGDS6\CONTROLS\2013-docs\13-0422.pdf](http://cdsnas/OGDS6/CONTROLS/2013-docs/13-0422.pdf) p. 16 of 28.

²³² V:\DIVISION\BIO\BIO1\Email Reference\208891 Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder\Question about retention samples for Mylan's DPI product ANDA 208891 msg

firm. Similarly, to the best of ORS reviewer's knowledge, they did not discuss about sample selection from the shipment, and do not recall having any follow up communication on either of the topics with the firm after the meeting. In addition, from a logistical perspective, they think that retaining sufficient samples from the first consignment should be acceptable.

As mentioned by ORS above, the firm did not explicitly say that they will not retain samples from subsequent consignment(s). In addition, it should be noted that in ORS' response to the firm in CC13-0422, ORS did not explicitly say that the firm can reserve sample from only the first shipment.

As mentioned above, 6 out of 97 active clinical sites were identified with this reserve sample issue by OSIS. Based on discussion with OB management, in the absence of these reserve samples, the authenticity of the test and reference products used at these clinical sites could not be verified and, accordingly, the reliability of the data from these clinical sites could not be determined. We have concerns that the reserve samples retained by the remaining (91) clinical sites for Study MGR001-3001 are not representative of the test and reference products provided by the study sponsor to each clinical site. Therefore, for each of the remaining (91) clinical sites for Study MGR001-3001, the firm will be asked to provide (1) the number of shipments of test and reference product received from the study sponsor during the course of the study and (2) documentation to support that reserve samples were appropriately retained. Please note that the deficiency language to be issued to the firm has went through OGD Policy.

5.8.2.1.1.2 Parent ANDA Reviewer Comment for Related ANDAs:

Because this OSIS finding is related to the procedures used to conduct the BE studies, it is considered systemic. Reviewers of related ANDAs should evaluate the impact of this finding on his/her own respective ANDA.

☐ Isolated	☒ Systemic

Prestige Clinical Research Center, Inc. (Clinical site #3001010)

Reviewer's Note: The OSIS observation below was issued at one site, but the OSIS reviewer considers it likely to apply to all study sites.

5.8.2.1.2 OSIS Observation

Failure to retain sealed randomization schedule prior to commencement of subject enrollment. Specifically, a sealed randomization scheme, including blinding codes, was not maintained in the possession of the clinical site prior to the dosing of the initial subject (Run-in placebo on Nov 6, 2014 and Randomized dosing on December 5, 2014). The site completed the study and was closed by the IRB on September 2015; however, the randomization scheme, which was not sealed, was sent to your site from PPD on November 6, 2015.

Firm's Response to Form 483 (as summarized by OSIS) and OSIS Evaluation

The site's response to FDA-483 stated that the full randomization codes for study MGR001-3001 was managed centrally by PPD through their IVRS/IWRS [Interactive Voice Response System/Interactive Web Response System]. Protocol section 7.5 discussed that a manual containing complete instructions for use of IVRS/IWRS was provided to each study site prior to the study start. The site also stated the following:

“This study was a multi-center study, with central randomization and treatment allocation, CI did not understand it to be appropriate or necessary for a copy of the full randomization schedule to be held at our site, as this randomization schedule covered the entire study and was generated by and held at PPD within the IVRS/IWRS system.

The PPD IVRS/IWRS was in place, CI and site staff had been trained and had access to the system, prior to the consent of the first subject at my site, and thus a “a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding” was in place prior to randomization of the first subject, and emergency unblinding envelopes were not necessary for study MGR001-3001.”

The study instructions to the sites did not call for keeping a copy of the full randomization schedule or emergency unblinding envelopes, as the CI and the site staff were trained and had access to the IVRS/IWRS prior to the consent of the first subject. The system had a mechanism that permitted rapid identification of the products in case of a medical emergency only. Thus, safety of subjects was not impaired.

In summary, the study was conducted from 10/22/2014 to 7/10/2015. Reserve samples were selected at all the inspected sites before the first subjects were dosed with the investigational products (IPs). In May 2015, each site was sent a sealed blinding code envelope for the reserve samples only.

In November 2015, after the study was completed, the database was locked, and the clinical study report was finalized, PPD provided the study sites with a CD of the full randomization schedule (listing of un-blinded treatment assignments for all subjects enrolled in the study) to facilitate future regulatory inspections. The clinical sites did not receive this randomization schedule until after the study report. However, the sites did not have similar sealed blinding codes for the IPs used for dosing the subjects. Instead, the investigator was provided an Excel file with randomization information about treatment assignment, kit number, subject number, and other dosing information after the study report finalized. **In this OSIS reviewer's opinion**, based on review of the EIRs and conversations with ORA investigators, this is likely to be common to all study sites.

On 8/29/2016 OSIS requested ORA investigator Byungja E. Marciante to return to the Princeton Center for Clinical Research, Skillman, NJ, to attempt to identify treatments for each subject through IVRS/IWRS audit trail records. On 8/31-9/1/2016 she revisited the site, but could not examine the audit trail records from IVRS/IWRS to confirm the blinding codes since there was no access to audit trail from the clinical site.

In this OSIS reviewer's opinion, blinding codes were not held at each clinical site before dosing the first subject, and ORA investigators could not access the IVRS/IWRS audit trails during inspections to confirm the identity of drug products that were administered to each subject. Therefore, we cannot assure that subjects received the treatments as intended or described in the study report.

5.8.2.1.2.1 DB Reviewer Comment for Current ANDA 208891:

As mentioned above, on 8/29/2016, OSIS requested Office of Regulatory Affairs (ORA) investigator to re-visit the site. However, the ORA investigator could not examine the audit trail records from IVRS/IWRS to confirm the blinding codes since there was no access to audit trail from the clinical site. Therefore, the ORA investigator could not verify the identities of blinded drug products received at the study site for dosing subjects.

The reviewer had an email communication with the OSIS reviewer regarding the follow up of ORA investigator not being able to access to audit trail. According to the OSIS reviewer²³³, during the revisit, the electronic IVRS/IWRS records, original or through audit trails, were no longer accessible. The site also sought assistance from PPD, the CRO/SMO provider of the IVRS/IWRS system used at all sites in the study. During the tele-conference between the site and PPD, a person who identified himself as the Associate Director/Project Manager for this study and employee of PPD agreed to email the audit trail for the assignment of the kits containing the test article for dosing subjects. However, OSIS reviewers found that the document PPD provided did not contain the information OSIS want to confirm.

According to the 1/18/2017-1/19/2017 meeting with OB management¹²⁷, the firm will be asked to provide necessary documentation which can be used to identify and confirm treatment for each subject. Based on email communication with OSIS²³⁴, according to the EIRs, none of the 16 inspected clinical sites possessed the blinding codes for subject dosing materials. The packager (b) (4) did not send the records with subject dosing materials, at the time of the study or before the study start. OSIS believes that this finding applies to all 97 sites. To OSIS' understanding, it is possible that the documents can come from (b) (4), since (b) (4), since (b) (4) assigned kit numbers to the blinded products that were packaged and shipped to clinical sites. As recommended by OSIS, to examine documents that trace the history of actions from the time when blinding codes were assigned to dosing materials until today, the firm will be asked to provide a copy of (b) (4) original blinding-packaging records and any log/event history, for all shipments to all 97 clinical sites.

5.8.2.1.2.2 Parent ANDA Reviewer Comment for Related ANDAs:

²³³ V:\DIVISION\BIO\BIO1\Email Reference\208891 Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder\ RE questions regarding OSIS EIR memo for the clinical endpoint study of ANDA 208891 (Mylans Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder).msg

²³⁴ V:\DIVISION\BIO\BIO1\Email Reference\208891 Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder\ RE questions regarding OSIS EIR memo for the clinical endpoint study of ANDA 208891 (Mylans Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder) 2 msg

Because this OSIS finding is related to the procedures used to conduct the BE studies, it is considered systemic. Reviewers of related ANDAs should evaluate the impact of this finding on his/her own respective ANDA.

☐ Isolated	☒ Systemic

Princeton Center for Clinical Research (Clinical site #3001033)

5.8.2.1.3 OSIS Comment #1 for This Clinical Site #3001033

The informed consent document lacked a description of reasonably foreseeable risks or discomforts to the subject. Specifically, the informed consent form failed to include:

- a. the following potential adverse events the subjects may encounter: nausea, vomiting, thrush, and tremors
- b. the volume of blood collected may range from 50 mL to 500 mL during their participation in the study
- c. the frequency of blood samples to be collected during the study
- d. what the blood samples collected would be analyzed for

Firm’s Response to Form 483 (as summarized by OSIS) and OSIS Evaluation

In the clinical site’s response, they acknowledge the observation. The response indicated that this was a multicenter study and the writing of the standard informed consent document was managed centrally by the sponsor, Mylan, their appointed Contract Research Organization (CRO/SMO), PPD, and the central IRB, (b) (4) IRB. Therefore, this observation does not apply to Princeton Center for Clinical Research. We find the site’s response acceptable. This observation does not affect subject safety or data integrity.

5.8.2.1.3.1 DB Reviewer Comment for Current ANDA 208891:

This observation is related to the writing of the standard informed consent document, which was managed centrally by the firm and their appointed CRO/SMO PPD. The current reviewer agrees with the OSIS’ evaluation that this finding does not affect subject safety or data integrity of the current ANDA.

5.8.2.1.3.2 Parent ANDA Reviewer Comment for Related ANDAs:

Because this OSIS finding is related to the procedures used to conduct the BE studies, it is considered systemic. Reviewers of related ANDAs should evaluate the impact of this finding on his/her own respective ANDA.

☐ Isolated	☒ Systemic

5.8.2.1.4 OSIS Comment #2 for This Clinical Site #3001033

Failure to assure that an IRB complying with applicable regulatory requirements was responsible for the initial and continuing review and approval of a clinical study. Specifically, there is no documentation the clinical investigator assured the composition of the IRB met the regulatory requirement for the initial and continuing review of this clinical study nor was the clinical investigator aware of which panel met to review and approve this study. Furthermore, none of the panel members or alternate members were identified as having specialization in asthma or respiratory disease nor was there documentation the IRB consulted or invited an expert in the area of asthma or respiratory disease in reviewing this study.

Firm’s Response to Form 483 (as summarized by OSIS) and OSIS Evaluation

The firm acknowledged the observation. In their response, the PI stated that it seems unusual that PI cannot rely on the central IRB. (b) (4) is an established IRB and standard IRB documents from (b) (4) were maintained in the investigator site file. (b) (4) IRB had reassured the PI that their panel members hold a comprehensive range of expertise and therefore were fully qualified to review the study protocol, which was for a bioequivalence study for a generic asthma medicine with a well understood safety profile and utilizing a study design that adhered to FDA guidance on demonstrating clinical bioequivalence for that particular product.

The firm’s response is acceptable. This observation does not affect subject safety and data integrity.

5.8.2.1.4.1 DB Reviewer Comment for Current ANDA 208891:

The current reviewer agrees with the OSIS’ evaluation that this finding does not affect subject safety or data integrity of the current ANDA.

5.8.2.1.4.2 Parent ANDA Reviewer Comment for Related ANDAs:

Because this OSIS finding is related to the procedures used to conduct the BE studies, it is considered systemic. Reviewers of related ANDAs should evaluate the impact of this finding on his/her own respective ANDA.

☐ Isolated	☒ Systemic

5.8.2.1.5 OSIS Comment #3 for This Clinical Site #3001033

Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.

Specifically.

- a. For 7 out of 7 subjects reviewed, there is no documentation that the study subjects met exclusion criteria #15 which states that the subject should not be enrolled if they have been treated with "an investigational drug within 1 month or at least 5 half-lives (whichever is longer) preceding the first dose of the trial medication."

- b. Clinical investigator failed to retain the results for all Forced Spirometry results for four out of seven subjects reviewed.

Firm’s Response to Form 483 (as summarized by OSIS) and OSIS Evaluation

The firm acknowledged the observation. In their response, they stated:

- In the future the PI will review the ICF compared to Adverse Effects listed in the medication guide for any approved products and the PI will contact the sponsor, CRO or IRB if they identify a problem. The PI will also continue to advise patients of any study issue to make sure they are fully informed prior to entering any clinical studies.
- The PI will implement a new SOP into future studies that incorporates each protocol's individual inclusion and exclusion criteria, with a corresponding check box and investigator signature and date, into all study source documents.
- In the future the site will request all data from centralized vendors, including unacceptable Spirometry efforts to be retained at site.

The response and corrective action are acceptable. A new SOP has been implemented in the future studies. There is no impact on subject safety and data integrity.

5.8.2.1.5.1 DB Reviewer Comment for Current ANDA 208891:

The current reviewer agrees with the OSIS’ evaluation that this finding does not affect subject safety or data integrity of the current ANDA.

5.8.2.1.5.2 Parent ANDA Reviewer Comment for Related ANDAs:

Because this OSIS finding is related to the procedures used to conduct the BE studies, it is considered systemic. Reviewers of related ANDAs should evaluate the impact of this finding on his/her own respective ANDA.

☐ Isolated	☒ Systemic

Timber Lane Allergy & Asthma Research, LLC (Clinical site #3001018)

5.8.2.1.6 OSIS Comment #1 for This Clinical Site #3001018

Samples of the test article and reference standard used in a bioequivalence study were not retained.

Specifically,

The 50 reserve samples retained by Timber Lane Allergy & Asthma Research, LLC were not representative of each sample of the test article and reference standard provided by the applicant for the testing. The reserve samples were selected only from the initial shipment of 72 test kits. An additional 70 kits were received at the clinical site in subsequent shipments which were not sampled; therefore the reserve samples were not representative of these kits. The Study Drug Retention System Module of the Interactive Web Response System (IWRS) was designed by the Contract Research Organization (CRO) in such a way that exactly 50 reserve samples had to be

selected from the initial shipment. Fifty reserve samples was the total amount to be collected from each clinical site and there was no option to collect additional samples from subsequent shipments.

Firm’s Response to Form 483 (as summarized by OSIS) and OSIS Evaluation

This observation has been addressed in the previous sections.

5.8.2.1.6.1 DB Reviewer Comment for Current ANDA 208891:

Please see reviewer’s comments in Section 5.8.2.1.1.1.

5.8.2.1.6.2 Parent ANDA Reviewer Comment for Related ANDAs:

Because this OSIS finding is related to the procedures used to conduct the BE studies, it is considered systemic. Reviewers of related ANDAs should evaluate the impact of this finding on his/her own respective ANDA.

☐ Isolated	☒ Systemic

5.8.2.1.7 OSIS Comment #2 for This Clinical Site #3001018

The general requirements for informed consent were not met in that the investigator did not seek consent under circumstances that minimized the possibility of coercion or undue influence.

Specifically,

Advertising for clinical subjects placed on Craigslist.org as a part-time employment posting was not approved by the IRB. The Craigslist.org posting was based on advertising approved by the IRB, with the exception that the amount of the compensation was not included on the IRB approved advertising. The Craigslist.org posting emphasized the amount of the compensation by using a bold print, enclosing it in a separate text box, and being placed under the job postings as part time employment.

Firm’s Response to Form 483 (as summarized by OSIS) and OSIS Evaluation

The firm acknowledged the observation. In their response, they acknowledged insufficient oversight (i.e., review and approval of screen captures) for staff placing advertisements on Craigslist.org. The clinical site immediately removed all current ads from Craigslist.org, completed on June 15, 2016. The proposed CAPA is a revision of procedures for Craigslist.org advertisements and an updated training of staff regarding advertising, recruitment, and the IRB approval process.

The response and corrective action are acceptable. There is no impact on subject safety and data integrity.

5.8.2.1.7.1 DB Reviewer Comment for Current ANDA 208891:

The current reviewer agrees with the OSIS' evaluation that this finding does not affect subject safety or data integrity of the current ANDA.

5.8.2.1.7.2 Parent ANDA Reviewer Comment for Related ANDAs:

Because this OSIS finding is related to the procedures used to conduct the BE studies, it is considered systemic. Reviewers of related ANDAs should evaluate the impact of this finding on his/her own respective ANDA.

☐ Isolated	☒ Systemic

5.8.2.1.8 OSIS Comment #3 for This Clinical Site #3001018

An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,

Section 8.1 Screening Procedures of the protocol states, "The Principal Investigator or Medical Sub-Investigator will review the inclusion and exclusion criteria to confirm eligibility of each subject prior to enrollment." Section 8.1.1 Screening Visit (Visit 1) states "Subjects will be screened approximately 28 days (+2 days) prior to administration of the study medication to confirm that they meet the subject selection criteria for the study." and "The following procedures will be completed:"..."Full physical examination"...“Standard 12-lead electrocardiogram (ECG)”...and "Inclusion/Exclusion criteria." The inclusion/exclusion criteria checklists for seven subjects and ECGs for five subjects were reviewed after the date the subjects received run-in medication. Additionally, the physical examination was performed after one subject received run-in medication.

Subject #	Run-In Kit Assignment Date	Inclusion/Exclusion Reviewed	ECG Reviewed	Physical Exam Reviewed
(b) (6)				

Firm’s Response to Form 483 (as summarized by OSIS) and OSIS Evaluation

The firm acknowledged the observation. In their response, they stated that development of a new PI/Sub-Investigator (Sub-1) worksheet to include a physical exam and a checklist of all items reviewed at the time of the visit will be utilized in future studies. The signature and date on this worksheet will represent the date of review of all applicable criteria.

5.8.2.1.8.1 DB Reviewer Comment for Current ANDA 208891:

According to the site’s investigation report of this issue²³⁵, “[b]ased on timing of the Principal Investigator’s (PI) presence at the Screen Visit, information regarding data collected during the baseline visit was provided verbally to the PI and placed in the source documents after the physical exam (PE) and review of criteria has been completed.” The firm also stated that in all cases listed in OSIS’ observation, source documentation, review and signatures were completed prior to subject randomization to study drug. The current reviewer considers this finding not affect data integrity of the current ANDA.

5.8.2.1.8.2 Parent ANDA Reviewer Comment for Related ANDAs:

Because this OSIS finding is related to the procedures used to conduct the BE studies, it is considered systemic. Reviewers of related ANDAs should evaluate the impact of this finding on his/her own respective ANDA.

☐ Isolated	☒ Systemic

²³⁵ GDRP: ANDA 208891, Clinical Endpoint Sites, EIR Cover Memo ANDA 208891, 10/28/2016 (p. 45-49 of 102).

5.8.2.1.9 Overall Comments for OSIS Findings at the Clinical Sites for Clinical Endpoint Studies

As mentioned above, the firm will be asked to provide additional documentations to address the reserve sample issue and blinding codes/audit trail issue.

5.8.3 OSIS Inspection Report for In Vitro BE Studies

During the course of the current review, it was noticed that GDRP did not have a task for in vitro BE study inspection. However, since in vitro BE studies are one of the studies recommended by the product-specific guidance, DBI believes that these studies need to be inspected. Therefore, DBI submitted an OSIS inspection request consult to OSIS for routine inspection of the in vitro BE study analytical sites (b)(4) and Mylan Global Respiratory Group).²³⁶ On 3/15/2017, OSIS provided the inspection report for one of the in vitro study sites (b)(4).²³⁷ On 3/16/2017, OSIS issued decline to inspect memo for the other invitro study site (Mylan Global Respiratory Group).²³⁸

5.8.3.1 Analytical Site (b)(4)

The OSIS conducted an inspection at (b)(4) to audit the in vitro BE studies [057755-02-04 (100/50 mcg strength) and 057755-02-07 (500/50 mcg strength)] of the current ANDA from 2/27/2017 to 3/3/2017. According to internal discussion with OSIS, in addition to the aforementioned studies, OSIS also inspected other in vitro BE studies conducted at this analytical site for (b)(4).

Per the inspection report dated 3/14/2017 from the OSIS, no Form FDA-483 observation is relevant to the inspected in vitro BE studies for the current ANDA. The OSIS outcome was VAI for (b)(4). The OSIS recommended accepting the in vitro studies 057755-02-04 and 057755-02-07 for further Agency review.

The OSIS provided the DBI with the following comments. Please note that as mentioned above, the inspected in vitro BE studies for the current ANDA does not have relevant Form FDA-483 observations.

5.8.3.1.1 OSIS Comment

The analytical methods performed by (b)(4) were developed and validated by the sponsor (Mylan Global Respiratory Group) prior to the transfer to (b)(4) according to (b)(4) method transfer protocol. A table of comparison of chromatographic conditions between the sponsor and the firm (provided by (b)(4); Attachment 1²³⁹) is attached. A standard curve range showing linearity using six calibrators was evaluated by the sponsor during method validation and by

²³⁶ GDRP: ANDA 208891, Documents, A208891_Conult to OSIS.doc, 1/17/2017.

²³⁷ GDRP: ANDA 208891, In Vitro BE Sites, EIR Review-(b)(4)_ANDA208891_final, 3/15/2017.

²³⁸ GDRP: ANDA 208891, In Vitro BE Sites, Decline to Inspect_ANDA 208891_Mylan UK_Analy, 3/16/2017.

²³⁹ Please see Section 5.10.2.

(b) (4) during the initial method transfer. However it was noted that the (b) (4) site, which received the method from (b) (4), did not conduct the same standard curve using the six calibrators in light of the fact that it was an internal method transfer and (b) (4) sites use the same equipment and instrumentation for the in-vitro bioequivalence studies. During sample analysis, (b) (4) included two calibrators prepared from two separately prepared standard solutions from two separate stock solutions of fluticasone propionate and salmeterol as xinafoate salt (SX) reference materials. Although no independent QCs were evaluated, one of the two prepared standards used in the calibration curve was repeated throughout the chromatography analysis for the Emitted Dose test method and Aerodynamic Particle Size Distribution (ASPD) using the (b) (4) Impactor test method. Despite these limitations, the sample test method and sample analysis runs were acceptable. Reserve samples were collected during the inspection. For the inspection covering ANDA 208891, there were no Form FDA-483 observations issued at (b) (4) at the inspection closeout.

5.8.3.1.1.1 DB Reviewer Comment for Current ANDA 208891:

- As mentioned in Section 5.3.2, based on the firm's submissions to the current ANDA, it is unclear whether the method validation studies were conducted at the same study site as the pivotal in vitro BE studies. However, according to the OSIS inspection report, the analytical methods performed by (b) (4) were developed and validated by the sponsor (Mylan Global Respiratory Group) prior to the transfer to (b) (4) according to (b) (4) method transfer protocol. The method was initially transferred to (b) (4), and was then transferred from (b) (4), where the pivotal in vitro BE studies for the 100/50 and 500/50 mcg strengths were conducted. Therefore, it is clear that method validation and in vitro BE studies for the 100/50 and 500/50 mcg strengths were conducted at different sites.

As mentioned in Section 5.3.2.1.2, since OSIS mentioned the existence of (b) (4) method transfer protocol, it is likely that the firm conducted studies for method transfer from Mylan Global Respiratory Group to (b) (4). Since the firm did not provide method transfer report in the current submission, the firm will be asked to provide so, because method transfer studies (e.g. precision and accuracy studies for the HPLC method; and precision study for the SAC and ASPD methods) are needed to support method transfer between different study sites. The firm will be advised that method transfer studies for the SAC and ASPD methods should be conducted using unexpired RLD product.

- According to OSIS inspection report, a standard curve range showing linearity using 6 calibrators was evaluated by the sponsor during method validation and by (b) (4) during the initial method transfer. However, (b) (4), which received the method from (b) (4) did not conduct the same standard curve. Since details were not provided in the OSIS inspection report, and the firm will be asked to provide method validation transfer report for method transfer from the sponsor to (b) (4), this issue will be evaluated upon receipt of the method transfer report.
- OSIS reviewer also stated that during sample analysis, (b) (4) included 2 calibrators prepared from 2 separately prepared standard solutions prepared from 2 separate stock

solutions of FP and SA. Although no independent QCs were evaluated, one of the 2 standards used in the calibration curve was repeated throughout the analysis for the SAC and APSD test. For the impact of this on APSD studies, please see reviewer's comments in Section 5.3.2.2.1. Please note that for SAC studies, the product-specific guidance and nasal BA/BE guidance do not contain recommendations for QC inclusion in analytical runs for SAC studies.

5.8.3.1.2 Overall Comments for OSIS Findings at Analytical Site for In Vitro BE Studies

(b) (4)

As mentioned above, the firm will be asked to provide additional documentations for their method transfer.

5.8.3.2 Analytical Site (Mylan Global Respiratory Group, Kent, UK)

The DGDBE within the OSIS declines to conduct a biopharmaceutical inspection.²⁴⁰ Although OSIS has no inspection history at the site, inspections have been conducted at Mylan-associated bioanalytical sites seven times since 2010 resulting in six NAI and one VAI classification. In addition, sixteen clinical endpoint inspections, one in vivo BE bioanalytical inspection and one in vitro BE analytical inspection have been conducted on this ANDA alone. Therefore, OSIS recommends that a biopharmaceutical inspection of the studies conducted at the site is not necessary.

²⁴⁰ GDRP: ANDA 208891, In Vitro BE Sites, Decline to Inspect_ANDA 208891_Mylan UK_Analy, 3/16/2017.

5.9 SAS Output

5.9.1 Fasting Study MGR001-1006

5.9.1.1 Fasting Study Data (FP)

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE
1	(b) (6)	1	1	1	T	0	18.380	33.73	69.98	85.75	101.00	115.00	119.50	119.50	111.60	97.61	68.16	50.39	39.330	28.860	17.990	6.778	3.659	2.691	
2		1	1	2	R	0	62.700	70.49	104.90	113.20	142.20	132.10	136.00	140.10	119.10	107.10	77.92	60.41	42.650	32.690	16.820	7.945	4.242	2.878	
3		1	2	1	R	0	20.690	46.23	65.62	84.29	93.36	101.80	106.80	96.26	79.67	62.02	42.91	37.32	19.770	12.560	6.734	2.276	1.218	0.000	
4		1	2	2	T	0	15.380	35.57	56.53	67.86	81.43	85.48	97.87	91.70	72.18	58.72	42.14	30.39	19.050	14.460	6.892	2.318	1.197	0.000	
5		1	2	1	R	0	64.530	63.23	89.60	114.00	116.40	135.90	129.90	127.10	113.50	99.44	72.18	61.02	40.410	31.810	17.900	7.079	2.765	2.435	
6		1	2	2	T	0	43.640	51.26	60.54	76.68	83.25	98.17	104.10	104.40	98.49	83.01	66.18	59.28	42.400	32.660	18.970	6.222	4.142	1.935	
7		1	1	1	T	0	8.317	15.20	35.56	53.75	56.74	65.88	69.22	62.28	55.32	49.00	37.52	30.61	15.360	11.150	6.552	2.271	1.401	0.000	
8		1	1	2	R	0	13.760	19.53	38.01	49.89	58.06	64.09	69.59	64.34	60.51	53.48	38.27	33.51	14.820	11.840	6.137	2.173	1.163	0.000	
9		1	1	1	T	0	6.610	19.11	28.07	44.78	44.64	53.16	52.08	44.11	33.73	26.41	18.43	12.12	5.718	3.624	2.213	0.000	0.000	0.000	
10		1	1	2	R	0	15.560	24.68	39.44	48.27	64.91	64.42	61.49	58.16	39.75	31.52	19.50	14.39	7.074	4.230	1.907	0.000	0.000	0.000	
11		1	2	1	R	0	27.910	46.13	82.76	123.80	141.90	166.30	169.70	157.20	127.00	93.35	63.45	47.34	24.080	17.730	9.651	3.655	2.802	2.319	
12		1	2	2	T	0	40.980	67.40	97.28	137.30	143.00	166.10	170.90	151.80	122.70	99.08	70.48	50.12	26.680	19.970	10.460	4.770	3.069	2.246	
13		1	1	1	T	0	18.690	29.45	50.03	52.22	69.86	94.65	113.70	120.70	109.50	104.80	80.03	70.18	42.250	33.310	18.060	7.324	2.524	1.823	
14		1	1	2	R	0	12.870	43.15	47.24	71.67	76.00	99.37	110.90	99.49	86.49	83.80	57.46	56.99	30.840	22.920	12.550	4.668	1.802	0.000	
15		1	1	1	T	0	7.706	37.53	48.10	73.23	53.60	76.92	72.09	55.71	38.24	34.63	26.36	21.85	10.990	7.567	4.135	1.553	0.000	0.000	
16		1	1	2	R	0	26.990	38.24	41.68	62.36	77.06	83.79	84.28	77.38	54.78	46.31	33.98	28.05	15.050	11.280	5.247	1.929	0.000	0.000	
17		1	2	1	R	0	26.350	28.56	52.77	57.49	70.68	72.83	70.56	68.95	65.09	60.59	50.73	39.03	23.160	15.850	8.775	3.027	1.807	1.006	
18		1	2	2	T	0	10.920	19.46	37.47	41.50	63.35	65.53	65.84	67.10	64.56	55.68	55.22	43.41	28.050	17.350	9.930	3.341	1.436	0.000	
19		1	2	1	R	0	47.740	64.82	86.50	101.80	115.10	133.30	106.30	112.00	93.10	83.27	60.52	53.16	40.710	28.430	17.690	7.053	2.696	2.439	
20		1	2	2	T	0	44.710	54.16	75.86	78.69	64.11	97.01	97.18	87.21	93.26	87.25	66.10	50.11	37.930	31.390	16.860	5.670	2.787	1.994	
21		1	2	1	R	0	14.730	36.56	52.38	48.94	59.52	89.75	84.04	95.20	80.31	64.10	49.32	36.75	21.290	16.560	9.324	3.589	1.733	1.312	
22		1	2	2	T	0	7.764	23.20	31.37	31.69	50.28	83.25	74.05	86.58	79.24	65.87	51.41	39.31	25.560	17.550	11.490	4.256	2.220	1.025	
23		1	1	1	T	0	35.710	42.66	62.83	101.30	139.10	142.30	126.60	105.70	84.81	85.45	72.50	57.92	34.310	22.340	15.130	4.326	2.056	1.536	
24		1	1	2	R	0	20.460	33.81	47.88	61.87	63.79	84.27	106.70	99.20	78.57	76.54	63.40	47.86	36.300	24.070	14.360	4.439	2.538	1.123	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE
25	(b) (6)	1	1	1	T	0	6.039	12.15	26.11	41.60	43.48	64.99	63.32	68.34	62.30	55.26	53.40	43.16	23.970	20.700	10.590	3.053	1.045	0.000	
26		1	1	2	R	0	7.456	31.76	42.72	56.15	55.48	84.24	90.90	97.01	86.68	77.24	58.65	48.71	30.920	16.840	11.410	3.659	1.710	0.000	
27		1	1	1	T	0	96.750	103.30	93.52	164.20	210.10	180.10	147.00	141.80	110.30	99.84	71.00	64.17	35.990	26.710	16.490	7.214	4.278	3.226	
28		1	1	2	R	0	34.610	59.25	96.36	101.90	130.50	142.00	145.00	135.30	116.70	87.90	67.89	54.60	30.980	18.730	11.430	5.518	3.200	2.375	
29		1	2	1	R	0	7.236	42.57	95.47	81.04	127.00	121.60	116.10	129.70	102.10	90.95	73.84	58.19	33.050	25.760	13.170	4.107	1.440	0.000	
30		1	2	2	T	0	15.160	44.88	56.33	98.47	98.43	121.00	122.10	105.50	96.16	87.99	74.71	60.96	35.290	26.220	15.120	5.337	1.573	1.025	
31		1	2	1	R	0	20.480	30.50	47.55	56.57	67.10	81.54	88.20	76.26	61.86	50.94	32.32	32.96	16.260	10.460	6.686	4.246	1.922	1.468	
32		1	2	2	T	0	8.782	18.73	40.40	53.28	61.75	62.21	74.40	68.18	57.44	49.74	30.86	25.92	14.760	12.380	6.706	3.446	1.469	1.306	
33		1	2	1	R	0	59.520	78.92	108.70	127.10	141.50	187.80	175.00	150.00	132.70	100.60	81.21	62.52	31.320	24.360	15.730	5.615	3.006	1.389	
34		1	2	2	T	0	50.170	55.63	104.80	101.60	105.70	122.50	137.50	147.70	121.60	119.70	80.42	68.53	37.210	31.250	17.310	5.471	2.896	1.708	
35		1	2	1	R	0	9.570	49.26	42.55	53.18	68.81	74.07	84.48	86.88	80.02	64.96	53.61	43.33	26.200	16.230	10.480	3.353	0.000	0.000	
36		1	2	2	T	0	4.284	14.49	22.66	31.60	40.87	53.58	56.03	57.65	52.31	45.65	35.65	29.11	15.520	11.430	6.311	2.234	0.000	0.000	
37		1	1	1	T	0	19.850	42.59	82.27	113.40	105.30	116.10	131.70	132.70	116.80	105.80	84.19	77.74	39.560	29.010	16.680	6.249	3.099	1.369	
38		1	1	2	R	0	19.870	42.85	57.05	101.50	114.20	89.82	98.96	98.99	107.10	94.08	77.71	62.27	36.390	27.040	15.140	5.083	1.678	0.000	
39		1	2	1	R	0	25.020	50.42	70.17	91.50	80.98	113.90	111.60	122.50	106.60	76.42	61.72	51.69	33.730	26.230	15.540	6.544	4.170	2.214	
40		1	2	2	T	0	12.690	22.03	66.76	57.17	93.50	105.80	113.80	91.03	90.80	73.38	51.88	45.94	29.520	19.550	13.100	6.132	3.458	2.138	
41		2	1	1	T	0	9.814	23.41	41.83	68.71	54.38	70.49	87.16	81.55	82.80	82.25	61.69	55.01	31.870	22.340	10.600	4.191	1.722	0.000	
42		2	1	2	R	0	34.570	29.38	55.31	73.58	101.60	149.30	111.40	110.70	103.20	91.74	74.24	69.90	32.890	20.900	11.680	4.458	2.345	1.090	
43		2	1	1	T	0	4.603	14.04	16.52	32.52	41.43	64.74	57.95	72.56	70.91	65.83	45.51	38.95	25.890	19.450	9.888	3.354	1.633	1.264	
44		2	1	2	R	0	14.660	24.85	51.62	56.47	69.98	87.44	92.84	95.27	92.24	79.14	56.74	45.72	27.970	21.850	11.240	3.833	2.086	1.055	
45		2	1	1	T	0	20.620	42.26	49.80	92.26	94.28	116.10	124.90	120.00	111.90	94.45	74.13	61.10	32.000	27.390	15.210	6.230	2.657	1.874	
46		2	1	2	R	0	24.700	32.37	73.15	83.15	77.20	106.10	112.30	109.50	98.67	88.78	56.85	51.84	27.050	23.630	12.540	5.666	2.192	1.301	
47		2	2	1	R	0	30.630	61.63	81.60	82.04	93.79	114.60	111.90	121.80	102.20	91.00	62.84	44.62	26.210	20.970	10.550	3.616	1.507	0.000	
48		2	2	2	T	0	11.880	37.59	45.30	78.34	94.85	99.25	115.00	117.70	96.54	80.89	64.89	48.57	31.760	24.430	12.200	4.204	1.804	1.166	
49		2	1	1	T	0	16.610	36.50	56.84	89.77	92.17	96.30	97.77	100.80	91.23	74.97	54.32	43.54	25.990	19.180	10.380	4.268	2.484	1.136	
50		2	1	2	R	0	24.120	57.51	76.44	84.71	109.00	112.30	113.20	109.10	91.24	77.65	53.05	39.26	22.180	15.340	8.505	2.209	1.077	0.000	
51		2	1	1	T	0	9.802	14.61	26.28	81.20	41.03	47.48	61.98	66.37	56.33	57.77	45.38	37.77	22.000	16.510	8.406	3.289	1.255	0.000	
52		2	1	2	R	0	3.486	42.76	36.82	43.04	50.85	57.75	59.77	60.78	60.37	54.68	39.76	32.95	17.520	13.520	6.699	2.366	0.000	0.000	
53		2	2	1	R	0	8.264	16.10	41.75	67.08	47.35	75.14	79.46	63.55	55.16	51.98	40.91	32.16	17.960	11.180	6.373	2.133	0.000	0.000	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE
54	(b) (6)	2	2	2	T	0	3.130	14.78	23.77	35.74	52.73	80.14	73.52	83.58	81.01	81.15	62.11	49.13	30.310	20.970	10.850	4.346	1.536	1.291	
55		2	2	1	R	0	4.580	18.44	29.10	41.93	43.56	48.66	65.73	60.17	47.60	46.32	34.75	29.33	14.260	12.230	5.309	1.922	0.000	0.000	
56		2	2	2	T	0	1.699	10.35	28.31	35.80	44.91	68.19	67.10	71.59	77.36	64.47	44.70	38.91	24.200	18.660	9.364	3.683	0.000	0.000	
57		2	1	1	T	0	22.710	41.74	76.91	107.30	133.80	141.10	121.70	125.80	86.83	68.52	57.03	45.21	26.430	19.750	12.260	4.646	3.257	2.452	
58		2	1	2	R	0	20.390		66.70	71.21	112.10	128.90	118.70	107.50	83.23	67.00	49.94	39.43	24.690	19.030	9.978	3.537	2.306	0.000	
59		2	2	1	R	0	61.390	108.80	83.20	140.70	108.70	120.70	100.30	79.40	70.01	62.13	36.21	31.90	17.340	11.560	8.004	1.860	1.913	0.000	
60		2	2	2	T	0	10.140	110.80	53.95	113.70	99.82	106.30	101.30	90.39	77.30	56.56	45.29	37.10	25.600	19.190	9.437	3.013	2.071	1.123	
61		2	2	1	R	0	34.820	128.40	110.80	97.97	127.50	142.80	144.70	127.50	104.50	94.90	71.23	55.10	48.170	31.290	15.370	6.326	1.527	1.386	
62		2	2	2	T	0	20.540	46.64	80.60	118.40	147.30	145.00	130.60	130.90	110.40	109.00	78.54	74.32	53.790	38.240	19.690	6.692	2.293	1.828	
63		2	1	1	T	0	9.756	24.78	39.92	60.51	89.71	87.16	100.30	89.50	87.13	67.37	45.47	38.16	21.440	16.720	9.214	3.314	1.520	0.000	
64		2	1	2	R	0	16.330	53.21	74.72	113.30	133.60	132.00	122.90	108.00	99.09	76.53	56.93	43.03	23.580	19.340	9.258	3.340	1.329	1.023	
65		2	2	1	R	0	17.140	43.26	67.44	79.59	104.20	119.10	122.70	120.40	102.30	90.12	69.14	58.65	32.850	23.000	12.080	5.355	1.851	1.346	
66		2	2	2	T	0	7.882	32.65	44.02	71.14	73.52	102.30	101.20	107.90	102.10	96.78	73.56	66.88	38.740	27.610	12.920	5.760	1.979	1.608	
67		2	1	1	T	0	9.635	29.76	46.24	74.67	84.24	105.10	96.95	83.91	77.15	63.04	45.43	34.48	19.490	14.810	8.401	3.031	1.946	0.000	
68		2	1	2	R	0	18.510	39.94	72.00	73.62	98.59	123.30	119.80	111.20	90.75	83.66	59.42	46.64	25.550	17.510	9.315	3.238	1.363	1.027	
69		2	1	1	T	0	31.610	56.80	86.39	84.31	88.64	99.57	91.45	80.99	69.74	55.83	52.10	45.20	27.650	20.350	16.090	5.542	3.061	1.681	
70		2	1	2	R	0	63.010	79.45	67.81	86.19	117.30	102.30	89.11	85.45	80.00	68.41	43.37	41.63	24.470	17.410	11.950	4.252	2.527	1.566	
71		2	1	1	T	0	113.000	129.00	129.80	165.30	184.20	164.70	135.20	125.00	92.15	79.78	56.96	46.01	32.060	22.920	11.970	4.718	2.337		
72		2	1	2	R	0	83.710	166.20	86.50	138.80	148.30	137.20	124.30	106.60	79.59	63.74	48.00	42.21	27.120	19.780	10.520	3.521	1.913	1.768	
73		2	2	1	R	0	34.920	71.95	94.21	99.84	117.90	137.50	140.70	123.10	105.40	81.38	66.66	47.21	30.770	18.140	10.230	4.378	2.331	1.553	
74		2	2	2	T	0	19.200	32.37	57.78	81.90	96.37	104.20	120.20	110.80	92.93	68.77	59.63	47.68	28.140	20.590	11.170	4.602	2.146	1.583	
75		2	2	1	R	0	19.150	32.70	58.97	83.62	90.56	115.40	115.70	103.10	78.17	57.18	39.64	29.37	16.860	10.710	6.271	1.893	0.000	0.000	
76		2	2	2	T	0	10.220	38.31	71.63	92.58	101.90	109.40	128.70	118.20	78.86	72.48	47.03	37.13	20.570	16.450	8.341	3.260	1.901	1.555	
77		2	1	1	T	0	22.360	38.23	51.19	52.75	83.51	91.87	86.76	69.44	67.00	62.38	47.66	38.90	24.300	17.660	9.685	2.947	1.655	1.034	
78		2	1	2	R	0	13.790	31.02	39.83	60.09	62.71	89.82	102.90	87.60	86.11	73.63	58.13	42.60	25.820	20.500	9.476	3.642	1.602	1.024	
79		2	2	1	R	0	14.930	22.62	30.18	41.40	46.99	55.51	66.74	69.76	70.22	68.37	54.45	44.62	27.360	19.950	12.480	4.983	2.270	1.356	
80		2	2	2	T	0	5.068	11.82	19.99	34.39	45.08	54.51	57.12	73.76	74.72	70.14	54.39	50.46	27.820	24.700	13.840	5.553	2.124	1.629	
81		3	1	1	T	0	6.274	21.59	61.00	37.31	62.29	47.47	45.11	48.76	38.34	33.05	21.70	19.56	12.500	9.055	6.026	2.473	1.709	0.000	
82		3	1	2	R	0	74.900	85.35	104.70	115.60	85.44	97.77	71.55	62.24	46.36	40.28	29.72	22.49	14.230	12.690	6.755	2.622	1.073	0.000	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE
83	(b) (6)	3	1	1	T	0	19.980	30.08	52.25	66.15	82.52	103.30	103.60	116.50	97.48	83.26	62.62	45.17	28.870	21.100	14.500	5.498	2.244	1.880	
84		3	1	2	R	0	40.500	47.93	62.15	82.91	87.61	96.20	84.87	92.43	70.16	75.41	51.90	43.30	24.550	21.160	11.320	4.549	2.074	2.383	
85		3	2	1	R	0	67.590	137.20	168.10	136.70	127.60	134.70	121.00	105.20	79.30	69.32	64.07	53.67	31.780	26.460	16.300	5.959	2.594	1.774	
86		3	2	2	T	0	87.370	75.36	106.90	106.80	75.31	87.58	113.30	107.90	109.80	96.94	79.58	65.64	35.390	28.250	15.350	6.589	3.234	2.583	
87		3	2	1	R	0	6.430	19.15	38.35	55.09	78.65	68.74	85.57	86.47	80.09	75.68	64.92	49.77	28.960	21.390	12.050	4.576	2.497	0.000	
88		3	2	2	T	0	5.037	12.77	45.10	33.12	36.97	50.66	53.80	71.35	70.26	67.80	53.11	45.92	29.810	23.760	11.620	5.156	1.836	1.045	
89		3	2	1	R	0	31.430	70.60	83.70	105.40	133.30	135.10	156.20	147.00	114.60	102.60	70.23	54.74	27.280	20.160	9.941	4.156	1.667	1.229	
90		3	2	2	T	0	14.380	40.01	65.02	71.45	98.10	118.20	142.60	137.80	111.70	106.40	76.69	60.64	35.570	23.390	12.150	5.420	2.084	1.891	
91		3	1	1	T	0	38.610	74.09	121.00	160.20	154.80	199.00	224.10	200.00	160.70	154.90	116.40	87.30	47.580	35.810	17.990	6.822	3.594	3.075	
92		3	1	2	R	0	37.520	82.87	132.80	166.20	207.60	214.50	220.20	210.90	169.00	143.50	99.34	75.66	43.820	35.780	17.910	6.022	4.141	2.800	
93		3	2	1	R	0	23.250	79.61	88.43	109.80	118.50	137.90	149.90	141.90	128.40	106.50	73.74	59.93	39.230	28.200	16.640	7.638	4.103	2.443	
94		3	2	2	T	0	34.700	28.45	59.03	88.45	103.30	132.70	140.70	147.70	128.90	115.30	83.37	74.10	42.600	32.860	16.290	7.727	4.058	2.262	
95		3	1	1	T	0	12.810	33.50	43.75	54.98	68.79	67.60	88.62	85.53	80.71	73.31	56.95	47.95	30.350	22.370	12.210	4.220	1.927	1.048	
96		3	1	2	R	0	14.720	45.36	63.25	71.29	100.00	86.38	112.70	103.40	98.16	94.15	70.54	53.60	33.660	25.750	11.640	3.772	1.599	0.000	
97		3	2	1	R	0	11.450	26.33	49.19	66.77	84.71	95.32	104.20	121.50	113.80	97.53	77.38	59.26	35.780	26.090	14.690	5.454	2.233	1.101	
98		3	2	2	T	0	9.008	26.56	43.71	64.04	69.11	78.73	107.30	98.05	106.50	103.60	82.65	69.28	39.980	30.090	17.800	5.760	2.566	1.999	
99		3	1	1	T	0	63.740	94.57	127.40	135.10	172.40	154.60	186.40	169.50	124.50	79.22	67.12	53.51	28.420	22.500	14.050	5.435	2.089	1.481	
100		3	1	2	R	0		149.00	112.20	191.80	217.20	167.70	154.10	119.90	92.91	73.66	59.95	43.33	27.900	19.260	10.480	5.725	2.505	1.690	
101		3	1	1	T	0	4.963	14.17	36.37	57.77	60.87	77.24	89.70	107.70	99.42	90.77	87.07	74.21	57.160	42.380	23.460	8.973	3.079	1.620	
102		3	1	2	R	0	18.580	31.80	69.05	94.26	80.42	99.87	85.30	103.80	102.90	90.72	78.35	64.16	44.870	35.060	18.960	6.879	2.402	1.876	
103		3	2	1	R	0	16.430	43.97	33.88	64.43	70.44	74.44	69.79	56.01	58.83	47.81	29.19	24.50	14.330	10.550	6.369	2.915	2.122	1.062	
104	3	2	2	T	0	9.030	26.68	46.51	72.43	84.74	75.45	113.00	83.72	67.08	54.82	38.22	25.01	17.930	13.040	6.598	3.740	1.619	1.145		
105	3	2	1	R	0	13.280	85.84	79.97	131.80	152.70	135.20	116.80		105.40	101.60	77.68	60.57	30.630	22.270	13.010	5.108	2.104	1.693		
106	3	2	2	T	0	9.346	32.31	57.28	124.40	123.80	128.50	114.40	124.50	122.80	124.40	85.39	69.95	41.040	29.940	17.620	6.005	2.733	2.517		
107	3	2	1	R	0	33.240	75.61	77.03	100.80	96.25	105.00	107.20	99.06	70.54	57.16	40.68	27.96	20.860	15.070	9.054	4.007	1.790	1.524		
108	3	2	2	T	0	27.230	56.40	84.97	106.60	122.80	142.00	146.60	154.40	114.30	94.19	84.14	60.05	39.740	29.680	15.430	7.812	4.987	2.765		
109	3	1	1	T	0	34.310	30.03	40.97	58.11	76.10	72.96	74.92	73.24	58.65	51.01	36.85	30.83	16.400	13.320	8.777	4.324	2.352	1.385		
110	3	1	2	R	0	13.170	38.68	60.94	71.45	86.61	98.99	103.10	91.56	74.51	61.63	48.62	37.53	20.830	16.100	9.052	4.331	2.596	1.308		
111	3	1	1	T	0	28.690	46.16	57.93	68.12	73.42	105.50	105.70	109.30	87.87	74.36	60.76	48.69	27.430	22.130	12.860	5.638	2.399	1.376		

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE
112	(b) (6)	3	1	2	R	0	52.620	62.47	72.87	104.90	112.80	113.60	92.36	108.80	78.29	67.04	53.35	46.48	25.660	19.300	10.520	4.004	1.711	1.044	
113		3	2	1	R	0	27.790	41.66	65.03	89.54	131.90	112.10	123.10	119.00	102.50	93.71	64.23	60.99	41.570	29.580	16.310	7.271	2.765	1.900	
114		3	2	2	T	0	19.890	21.75	38.75	57.18	83.49	87.30	108.00	98.68	82.48	89.48	65.99	57.10	35.190	27.700	14.110	6.015	2.573	1.072	
115		3	2	1	R	0	14.820	32.22	48.54	74.85	77.02	95.08	94.04	95.80	87.21	80.65	62.98	49.12	26.540	22.170	11.020	4.606	1.548	1.070	
116		3	2	2	T	0	16.190	27.87	43.11	58.43	67.09	71.88	74.15	81.99	79.10	79.01	64.57	52.77	33.050	25.030	12.500	4.788	2.206	1.025	
117		3	1	1	T	0	16.360	70.57	73.23	102.50	113.60	114.00	112.70	116.10	101.40	82.21	63.03	47.51	25.700	19.070	10.110	3.333	1.191	1.086	
118		3	1	2	R	0	36.810	78.60	74.86	73.78	96.45	87.86	87.98	97.89	83.29	75.58	53.95	41.99	21.060	15.630	7.341	2.925	1.423	0.000	
119		3	2	1	R	0	24.250	101.20	143.70	112.00	104.90	121.40	119.70	119.00	105.90	85.44	64.33	52.47	26.960	19.130	10.670	5.146	2.947	2.378	
120		3	2	2	T	0	65.820	115.10	67.43	90.74	88.97	105.60	112.90	113.70	99.60	96.10	64.82	52.03	29.710	21.090	11.050	5.324	3.637	2.575	
121		3	1	1	T	0	23.210	56.97	75.04	87.63	92.49	100.80	126.60	127.80	121.50	109.20	78.66	66.01	37.940	26.990	13.350	4.820	2.748	1.613	
122		3	1	2	R	0	25.800	35.41	72.05	82.64	106.60	114.90	131.00	129.30	113.20	87.82	65.03	51.17	24.160	20.230	10.140	3.991	2.328	1.837	
123		3	1	1	T	0	4.387	17.05	24.77	44.62	58.05	66.55	71.45	76.44	73.61	64.34	49.70	46.23	26.050	20.950	10.300	4.271	1.703	0.000	
124		3	1	2	R	0	10.520	35.34	48.59	64.85	73.10	102.40	94.51	98.25	90.19	72.36	59.15	45.69	26.010	19.240	9.704	3.740	1.230	0.000	

Obs	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	trt
1	19	0	0.033333	0.083333	0.166667	0.250000	0.333333	0.533333	0.75	1.000000	1.500000	2.000000	3.000000	4	6.000000	8.000000	12.0000	24.0000	36.0000	48.0000	1
2	19	0	0.033333	0.083333	0.166667	0.250000	0.333333	0.500000	0.75	1.050000	1.500000	2.000000	3.000000	4	6.000000	8.000000	12.0000	24.0000	36.0000	48.0000	2
3	18	0	0.033333	0.083333	0.166667	0.250000	0.333333	0.500000	0.75	1.000000	1.500000	2.000000	3.000000	4	6.000000	8.000000	12.0000	24.0000	36.0000	48.0000	2
4	18	0	0.033333	0.083333	0.166667	0.250000	0.333333	0.500000	0.75	1.000000	1.500000	2.000000	3.000000	4	6.000000	8.000000	12.0000	24.0000	36.0000	48.0000	1
5	19	0	0.033333	0.083333	0.166667	0.250000	0.333333	0.500000	0.75	1.000000	1.500000	2.000000	3.000000	4	6.000000	8.000000	12.0000	24.0000	36.0000	48.0000	2
6	19	0	0.033333	0.083333	0.166667	0.250000	0.333333	0.500000	0.75	1.000000	1.500000	2.000000	3.000000	4	6.000000	8.000000	12.0000	24.0000	36.0000	48.0000	1
7	18	0	0.033333	0.083333	0.166667	0.250000	0.333333	0.500000	0.75	1.000000	1.500000	2.000000	3.000000	4	6.000000	8.000000	12.0000	24.0000	36.0000	48.0000	1
8	18	0	0.033333	0.083333	0.166667	0.250000	0.333333	0.500000	0.75	1.000000	1.500000	2.000000	3.000000	4	6.000000	8.000000	12.0000	24.0000	36.0000	48.0000	2
9	16	0	0.033333	0.083333	0.166667	0.250000	0.333333	0.500000	0.75	1.000000	1.500000	2.000000	3.000000	4	6.000000	8.000000	12.0000	24.0000	36.0000	48.0000	1
10	16	0	0.033333	0.083333	0.166667	0.250000	0.333333	0.500000	0.75	1.000000	1.500000	2.000000	3.000000	4	6.000000	8.000000	12.0000	24.0000	36.0000	48.0000	2
11	19	0	0.033333	0.083333	0.166667	0.250000	0.333333	0.500000	0.75	1.000000	1.500000	2.000000	3.000000	4	6.000000	8.000000	12.0000	24.0000	36.0000	48.0000	2
12	19	0	0.033333	0.083333	0.166667	0.250000	0.333333	0.500000	0.75	1.000000	1.500000	2.000000	3.000000	4	6.000000	8.000000	12.0000	24.0000	36.0000	48.0000	1
13	19	0	0.033333	0.083333	0.166667	0.250000	0.333333	0.500000	0.75	1.000000	1.500000	2.000000	3.000000	4	6.000000	8.000000	12.0000	24.0000	36.0000	48.0000	1
14	18	0	0.033333	0.083333	0.166667	0.250000	0.333333	0.550000	0.75	1.000000	1.500000	2.000000	3.000000	4	6.000000	8.000000	12.0000	24.0000	36.0000	48.0000	2

5.9.1.2 Fasting Study Output (FP)

Group 1

Fasting STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	20	(b) (6)
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	40
Number of Observations Used	40

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	7.35691974	0.35032951	24.41	<.0001
Error	18	0.25834205	0.01435234		
Corrected Total	39	7.61526179			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.966076	1.883497	0.119801	6.360576

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.22405426	0.22405426	15.61	0.0009
sub(seq)	18	7.11628173	0.39534898	27.55	<.0001
per	1	0.01023950	0.01023950	0.71	0.4094
trt	1	0.00634425	0.00634425	0.44	0.5146

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.22405426	0.22405426	15.61	0.0009
sub(seq)	18	7.11628173	0.39534898	27.55	<.0001
per	1	0.00859665	0.00859665	0.60	0.4490
trt	1	0.00634425	0.00634425	0.44	0.5146

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.22405426	0.22405426	0.57	0.4613

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.02531469	0.03807533	-0.66	0.5146

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	7.26038066	0.34573241	24.77	<.0001
Error	18	0.25119749	0.01395542		
Corrected Total	39	7.51157815			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.966559	1.844434	0.118133	6.404839

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.22951421	0.22951421	16.45	0.0007
sub(seq)	18	7.01158110	0.38953228	27.91	<.0001
per	1	0.01312919	0.01312919	0.94	0.3449
trt	1	0.00615616	0.00615616	0.44	0.5150

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.22951421	0.22951421	16.45	0.0007
sub(seq)	18	7.01158110	0.38953228	27.91	<.0001
per	1	0.01127042	0.01127042	0.81	0.3807
trt	1	0.00615616	0.00615616	0.44	0.5150

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.22951421	0.22951421	0.59	0.4527

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.02493661	0.03754515	-0.66	0.5150

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	4.01409857	0.19114755	11.17	<.0001
Error	18	0.30788998	0.01710500		
Corrected Total	39	4.32198855			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.928762	2.814953	0.130786	4.646120

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.03720615	0.03720615	2.18	0.1575
sub(seq)	18	3.83072986	0.21281833	12.44	<.0001
per	1	0.08689331	0.08689331	5.08	0.0369
trt	1	0.05926925	0.05926925	3.47	0.0791

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.03720615	0.03720615	2.18	0.1575
sub(seq)	18	3.83072986	0.21281833	12.44	<.0001
per	1	0.07233617	0.07233617	4.23	0.0545
trt	1	0.05926925	0.05926925	3.47	0.0791

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.03720615	0.03720615	0.17	0.6808

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.07737437	0.04156655	-1.86	0.0791

Group 2

Fasting STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	20	(b) (6)
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	40
Number of Observations Used	40

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	1.82419860	0.08686660	5.63	0.0003
Error	18	0.27766821	0.01542601		
Corrected Total	39	2.10186681			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.867894	1.949697	0.124201	6.370299

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00021816	0.00021816	0.01	0.9067
sub(seq)	18	1.67493435	0.09305191	6.03	0.0002
per	1	0.06527674	0.06527674	4.23	0.0545
trt	1	0.08376935	0.08376935	5.43	0.0316

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00021816	0.00021816	0.01	0.9067
sub(seq)	18	1.67493435	0.09305191	6.03	0.0002
per	1	0.08017697	0.08017697	5.20	0.0350
trt	1	0.08376935	0.08376935	5.43	0.0316

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00021816	0.00021816	0.00	0.9619

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.09198669	0.03947383	2.33	0.0316

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	1.73676828	0.08270325	5.58	0.0003
Error	18	0.26677848	0.01482103		
Corrected Total	39	2.00354676			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.866847	1.899260	0.121742	6.409950

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00008191	0.00008191	0.01	0.9416
sub(seq)	18	1.58416618	0.08800923	5.94	0.0002
per	1	0.06117278	0.06117278	4.13	0.0572
trt	1	0.09134741	0.09134741	6.16	0.0231

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00008191	0.00008191	0.01	0.9416
sub(seq)	18	1.58416618	0.08800923	5.94	0.0002
per	1	0.07635013	0.07635013	5.15	0.0358
trt	1	0.09134741	0.09134741	6.16	0.0231

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00008191	0.00008191	0.00	0.9760

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.09605733	0.03869203	2.48	0.0231

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	2.36570016	0.11265239	6.08	0.0001
Error	18	0.33342146	0.01852341		
Corrected Total	39	2.69912162			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.876470	2.906684	0.136101	4.682338

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.01090370	0.01090370	0.59	0.4529
sub(seq)	18	2.30264526	0.12792474	6.91	<.0001
per	1	0.02150539	0.02150539	1.16	0.2955
trt	1	0.03064581	0.03064581	1.65	0.2147

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01090370	0.01090370	0.59	0.4529
sub(seq)	18	2.30264526	0.12792474	6.91	<.0001
per	1	0.01648813	0.01648813	0.89	0.3579
trt	1	0.03064581	0.03064581	1.65	0.2147

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01090370	0.01090370	0.09	0.7737

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.05563755	0.04325566	-1.29	0.2147

Group 3

Fasting STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	22	(b) (6)
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	44
Number of Observations Used	44

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	23	3.21346749	0.13971598	10.12	<.0001
Error	20	0.27621214	0.01381061		
Corrected Total	43	3.48967963			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.920849	1.802062	0.117519	6.521338

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.10198173	0.10198173	7.38	0.0133
sub(seq)	20	3.05110928	0.15255546	11.05	<.0001
per	1	0.01273438	0.01273438	0.92	0.3484
trt	1	0.04764210	0.04764210	3.45	0.0781

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.10198173	0.10198173	7.38	0.0133
sub(seq)	20	3.05110928	0.15255546	11.05	<.0001
per	1	0.01273438	0.01273438	0.92	0.3484
trt	1	0.04764210	0.04764210	3.45	0.0781

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.10198173	0.10198173	0.67	0.4232

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.06581109	0.03543317	1.86	0.0781

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	23	3.15639754	0.13723468	10.58	<.0001
Error	20	0.25937572	0.01296879		
Corrected Total	43	3.41577327			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.924065	1.734982	0.113881	6.563791

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.10882137	0.10882137	8.39	0.0089
sub(seq)	20	2.98468049	0.14923402	11.51	<.0001
per	1	0.01349291	0.01349291	1.04	0.3199
trt	1	0.04940277	0.04940277	3.81	0.0651

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.10882137	0.10882137	8.39	0.0089
sub(seq)	20	2.98468049	0.14923402	11.51	<.0001
per	1	0.01349291	0.01349291	1.04	0.3199
trt	1	0.04940277	0.04940277	3.81	0.0651

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.10882137	0.10882137	0.73	0.4033

Parameter	Estimate	Standard Error	t Value	Pr > t

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.06701613	0.03433629	1.95	0.0651

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	23	3.14134022	0.13658001	4.63	0.0005
Error	20	0.58939586	0.02946979		
Corrected Total	43	3.73073608			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.842016	3.604866	0.171668	4.762110

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00328317	0.00328317	0.11	0.7420
sub(seq)	20	3.03853717	0.15192686	5.16	0.0003
per	1	0.00501576	0.00501576	0.17	0.6843
trt	1	0.09450412	0.09450412	3.21	0.0885

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00328317	0.00328317	0.11	0.7420
sub(seq)	20	3.03853717	0.15192686	5.16	0.0003
per	1	0.00501576	0.00501576	0.17	0.6843
trt	1	0.09450412	0.09450412	3.21	0.0885

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00328317	0.00328317	0.02	0.8846

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.09268918	0.05175975	-1.79	0.0885

AUCT/AUCI Ratio for Individual Subjects

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	trt	AUCRATIO
1	(b) (6)	1	0.94
2		1	0.97
3		1	0.96
4		1	0.95
5		1	0.93
6		1	0.93
7		1	0.97
8		1	0.95
9		1	0.97
10		1	0.96
11		1	0.97
12		1	0.97
13		1	0.98
14		1	0.93
15		1	0.98
16		1	0.94
17		1	0.97
18		1	0.94
19		1	0.98
20		1	0.94
21		1	0.97
22		1	0.96
23		1	0.96
24		1	0.97
25		1	0.97
26		1	0.97
27		1	0.97
28		1	0.93
29		1	0.92
30		1	0.97
31		1	0.97
32		1	0.97
33		1	0.97
34		1	0.95
35		1	0.96
36		1	0.96
37		1	0.96
38		1	0.94

Obs	sub	trt	AUCRATIO
39	(b) (6)	1	0.97
40		1	0.96
41		1	0.91
42		1	0.96
43		1	0.94
44		1	0.97
45		1	0.96
46		1	0.95
47		1	0.96
48		1	0.98
49		1	0.96
50		1	0.97
51		1	0.98
52		1	0.95
53		1	0.95
54		1	0.94
55		1	0.94
56		1	0.97
57		1	0.98
58		1	0.98
59		1	0.97
60		1	0.92
61		1	0.97
62		1	0.96
63		2	0.94
64		2	0.97
65		2	0.95
66		2	0.96
67		2	0.96
68		2	0.92
69		2	0.97
70		2	0.95
71		2	0.97
72		2	0.95
73		2	0.96
74		2	0.98
75		2	0.97
76		2	0.93
77		2	0.98
78		2	0.93

Obs	sub	trt	AUCRATIO
79	(b) (6)	2	0.98
80		2	0.94
81		2	0.98
82		2	0.95
83		2	0.98
84		2	0.97
85		2	0.97
86		2	0.97
87		2	0.98
88		2	0.94
89		2	0.95
90		2	0.95
91		2	0.95
92		2	0.94
93		2	0.98
94		2	0.97
95		2	0.97
96		2	0.97
97		2	0.95
98		2	0.95
99		2	0.96
100		2	0.96
101		2	0.97
102		2	0.96
103		2	0.97
104		2	0.92
105		2	0.96
106		2	0.95
107		2	0.97
108		2	0.95
109		2	0.95
110		2	0.98
111		2	0.98
112		2	0.96
113		2	0.97
114		2	0.94
115		2	0.96
116		2	0.95
117		2	0.96
118		2	0.97

Obs	sub	trt	AUCRATIO
119	(b) (6)	2	0.96
120	(b) (6)	2	0.98
121	(b) (6)	2	0.97
122	(b) (6)	2	0.93
123	(b) (6)	2	0.95
124	(b) (6)	2	0.98

T/R ratios for individual Subjects

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	1	0.90	0.90	0.84	3.00	1.07	0.94
(b) (6)	2	0.95	0.95	0.92	1.00	1.05	0.95
(b) (6)	2	0.95	0.94	0.77	2.00	1.05	0.95
(b) (6)	1	0.98	0.99	0.99	1.00	0.91	1.09
(b) (6)	1	0.84	0.86	0.82	1.50	0.82	1.21
(b) (6)	2	1.07	1.06	1.01	1.00	1.11	0.90
(b) (6)	1	1.36	1.36	1.09	1.33	0.75	1.33
(b) (6)	1	0.77	0.77	0.91	0.67	0.93	1.07
(b) (6)	2	1.02	1.01	0.92	1.94	1.50	0.67
(b) (6)	2	0.94	0.94	0.73	1.50	1.03	0.97
(b) (6)	2	1.07	1.05	0.91	1.00	1.20	0.84
(b) (6)	1	1.09	1.10	1.33	0.67	0.93	1.08
(b) (6)	1	0.85	0.83	0.70	1.00	1.26	0.79
(b) (6)	1	1.22	1.23	1.45	0.44	1.03	0.97
(b) (6)	2	1.06	1.05	0.94	0.75	0.77	1.29
(b) (6)	2	0.91	0.90	0.84	1.00	1.08	0.93
(b) (6)	2	1.03	1.04	0.79	2.27	0.96	1.04
(b) (6)	2	0.65	0.65	0.66	1.00	0.97	1.03
(b) (6)	1	1.19	1.19	1.16	3.00	0.71	1.42
(b) (6)	2	0.86	0.87	0.93	0.73	0.95	1.05
(b) (6)	1	0.83	0.83	0.58	1.50	1.35	0.74
(b) (6)	1	0.83	0.84	0.76	1.00	0.89	1.12
(b) (6)	1	1.16	1.17	1.11	1.00	0.92	1.09
(b) (6)	2	1.08	1.08	0.97	0.95	0.72	1.38
(b) (6)	1	1.16	1.17	0.89	1.33	0.57	1.75
(b) (6)	1	1.21	1.18	1.34	0.25	0.80	1.24
(b) (6)	2	1.66	1.63	1.05	1.33	0.55	1.81
(b) (6)	2	1.45	1.48	1.18	2.00	0.92	1.09
(b) (6)	1	1.20	1.23	1.09	1.00	0.59	1.70

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	2	1.21	1.18	0.81	1.00	0.82	1.23
	2	1.15	1.15	1.02	0.44	0.95	1.05
	1	0.85	0.85	0.75	1.96	1.33	0.75
	2	1.06	1.06	0.88	1.33	0.96	1.04
	1	0.80	0.82	0.85	1.00	1.14	0.87
	1	1.10	1.10	0.85	1.50	1.11	0.90
	1	1.13	1.12	1.11	4.00	1.58	0.63
	2	0.94	0.94	0.85	1.00	1.05	0.95
	2	1.35	1.37	1.11	1.00	0.40	2.49
	1	0.90	0.90	0.89	0.67	0.97	1.03
	2	1.07	1.08	1.06	1.00	0.99	1.01
	1	0.78	0.83	0.54	1.33	0.70	1.42
	1	1.14	1.10	1.21	2.00	1.29	0.78
	2	1.09	1.11	0.67	4.50	0.81	1.24
	2	0.96	0.93	0.83	1.00	0.92	1.09
	2	1.09	1.11	0.91	1.00	0.91	1.10
	1	1.03	1.04	1.02	1.00	1.00	1.00
	2	1.05	1.04	0.99	1.33	1.03	0.97
	1	0.91	0.91	0.79	1.00	0.71	1.40
	2	1.09	1.11	0.88	0.75	0.84	1.20
	1	1.12	1.10	0.86	2.25	1.22	0.82
	1	1.14	1.13	1.04	1.00	1.14	0.88
	2	1.17	1.16	1.52	1.50	1.07	0.93
	2	1.19	1.20	0.84	1.50	0.95	1.06
	2	1.78	1.80	1.44	1.33	0.91	1.10
	1	0.85	0.86	0.74	0.44	0.97	1.03
	1	1.12	1.13	0.96	2.00	0.97	1.03
	2	0.88	0.86	0.82	2.25	1.16	0.86
	2	1.04	1.04	0.86	1.00	1.02	0.98
	1	1.22	1.21	1.19	1.00	0.79	1.26
	2	1.02	1.03	0.80	0.50	0.94	1.07
	1	1.21	1.18	0.98	1.33	1.22	0.82
1	0.94	0.96	0.75	2.00	0.91	1.10	

5.9.1.3 Firm Reviewer Ratio (FP)

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUICI	FDACMAX	treat	FIRMAREA	FIRMAUICI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	(b) (6)	1	1	1	1	850.26	901.38	119.50	T	833.15	872.835	119.50	0.97988	0.96833	1
2		1	1	2	2	947.59	1005.89	142.20	R	931.86	990.164	142.20	0.98340	0.98436	1
3		1	2	1	2	463.06	477.99	106.80	R	453.08	470.179	106.80	0.97845	0.98367	1
4		1	2	2	1	439.69	453.61	97.87	T	430.03	446.438	97.87	0.97803	0.98418	1
5		1	2	1	2	894.10	936.30	135.90	R	874.73	905.931	135.90	0.97833	0.96757	1
6		1	2	2	1	849.82	881.83	104.40	T	829.05	856.087	104.40	0.97556	0.97081	1
7		1	1	1	1	370.37	389.42	69.22	T	362.27	379.887	69.22	0.97813	0.97552	1
8		1	1	2	2	377.54	391.99	69.59	R	368.48	385.259	69.59	0.97599	0.98283	1
9		1	1	1	1	153.85	164.72	53.16	T	151.99	159.559	53.16	0.98791	0.96868	1
10		1	1	2	2	183.57	191.30	64.91	R	180.87	188.218	64.91	0.98530	0.98391	1
11		1	2	1	2	713.14	774.39	169.70	R	700.46	.	169.70	0.98223	.	1
12		1	2	2	1	763.69	817.00	170.90	T	751.56	804.861	170.90	0.98411	0.98515	1
13		1	1	1	1	890.08	917.61	120.70	T	868.75	892.425	120.70	0.97604	0.97255	1
14		1	1	2	2	654.39	674.87	110.90	R	637.98	660.266	110.90	0.97492	0.97836	1
15		1	1	1	1	265.88	280.77	76.92	T	260.62	276.969	76.92	0.98020	0.98646	1
16		1	1	2	2	345.34	362.59	84.28	R	338.22	355.466	84.28	0.97937	0.98035	1
17		1	2	1	2	495.07	512.28	72.83	R	484.33	501.538	72.83	0.97829	0.97902	1
18		1	2	2	1	503.12	519.50	67.10	T	490.88	508.662	67.10	0.97565	0.97914	1
19		1	2	1	2	821.94	864.36	133.30	R	804.15	836.501	133.30	0.97836	0.96777	1
20		1	2	2	1	775.27	808.90	97.18	T	756.34	782.671	97.18	0.97558	0.96758	1
21		1	2	1	2	525.61	549.42	95.20	R	514.89	534.269	95.20	0.97962	0.97242	1
22		1	2	2	1	560.29	575.85	86.58	T	547.95	565.232	86.58	0.97798	0.98155	1
23		1	1	1	1	744.68	768.92	142.30	T	725.07	745.558	142.30	0.97367	0.96962	1
24		1	1	2	2	683.69	700.11	106.70	R	666.29	682.713	106.70	0.97455	0.97514	1

Obs	sub (b) (6)	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
25		1	1	1	1	495.54	505.55	68.34	T	479.85	490.676	68.34	0.96833	0.97057	1
26		1	1	2	2	584.99	605.72	97.01	R	570.76	591.491	97.01	0.97567	0.97651	1
27		1	1	1	1	924.68	996.14	210.10	T	909.02	980.480	210.10	0.98306	0.98428	1
28		1	1	2	2	757.32	811.52	145.00	R	745.97	800.166	145.00	0.98501	0.98602	1
29		1	2	1	2	723.77	738.13	129.70	R	704.31	719.921	129.70	0.97311	0.97533	1
30		1	2	2	1	763.62	776.85	122.10	T	743.55	755.402	122.10	0.97373	0.97239	1
31		1	2	1	2	438.69	471.68	88.20	R	431.75	461.809	88.20	0.98418	0.97908	1
32		1	2	2	1	397.16	424.36	74.40	T	390.10	411.895	74.40	0.98223	0.97062	1
33		1	2	1	2	873.33	894.41	187.80	R	853.81	877.676	187.80	0.97765	0.98129	1
34		1	2	2	1	902.04	929.07	147.70	T	878.76	901.597	147.70	0.97419	0.97043	1
35		1	2	1	2	501.78	532.87	86.88	R	490.25	524.555	86.88	0.97703	0.98440	1
36		1	2	2	1	326.49	347.78	57.65	T	319.33	340.614	57.65	0.97805	0.97939	1
37		1	1	1	1	898.54	918.57	132.70	T	877.21	898.852	132.70	0.97626	0.97853	1
38		1	1	2	2	753.31	770.62	114.20	R	733.03	751.342	114.20	0.97309	0.97498	1
39		1	2	1	2	787.84	830.04	122.50	R	773.50	815.696	122.50	0.98180	0.98272	1
40		1	2	2	1	680.26	722.94	113.80	T	669.18	711.862	113.80	0.98371	0.98467	1
41		2	1	1	1	608.51	628.32	87.16	T	594.37	617.108	87.16	0.97676	0.98216	1
42		2	1	2	2	736.90	753.76	149.30	R	719.82	738.392	149.30	0.97682	0.97961	1
43		2	1	1	1	511.00	533.01	72.56	T	498.69	514.061	72.56	0.97591	0.96444	1
44		2	1	2	2	616.36	632.79	95.27	R	601.85	618.274	95.27	0.97646	0.97707	1
45		2	1	1	1	806.12	837.65	124.90	T	788.56	815.398	124.90	0.97821	0.97344	1
46		2	1	2	2	695.12	715.27	112.30	R	679.61	699.764	112.30	0.97769	0.97832	1
47		2	2	1	2	629.80	646.36	121.80	R	614.93	633.518	121.80	0.97640	0.98013	1
48		2	2	2	1	677.61	695.33	117.70	T	661.63	679.356	117.70	0.97642	0.97702	1
49		2	1	1	1	618.02	638.96	100.80	T	605.76	626.696	100.80	0.98015	0.98080	1

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
50	(b) (6)	2	1	2	2	532.48	543.80	113.20	R	518.73	529.398	113.20	0.97418	0.97351	1
51		2	1	1	1	446.87	461.11	81.20	T	436.00	451.835	81.20	0.97568	0.97988	1
52		2	1	2	2	368.21	389.79	60.78	R	359.88	381.463	60.78	0.97739	0.97864	1
53		2	2	1	2	364.71	383.75	79.46	R	356.83	378.018	79.46	0.97840	0.98507	1
54		2	2	2	1	604.92	625.78	83.58	T	591.17	608.055	83.58	0.97727	0.97168	1
55		2	2	1	2	318.42	335.56	65.73	R	310.80	327.939	65.73	0.97606	0.97729	1
56		2	2	2	1	460.66	496.56	77.36	T	451.15	487.049	77.36	0.97935	0.98084	1
57		2	1	1	1	682.19	738.95	141.10	T	669.76	.	141.10	0.98179	.	1
58		2	1	2	2	569.24	600.56	128.90	R	557.75	586.729	128.90	0.97983	0.97696	1
59		2	2	1	2	454.91	482.61	140.70	R	442.40	.	140.70	0.97250	.	1
60		2	2	2	1	549.65	569.58	113.70	T	537.48	557.417	113.70	0.97787	0.97865	1
61		2	2	1	2	850.11	869.36	144.70	R	829.28	844.277	144.70	0.97550	0.97115	1
62		2	2	2	1	976.48	1003.23	147.30	T	950.90	969.654	147.30	0.97380	0.96653	1
63		2	1	1	1	511.62	529.82	100.30	T	499.99	520.237	100.30	0.97728	0.98190	1
64		2	1	2	2	603.70	620.00	133.60	R	590.19	603.397	133.60	0.97763	0.97322	1
65		2	2	1	2	731.58	752.82	122.70	R	716.16	735.188	122.70	0.97893	0.97657	1
66		2	2	2	1	772.07	798.43	107.90	T	754.84	775.837	107.90	0.97768	0.97170	1
67		2	1	1	1	482.26	509.51	105.10	T	472.64	497.892	105.10	0.98004	0.97720	1
68		2	1	2	2	603.40	619.85	123.30	R	589.83	603.128	123.30	0.97750	0.97303	1
69		2	1	1	1	657.57	684.94	99.57	T	641.77	668.251	99.57	0.97597	0.97563	1
70		2	1	2	2	595.59	623.99	117.30	R	582.72	608.739	117.30	0.97839	0.97555	1
71		2	1	1	1	708.11	737.87	184.20	T	694.59	728.854	184.20	0.98090	0.98778	1
72		2	1	2	2	623.98	659.58	166.20	R	610.52	.	166.20	0.97842	.	1
73		2	2	1	2	685.98	715.63	140.70	R	674.47	704.119	140.70	0.98322	0.98392	1
74	2	2	2	1	647.03	675.70	120.20	T	634.46	663.137	120.20	0.98058	0.98140	1	

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
75	(b) (6)	2	2	1	2	411.08	427.41	115.70	R	402.17	419.970	115.70	0.97832	0.98260	1
76		2	2	2	1	553.69	587.14	128.70	T	542.78	.	128.70	0.98029	.	1
77		2	1	1	1	516.23	533.26	91.87	T	503.70	517.474	91.87	0.97573	0.97040	1
78		2	1	2	2	574.42	590.81	102.90	R	561.77	578.158	102.90	0.97797	0.97858	1
79		2	2	1	2	585.45	607.30	70.22	R	572.70	594.552	70.22	0.97822	0.97900	1
80		2	2	2	1	626.87	653.35	74.72	T	611.27	634.122	74.72	0.97513	0.97056	1
81		3	1	1	1	292.43	321.10	62.29	T	287.29	313.410	62.29	0.98242	0.97604	1
82		3	1	2	2	374.82	387.47	115.60	R	366.76	380.772	115.60	0.97847	0.98272	1
83		3	1	1	1	696.91	729.03	116.50	T	681.74	709.636	116.50	0.97822	0.97340	1
84		3	1	2	2	609.24	661.62	96.20	R	596.13	.	96.20	0.97847	.	1
85		3	2	1	2	773.91	802.35	168.10	R	756.22	781.148	168.10	0.97714	0.97358	1
86		3	2	2	1	840.27	891.43	113.30	T	823.88	864.474	113.30	0.98050	0.96976	1
87		3	2	1	2	612.19	645.54	86.47	R	599.29	637.360	86.47	0.97892	0.98733	1
88		3	2	2	1	586.23	601.41	71.35	T	572.53	587.716	71.35	0.97663	0.97722	1
89		3	2	1	2	719.17	739.69	156.20	R	704.15	724.681	156.20	0.97913	0.97971	1
90		3	2	2	1	783.10	817.82	142.60	T	767.67	794.629	142.60	0.98029	0.97164	1
91		3	1	1	1	1155.64	1217.76	224.10	T	1132.20	.	224.10	0.97971	.	1
92		3	1	2	2	1119.27	1176.07	220.20	R	1095.63	.	220.20	0.97888	.	1
93		3	2	1	2	914.83	960.81	149.90	R	899.29	945.264	149.90	0.98301	0.98382	1
94		3	2	2	1	961.29	1002.62	147.70	T	943.29	984.627	147.70	0.98128	0.98205	1
95		3	1	1	1	617.66	633.09	88.62	T	602.72	620.775	88.62	0.97581	0.98055	1
96		3	1	2	2	675.48	692.23	112.70	R	658.37	677.703	112.70	0.97468	0.97901	1
97		3	2	1	2	776.47	791.72	121.50	R	758.27	773.519	121.50	0.97656	0.97701	1
98	3	2	2	1	843.03	876.12	107.30	T	821.11	848.535	107.30	0.97399	0.96852	1	
99	3	1	1	1	802.24	825.31	186.40	T	784.79	805.189	186.40	0.97825	0.97563	1	

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
100	(b) (6)	3	1	2	2	715.63	747.82	217.20	R	704.85	737.037	217.20	0.98494	0.98559	1
101		3	1	1	1	995.17	1016.56	107.70	T	968.91	990.296	107.70	0.97361	0.97417	1
102		3	1	2	2	871.12	899.28	103.80	R	849.03	870.309	103.80	0.97465	0.96778	1
103		3	2	1	2	383.86	406.26	74.44	R	377.41	399.805	74.44	0.98320	0.98412	1
104		3	2	2	1	450.19	472.74	113.00	T	443.14	465.699	113.00	0.98435	0.98510	1
105		3	2	1	2	769.04	798.04	152.70	R	752.51	776.561	152.70	0.97851	0.97308	1
106		3	2	2	1	913.05	958.64	128.50	T	891.38	927.806	128.50	0.97626	0.96784	1
107		3	2	1	2	517.93	547.66	107.20	R	508.98	531.625	107.20	0.98272	0.97072	1
108		3	2	2	1	924.49	983.67	154.40	T	910.37	969.554	154.40	0.98473	0.98565	1
109		3	1	1	1	463.29	490.32	76.10	T	455.56	482.595	76.10	0.98332	0.98424	1
110		3	1	2	2	547.46	572.31	103.10	R	538.30	563.154	103.10	0.98327	0.98400	1
111		3	1	1	1	675.68	697.52	109.30	T	661.87	683.710	109.30	0.97956	0.98020	1
112		3	1	2	2	603.55	619.65	113.60	R	590.00	606.102	113.60	0.97756	0.97814	1
113		3	2	1	2	843.50	874.24	131.90	R	825.98	856.722	131.90	0.97923	0.97996	1
114		3	2	2	1	738.74	753.73	108.00	T	721.78	736.768	108.00	0.97704	0.97750	1
115		3	2	1	2	630.69	646.57	95.80	R	616.00	629.576	95.80	0.97671	0.97372	1
116		3	2	2	1	657.66	672.56	81.99	T	642.25	658.301	81.99	0.97658	0.97879	1
117		3	1	1	1	626.64	643.52	116.10	T	611.62	625.379	116.10	0.97603	0.97182	1
118		3	1	2	2	514.87	532.38	97.89	R	504.07	524.889	97.89	0.97904	0.98593	1
119		3	2	1	2	710.14	766.52	143.70	R	698.87	755.256	143.70	0.98413	0.98530	1
120		3	2	2	1	726.39	791.43	115.10	T	714.91	779.954	115.10	0.98420	0.98549	1
121		3	1	1	1	815.78	843.83	127.80	T	798.01	826.056	127.80	0.97822	0.97894	1
122		3	1	2	2	675.48	714.40	131.00	R	661.85	691.114	131.00	0.97982	0.96741	1
123		3	1	1	1	537.98	557.99	76.44	T	525.40	548.113	76.44	0.97663	0.98229	1
124	3	1	2	2	569.87	582.97	102.40	R	556.48	570.770	102.40	0.97650	0.97907	1	

5.9.1.4 Fasting Study Data (SA)

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE
1	(b) (6)	1	1	1	T	0	219.90	268.10	191.80	146.70	132.20	116.60	111.30	108.00	81.59	67.65	59.57	42.39	30.78	22.480	15.520	6.558	3.357	1.948	
2		1	1	2	R	0	438.20	401.00	228.70	159.20	127.70	97.44	76.24	77.31	65.36	55.60	44.51	36.07	24.78	19.960	13.360	6.769	3.788	2.000	
3		1	2	1	R	0	215.50	295.60	186.00	163.00	135.20	129.00	124.40	120.40	92.50	75.14	56.68	41.93	27.88	16.760	10.370	5.467	1.803	1.208	
4		1	2	2	T	0	193.60	249.80	176.40	134.60	137.00	131.10	130.00	120.60	100.70	81.88	59.34	42.92	27.67	18.380	11.570	5.958	2.024	1.293	
5		1	2	1	R	0	549.60	510.00	327.70	225.60	167.40	145.70	101.70	94.01	65.92	54.27	44.76	35.18	23.76	17.760	12.690	5.625	2.433	1.292	
6		1	2	2	T	0	517.20	536.10	349.10	246.30	166.10	129.50	109.90	91.69	100.30	68.76	48.04	38.19	28.59	19.190	14.580	5.637	2.286	1.228	
7		1	1	1	T	0	87.74	125.80	120.60	124.10	131.50	147.20	151.60	135.20	116.60	100.10	66.98	48.07	28.47	20.820	12.470	6.260	2.603	1.612	
8		1	1	2	R	0	118.50	131.30	109.90	94.89	89.59	87.79	96.78	107.60	114.90	100.60	73.21	56.00	35.10	25.280	15.470	8.671	3.427	2.124	
9		1	1	1	T	0	41.85	74.91	81.84	87.59	92.04	106.80	126.00	130.10	143.90	141.40	89.77	61.81	38.22	23.010	13.810	6.603	2.436	1.442	
10		1	1	2	R	0	62.72	115.80	86.91	81.14	86.66	89.47	97.24	107.90	107.70	108.70	82.32	58.32	39.30	23.990	13.090	6.542	2.373	1.399	
11		1	2	1	R	0	244.60	298.40	244.60	220.10	189.20	177.10	171.30	153.60	181.30	236.90	196.40	153.40	96.09	64.030	32.770	15.950	7.144	4.476	
12		1	2	2	T	0	377.60	479.00	322.30	286.00	266.10	261.80	288.10	259.90	242.00	220.90	159.40	119.10	78.14	50.980	30.330	16.260	6.162	3.994	
13		1	1	1	T	0	257.90	468.10	265.70	181.70	132.10	92.76	70.10	58.39	45.29	44.22	32.52	26.00	20.29	16.610	10.420	5.723	2.434	2.301	
14		1	1	2	R	0	268.80	473.90	268.70	174.00	129.70	85.85	68.98	54.36	51.72	59.69	43.97	32.71	27.60	17.950	11.170	5.851	2.453	1.207	
15		1	1	1	T	0	108.10	221.70	151.00	120.80	99.91	96.91	86.28	84.03	80.09	60.59	39.19	28.80	19.23	13.280	7.834	4.034	1.719	0.000	
16		1	1	2	R	0	266.50	302.60	174.80	131.70	112.20	87.76	82.89	81.66	73.22	55.31	39.34	28.22	18.36	14.470	8.596	4.454	2.137	1.238	
17		1	2	1	R	0	254.70	356.20	218.90	151.20	112.50	90.30	78.76	76.47	54.75	47.47	40.67	30.09	24.04	17.650	10.040	4.915	2.923	1.672	
18		1	2	2	T	0	203.30	298.00	239.90	154.40	121.30	103.10	81.81	76.39	61.56	53.61	46.59	36.97	29.29	19.440	12.760	6.017	3.047	1.474	
19		1	2	1	R	0	304.70	480.40	360.00	222.10	194.20	157.80	120.40	108.90	99.91	99.92	74.32	51.72	39.23	25.470	17.490	7.583	2.951	1.450	
20		1	2	2	T	0	231.40	443.10	274.40	179.80	138.50	102.90	85.91	71.47	75.62	68.54	51.93	39.43	29.62	23.210	15.570	6.076	2.745	1.307	
21		1	2	1	R	0	167.30	238.20	137.40	96.01	74.42	59.98	51.44	49.35	36.74	30.56	21.43	18.39	14.26	11.150	7.252	4.395	2.585	1.576	
22		1	2	2	T	0	167.00	268.00	163.40	111.30	91.11	72.35	58.94	52.26	43.29	36.66	26.79	19.87	14.33	10.540	8.624	4.668	2.936	1.418	
23		1	1	1	T	0	259.50	428.50	289.60	187.00	156.20	128.10	101.00	86.46	64.49	61.77	47.00	38.16	23.99	17.460	11.050	4.840	2.606	1.057	
24		1	1	2	R	0	314.10	426.40	256.30	171.40	139.00	110.20	94.78	86.80	70.41	61.91	39.37	31.63	21.59	16.220	10.390	4.473	2.722	1.056	
25		1	1	1	T	0	138.90	248.00	177.40	129.40	102.80	91.18	103.70	95.07	78.13	61.98	41.71	32.02	21.03	15.390	9.130	4.607	1.893	1.005	
26		1	1	2	R	0	179.30	334.10	188.30	134.60	105.70	77.87	69.90	66.64	69.62	45.24	32.08	27.68	17.48	13.050	8.872	4.332	2.608	1.118	
27		1	1	1	T	0	366.60	586.00	339.50	247.30	197.90	156.50	135.10	116.20	85.04	75.45	46.96	39.35	27.77	19.160	12.710	6.814	3.027	1.878	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE
28	(b) (6)	1	1	2	R	0	294.70	418.10	321.80	203.80	157.50	124.00	110.80	96.15	75.50	51.11	41.27	33.26	24.05	15.690	9.185	5.734	3.068	1.644	
29		1	2	1	R	0	132.80	322.10	224.00	138.20	124.20	95.63	89.27	84.88	55.51	47.55	32.92	27.30	18.45	15.250	9.616	4.899	2.782	1.684	
30		1	2	2	T	0	190.50	345.90	228.70	172.60	133.20	120.00	109.90	84.63	74.53	50.16	40.83	30.17	18.17	14.950	10.990	5.850	3.178	2.087	
31		1	2	1	R	0	134.40	185.10	155.30	122.60	119.20	125.70	118.50	102.10	76.16	66.49	38.13	35.56	19.52	12.970	8.287	3.980	1.589	0.000	
32		1	2	2	T	0	111.20	157.80	138.30	113.80	113.80	99.38	102.00	82.57	79.79	77.48	52.23	38.61	21.15	15.440	10.150	4.193	1.460	0.000	
33		1	2	1	R	0	713.00	741.30	362.20	223.20	156.60	130.50	102.20	86.28	72.77	65.55	43.17	33.28	28.75	20.570	13.130	8.185	4.229	2.724	
34		1	2	2	T	0	894.00	655.10	325.60	256.90	187.80	129.50	104.90	90.77	80.16	76.38	54.48	44.89	32.90	24.100	16.850	8.227	4.730	3.181	
35		1	2	1	R	0	126.70	253.70	160.20	134.20	121.20	98.59	101.40	106.40	94.43	77.50	51.31	38.83	30.33	18.200	12.420	7.938	2.997	1.929	
36		1	2	2	T	0	65.94	143.80	108.80	87.73	82.99	74.32	71.88	61.20	55.56	52.33	40.47	31.74	20.50	15.020	11.170	6.274	3.196	1.878	
37		1	1	1	T	0	302.90	516.50	318.60	218.30	157.40	114.50	89.76	75.34	55.80	44.30	30.54	26.12	17.69	12.960	8.118	4.582	2.757	1.336	
38		1	1	2	R	0	339.40	458.50	254.40	201.30	143.80	91.28	74.93	63.00	50.22	44.33	30.91	23.58	16.95	12.010	7.867	4.511	2.139	1.469	
39		1	2	1	R	0	400.20	492.40	276.00	201.90	149.70	112.50	95.87	104.40	95.98	77.76	58.86	54.00	49.68	30.140	21.070	9.417	3.658	1.951	
40		1	2	2	T	0	295.10	386.60	260.60	171.40	140.60	109.50	103.40	89.34	83.24	74.57	66.37	50.54	37.25	24.240	17.020	8.540	3.693	2.205	
41		2	1	1	T	0	181.40	236.20	168.90	94.78	76.14	62.71	56.17	49.50	48.04	48.39	34.70	26.86	17.80	17.280	11.170	5.901	3.743	2.219	
42		2	1	2	R	0	208.70	287.80	181.40	113.50	88.71	68.07	51.85	57.93	36.26	37.25	30.88	23.68	16.57	13.170	9.737	7.048	4.097	3.251	
43		2	1	1	T	0	141.10	218.60	136.80	122.00	106.10	103.90	75.06	75.33	56.92	42.96	29.77	22.51	15.26	11.810	7.772	3.231	1.911	1.180	
44		2	1	2	R	0	292.00	303.30	201.50	135.80	110.40	85.32	72.21	69.27	49.58	43.12	29.31	22.72	15.26	12.250	7.965	3.913	2.299	1.232	
45		2	1	1	T	0	504.70	533.70	322.20	208.40	189.20	144.80	119.30	91.98	76.83	54.50	43.40	31.27	23.32	18.080	11.820	6.563	3.233	1.695	
46		2	1	2	R	0	445.60	450.10	292.40	208.60	153.10	126.20	91.71	81.55	53.80	47.42	32.98	26.71	16.24	13.580	9.509	5.654	2.092	1.462	
47		2	2	1	R	0	244.30	302.30	198.70	142.50	106.60	94.35	80.01	70.62	67.09	53.42	36.33	24.52	18.90	14.500	8.789	5.080	1.850	1.227	
48		2	2	2	T	0	209.70	331.70	227.00	177.20	154.40	136.90	105.50	94.02	76.88	66.99	47.64	32.22	24.92	19.290	12.080	5.407	2.755	1.755	
49		2	1	1	T	0	372.10	357.40	227.90	159.70	131.60	106.00	88.52	83.39	77.76	78.32	73.12	57.64	48.60	35.930	22.980	12.990	7.090	3.216	
50		2	1	2	R	0	360.70	426.80	252.40	180.90	162.20	133.20	117.60	111.30	114.70	114.70	103.00	92.73	83.87	56.200	40.560	19.350	9.740	5.353	
51		2	1	1	T	0	176.90	206.80	152.50	136.20	103.20	79.04	64.71	60.71	60.80	55.64	44.10	29.39	24.00	17.360	9.968	6.003	2.585	1.659	
52		2	1	2	R	0	116.30	161.50	145.60	104.70	76.78	52.65	51.94	53.47	59.37	51.00	34.08	25.60	17.51	13.430	7.865	4.973	2.266	1.813	
53		2	2	1	R	0	77.34	125.60	123.20	112.50	106.80	105.60	108.00	95.68	104.10	140.90	96.09	69.50	40.74	27.350	18.740	10.230	5.183	2.966	
54		2	2	2	T	0	113.70	253.40	187.20	155.00	142.10	136.30	127.00	127.00	109.00	98.48	71.14	54.34	38.85	28.650	18.790	13.170	6.165	3.949	
55		2	2	1	R	0	111.50	172.10	111.40	87.88	85.32	78.24	75.74	65.58	59.07	48.83	30.96	25.14	14.45	11.510	7.324	3.520	1.595	0.000	
56		2	2	2	T	0	105.70	252.30	195.70	127.20	120.70	146.90	119.30	115.30	96.28	78.85	49.16	35.97	22.74	18.060	13.310	6.118	3.220	1.737	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE
57	(b) (6)	2	2	1	R	0	199.60	230.40	148.40	134.70	114.10	103.70	88.44	81.25	73.37	66.38	44.86	38.65	31.01	21.710	13.020	5.874	3.178	1.850	
58		2	2	2	T	0	192.00	390.90	218.40	204.10	170.90	153.40	147.10	160.90	115.10	96.76	69.08	50.93	40.36	29.900	18.170	8.051	5.061	2.358	
59		2	2	1	R	0	294.90	473.40	280.40	218.60	136.30	108.30	80.43	79.54	61.55	47.47	43.86	28.20	22.19	16.150	11.650	6.646	2.402	1.478	
60		2	2	2	T	0	315.90	462.30	311.10	207.40	178.30	129.10	98.23	97.36	72.30	65.79	47.06	35.10	26.91	20.490	14.990	7.371	3.970	1.929	
61		2	1	1	T	0	336.10	372.90	248.50	179.10	179.70	155.90	192.00	182.20	161.20	117.30	89.66	72.40	50.16	35.210	21.750	10.880	5.049	2.917	
62		2	1	2	R	0	309.20	479.10	271.50	208.50	215.50	189.00	167.00	157.20	126.00	99.05	70.88	58.83	43.44	31.380	21.310	11.370	5.015	3.258	
63		2	2	1	R	0	337.50	483.40	290.10	194.30	146.30	108.10	80.75	69.16	55.41	52.60	34.23	27.02	18.05	13.840	8.734	4.463	1.870	1.555	
64		2	2	2	T	0	261.50	571.30	327.20	242.90	194.30	154.00	113.90	102.10	76.72	66.24	42.74	31.49	20.56	16.860	9.031	5.623	2.263	1.324	
65		2	1	1	T	0	216.60	280.30	200.60	167.60	139.40	130.40	116.40	108.40	100.80	94.79	69.30	52.34	43.48	28.640	18.940	9.827	3.915	2.095	
66		2	1	2	R	0	299.00	402.20	219.30	171.10	145.70	122.60	108.70	91.11	80.47	79.45	59.87	50.73	40.39	25.630	16.100	9.309	3.582	1.902	
67		2	1	1	T	0	403.80	283.90	219.10	159.50	118.60	86.72	71.00	63.31	53.32	43.33	30.67	25.41	18.17	14.110	10.080	5.334	2.362	1.214	
68		2	1	2	R	0	463.00	345.50	196.90	138.20	108.70	76.37	69.42	60.13	47.89	39.10	25.83	23.72	15.87	11.310	8.940	4.658	2.123	1.171	
69		2	1	1	T	0	319.50	398.40	259.00	192.50	161.60	129.00	110.50	103.10	78.87	65.64	42.97	32.80	20.79	16.740	9.671	4.060	1.757		
70		2	1	2	R	0	314.30	383.60	211.30	173.30	154.00	126.90	112.10	111.80	80.15	67.80	45.08	34.45	23.60	17.670	10.600	3.941	2.036	0.000	
71		2	2	1	R	0	422.30	577.50	356.30	238.80	184.50	138.00	114.50	103.00	92.52	71.33	51.29	35.58	25.79	17.540	11.370	4.950	2.251	1.122	
72		2	2	2	T	0	258.80	501.70	337.80	241.10	186.40	140.50	109.80	88.41	65.53	55.29	44.18	32.12	23.59	16.810	12.270	4.813	2.306	1.135	
73		2	2	1	R	0	217.20	234.10	171.10	142.80	119.60	108.80	86.32	74.21	73.85	65.13	47.91	33.08	25.29	17.830	10.380	4.396	1.417	0.000	
74		2	2	2	T	0	98.22	309.70	241.60	199.60	167.30	138.30	125.60	109.70	98.02	77.44	69.25	47.05	31.84	22.730	13.070	5.116	2.275	1.186	
75		2	1	1	T	0	156.50	263.20	187.70	126.00	105.40	82.87	70.64	54.19	44.74	37.81	24.01	18.34	12.66	9.975	6.842	3.342	1.943	1.990	
76		2	1	2	R	0	130.80	240.70	192.80	139.40	109.40	86.80	83.27	67.65	57.24	45.61	29.53	22.47	14.84	12.820	7.681	4.758	2.570	1.582	
77		2	2	1	R	0	309.90	285.00	190.80	119.80	103.10	85.29	74.66	69.13	52.05	46.09	28.71	23.62	14.55	11.800	8.320	4.642	2.189	1.661	
78		2	2	2	T	0	190.60	297.30	257.40	198.40	170.30	128.70	95.74	87.53	70.88	57.03	38.57	31.63	22.01	15.940	10.940	5.242	2.235	1.269	
79		3	1	1	T	0	123.00	146.50	141.60	102.50	107.60	97.96	110.30	106.40	90.44	68.83	51.78	33.28	20.49	14.790	10.210	4.353	2.597	1.299	
80		3	1	2	R	0	153.50	234.40	169.90	136.90	118.70	122.40	111.50	105.50	84.12	65.47	40.70	32.35	19.59	15.370	10.060	4.148	2.232	0.000	
81		3	1	1	T	0	456.40	433.00	255.00	188.00	169.10	145.20	121.00	124.90	121.60	91.24	80.69	59.22	38.68	28.230	19.990	8.888	3.093	1.906	
82		3	1	2	R	0	495.80	449.90	228.90	168.80	141.80	106.10	97.24	92.07	77.45	73.50	57.88	43.54	34.79	23.420	17.290	7.192	3.534	1.830	
83		3	2	1	R	0	308.30	458.00	274.10	181.90	146.10	116.80	97.60	87.94	70.58	56.27	43.07	35.30	23.65	17.640	14.210	6.722	3.630	2.408	
84		3	2	2	T	0	223.80	483.10	302.00	211.50	149.30	110.10	108.70	90.27	83.75	74.60	49.52	39.85	26.96	20.800	14.050	8.069	4.262	2.756	
85		3	2	1	R	0	237.00	290.60	172.80	128.70	103.60	76.14	61.09	55.00	49.92	43.04	34.96	26.51	20.47	15.190	9.746	5.167	2.912	1.298	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE
86	(b) (6)	3	2	2	T	0	184.30	297.50	170.50	138.00	119.60	81.36	67.89	70.76	59.13	49.35	38.21	29.67	21.68	17.210	10.760	6.101	2.669	1.314	
87		3	2	1	R	0	527.30	504.70	284.10	189.40	165.80	148.50	156.00	124.50	75.81	61.86	43.16	35.70	24.23	18.960	12.440	6.784	2.860	1.706	
88		3	2	2	T	0	422.80	454.70	255.80	174.00	145.50	108.70	87.70	94.53	88.19	85.04	56.85	42.37	29.59	23.050	14.520	7.774	3.272	2.620	
89		3	1	1	T	0	753.60	676.30	389.60	285.60	212.60	179.50	158.80	119.60	92.61	83.48	59.97	45.74	30.92	25.530	15.040	7.270	3.005	2.029	
90		3	1	2	R	0	744.60	674.10	365.10	223.40	201.70	130.10	104.00	89.16	71.67	72.82	47.28	34.86	28.34	23.300	13.040	5.929	3.269	1.720	
91		3	2	1	R	0	476.60	439.70	346.20	176.60	139.00	90.83	71.35	87.46	73.79	54.17	38.44	29.68	25.38	18.240	13.400	6.738	3.441	2.263	
92		3	2	2	T	0	671.30	546.10	324.30	209.20	178.80	116.20	92.10	68.14	76.82	72.49	48.90	34.83	23.69	18.180	14.230	7.084	3.385	2.408	
93		3	1	1	T	0	210.20	266.80	151.20	102.40	78.01	55.29	50.55	54.81	44.78	35.52	25.29	19.36	15.51	12.160	9.186	4.814	2.019	1.188	
94		3	1	2	R	0	310.70	348.80	185.50	125.80	103.90	66.37	67.49	57.20	43.60	35.99	25.04	19.84	16.30	13.450	9.227	5.130	1.944	1.247	
95		3	2	1	R	0	304.70	420.10	282.40	193.20	144.40	111.70	105.60	101.10	72.61	64.20	46.15	36.50	26.29	18.370	12.220	6.715	3.064	1.679	
96		3	2	2	T	0	261.60	430.50	284.00	191.40	141.80	98.84	77.21	62.28	59.39	56.76	45.36	36.63	23.43	17.910	11.400	5.964	2.612	1.807	
97		3	1	1	T	0	266.80	485.10	350.10	220.90	152.10	110.50	99.30	81.65	55.21	49.49	35.11	28.66	21.94	18.110	12.320	6.331	2.600	2.291	
98		3	1	2	R	0	433.10	398.90	260.40	180.40	129.10	91.52	78.30	65.85	50.61	42.44	31.38	24.99	17.67	14.730	10.870	4.660	2.569	1.534	
99		3	2	1	R	0	173.80	260.50	170.50	132.30	104.90	91.61	78.19	73.10	89.30	77.78	49.93	37.10	24.79	18.860	11.370	4.895	2.387	1.272	
100		3	2	2	T	0	139.10	230.20	176.10	139.00	125.60	109.00	130.40	107.80	91.19	77.85	50.94	35.46	24.10	18.960	10.470	6.198	2.001	1.063	
101		3	2	1	R	0	362.30	488.50	347.70	225.30	179.60	137.20	108.60		87.06	72.25	52.40	39.08	26.85	21.480	13.600	6.786	3.068	1.653	
102		3	2	2	T	0	294.40	476.70	367.20	275.40	215.40	156.20	110.10	89.21	78.02	72.21	49.27	41.66	29.18	22.640	15.430	7.087	3.379	2.137	
103		3	2	1	R	0	307.00	397.40	254.90	174.20	137.30	113.10	126.40	137.00	106.30	89.32	61.29	46.89	33.95	26.680	17.930	9.823	4.070	2.646	
104		3	2	2	T	0	373.60	737.10	408.50	284.80	206.30	152.60	126.20	119.80	121.10	111.50	79.24	58.47	45.27	32.120	21.810	13.060	5.450	3.491	
105		3	1	1	T	0	387.80	357.90	270.90	179.00	168.20	133.50	112.20	111.70	101.30	80.27	55.66	41.16	29.88	22.500	13.490	5.453	2.040	1.064	
106		3	1	2	R	0	355.90	519.30	317.70	207.10	170.90	119.10	95.96	83.19	82.28	89.03	58.93	44.75	30.64	23.820	12.660	6.083	2.306	1.041	
107		3	1	1	T	0	550.40	621.10	367.80	253.20	206.30	194.60	198.00	180.00	138.50	104.30	72.16	51.49	36.46	27.720	14.870	7.412	2.752	1.659	
108		3	1	2	R	0	536.30	505.60	306.10	183.50	145.10	106.20	99.88	119.30	114.40	90.93	59.20	42.02	29.23	20.510	10.940	6.294	2.787	1.491	
109		3	2	1	R	0	339.60	331.50	210.20	153.50	131.80	104.80	98.32	80.15	67.75	54.45	36.04	26.61	20.33	15.020	12.080	7.372	3.276	2.350	
110		3	2	2	T	0	252.50	262.50	187.50	142.00	114.80	99.47	112.30	106.20	74.26	61.95	39.39	31.21	21.54	17.770	13.160	8.075	3.563	1.935	
111		3	2	1	R	0	310.40	318.80	180.40	137.90	101.40	73.15	57.83	50.48	40.87	38.06	24.18	19.69	13.65	12.450	7.558	4.627	2.470	1.495	
112		3	2	2	T	0	301.00	332.30	230.00	139.50	105.10	69.52	49.52	42.39	33.29	30.09	27.24	20.89	14.72	12.460	7.430	5.012	2.804	1.353	
113		3	1	1	T	0	188.40	313.00	225.90	167.10	131.70	107.10	91.07	86.91	82.58	73.17	55.67	48.25	36.74	29.360	17.080	8.411	3.228	2.058	
114		3	1	2	R	0	143.80	269.90	168.50	118.10	101.10	80.71	69.72	65.33	63.06	71.51	51.07	38.50	31.79	22.920	13.540	8.120	2.890	2.216	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE
115	(b) (6)	3	2	1	R	0	363.90	407.70	317.90	221.30	180.50	184.70	178.00	136.50	101.50	83.09	57.92	52.39	36.00	27.570	15.870	8.908	4.295	2.683	
116		3	2	2	T	0	305.60	458.00	312.90	241.30	209.40	171.60	184.00	154.50	104.30	92.83	68.71	54.13	38.07	26.830	17.780	8.602	4.081	2.321	
117		3	1	1	T	0	423.60	487.50	321.90	212.90	173.00	143.00	130.00	107.50	91.77	80.33	50.81	39.08	26.92	18.860	12.700	5.780	2.350	1.159	
118		3	1	2	R	0	423.20	411.80	248.30	169.30	150.80	123.70	99.86	101.80	82.28	65.07	40.86	32.32	21.88	16.610	10.540	5.301	2.322	1.211	
119		3	1	1	T	0	83.15	248.30	217.80	199.70	168.60	160.70	140.30	130.00	113.50	91.54	55.73	42.36	24.34	20.490	12.380	5.457	3.678	1.651	
120		3	1	2	R	0	209.60	414.50	296.90	210.40	163.80	121.20	94.33	83.14	78.48	60.97	41.38	30.53	19.54	15.760	10.750	5.136	2.210	1.306	

Obs	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	tr
1	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.53333	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
2	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.05000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
3	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
4	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
5	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
6	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
7	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
8	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
9	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
10	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
11	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
12	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
13	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
14	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.55000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
15	18	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.2833	1
16	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0333	24.0000	36.0000	48.0000	2
17	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.51667	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
18	19	0	0.033333	0.08333	0.16667	0.25000	0.38333	0.50000	0.75	1.00000	1.60000	2.00000	3.00000	4	6.00000	8.06667	12.0500	24.0000	36.0000	48.0167	1
19	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0333	2
20	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
21	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2

Obs	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	tr
109	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
110	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
111	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
112	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.1333	1
113	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
114	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
115	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
116	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
117	19	0	0.033333	0.08333	0.16667	0.25000	0.36667	0.50000	0.75	1.00000	1.50000	2.01667	3.03333	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
118	19	0	0.033333	0.08333	0.16667	0.28333	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
119	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.03333	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
120	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2

5.9.1.5 Fasting Study Output (SA)

Fasting STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	60	(b) (6)
trt	2	1 2
per	2	1 2
seq	2	1 2
GRP	3	1 2 3

Number of Observations Read	120
Number of Observations Used	120

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	63	9.38410142	0.14895399	14.80	<.0001
Error	56	0.56373671	0.01006673		
Corrected Total	119	9.94783813			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.943331	1.535827	0.100333	6.532837

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.00981384	0.00981384	0.97	0.3277
GRP	2	0.07686390	0.03843195	3.82	0.0279
seq	1	0.08079074	0.08079074	8.03	0.0064
seq*GRP	2	0.08254983	0.04127492	4.10	0.0218
sub(seq*GRP)	54	8.85200129	0.16392595	16.28	<.0001
per(GRP)	2	0.10168703	0.05084352	5.05	0.0096
trt	1	0.18039480	0.18039480	17.92	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per	1	0.00945012	0.00945012	0.94	0.3368
GRP	2	0.07357589	0.03678794	3.65	0.0322
seq	1	0.08156724	0.08156724	8.10	0.0062
seq*GRP	2	0.08254983	0.04127492	4.10	0.0218
sub(seq*GRP)	54	8.85200129	0.16392595	16.28	<.0001
per(GRP)	2	0.11753371	0.05876686	5.84	0.0050
trt	1	0.18039480	0.18039480	17.92	<.0001

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.08156724	0.08156724	0.50	0.4836
GRP	2	0.07357589	0.03678794	0.22	0.7997

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.07773932	0.01836424	4.23	<.0001

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	63	9.08402822	0.14419092	15.65	<.0001
Error	56	0.51600045	0.00921429		
Corrected Total	119	9.60002867			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.946250	1.458758	0.095991	6.580333

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.01041279	0.01041279	1.13	0.2923
GRP	2	0.05786733	0.02893367	3.14	0.0510
seq	1	0.08231497	0.08231497	8.93	0.0042
seq*GRP	2	0.09328932	0.04664466	5.06	0.0095
sub(seq*GRP)	54	8.56765224	0.15866023	17.22	<.0001
per(GRP)	2	0.10535351	0.05267676	5.72	0.0055
trt	1	0.16713805	0.16713805	18.14	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per	1	0.01015540	0.01015540	1.10	0.2983
GRP	2	0.05673571	0.02836786	3.08	0.0539
seq	1	0.08164294	0.08164294	8.86	0.0043
seq*GRP	2	0.09328932	0.04664466	5.06	0.0095
sub(seq*GRP)	54	8.56765224	0.15866023	17.22	<.0001
per(GRP)	2	0.12095550	0.06047775	6.56	0.0027
trt	1	0.16713805	0.16713805	18.14	<.0001

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.08164294	0.08164294	0.51	0.4763
GRP	2	0.05673571	0.02836786	0.18	0.8368

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.07482839	0.01756951	4.26	<.0001

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	63	18.52301521	0.29401611	9.21	<.0001
Error	56	1.78740756	0.03191799		
Corrected Total	119	20.31042277			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.911996	3.049072	0.178656	5.859359

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.14317823	0.14317823	4.49	0.0386
GRP	2	1.13383253	0.56691627	17.76	<.0001
seq	1	0.04940306	0.04940306	1.55	0.2186
seq*GRP	2	0.10438524	0.05219262	1.64	0.2041
sub(seq*GRP)	54	16.97034295	0.31426561	9.85	<.0001
per(GRP)	2	0.12151800	0.06075900	1.90	0.1586
trt	1	0.00035520	0.00035520	0.01	0.9164

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per	1	0.14739362	0.14739362	4.62	0.0360
GRP	2	1.16247531	0.58123765	18.21	<.0001
seq	1	0.04918605	0.04918605	1.54	0.2196
seq*GRP	2	0.10438524	0.05219262	1.64	0.2041
sub(seq*GRP)	54	16.97034295	0.31426561	9.85	<.0001
per(GRP)	2	0.12031671	0.06015836	1.88	0.1614
trt	1	0.00035520	0.00035520	0.01	0.9164

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.04918605	0.04918605	0.16	0.6939
GRP	2	1.16247531	0.58123765	1.85	0.1671

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.00344956	0.03269991	-0.11	0.9164

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	trt	AUCRATIO
1	(b) (6)	1	0.96
2		1	0.97
3		1	0.98
4		1	0.97
5		1	0.98
6		1	0.96
7		1	0.92
8		1	0.95
9		1	0.96
10		1	0.97
11		1	0.94
12		1	0.98
13		1	0.97
14		1	0.96
15		1	0.93
16		1	0.97
17		1	0.93
18		1	0.94

Obs	sub	trt	AUCRATIO
19	(b) (6)	1	0.95
20		1	0.96
21		1	0.92
22		1	0.95
23		1	0.96
24		1	0.95
25		1	0.94
26		1	0.95
27		1	0.92
28		1	0.96
29		1	0.96
30		1	0.96
31		1	0.96
32		1	0.97
33		1	0.97
34		1	0.96
35		1	0.96
36		1	0.97
37		1	0.98
38		1	0.88
39		1	0.97
40		1	0.96
41		1	0.97
42		1	0.93
43		1	0.96
44		1	0.94
45		1	0.96
46		1	0.94
47		1	0.96
48		1	0.95
49		1	0.93
50		1	0.98
51		1	0.95
52		1	0.95
53		1	0.98
54		1	0.97
55		1	0.95
56		1	0.94
57		1	0.96
58		1	0.96

Obs	sub	trt	AUCRATIO
59	(b) (6)	1	0.98
60		1	0.96
61		2	0.95
62		2	0.97
63		2	0.97
64		2	0.96
65		2	0.97
66		2	0.96
67		2	0.97
68		2	0.96
69		2	0.94
70		2	0.98
71		2	0.92
72		2	0.97
73		2	0.96
74		2	0.95
75		2	0.94
76		2	0.96
77		2	0.93
78		2	0.95
79		2	0.94
80		2	0.97
81		2	0.84
82		2	0.95
83		2	0.96
84		2	0.96
85		2	0.94
86		2	0.92
87		2	0.95
88		2	0.95
89		2	0.95
90		2	0.96
91		2	0.95
92		2	0.95
93		2	0.97
94		2	0.96
95		2	0.96
96		2	0.98
97		2	0.97
98		2	0.93

Obs	sub	trt	AUCRATIO
99	(b) (6)	2	0.93
100	(b) (6)	2	0.95
101	(b) (6)	2	0.97
102	(b) (6)	2	0.94
103	(b) (6)	2	0.96
104	(b) (6)	2	0.96
105	(b) (6)	2	0.96
106	(b) (6)	2	0.94
107	(b) (6)	2	0.96
108	(b) (6)	2	0.96
109	(b) (6)	2	0.95
110	(b) (6)	2	0.97
111	(b) (6)	2	0.97
112	(b) (6)	2	0.95
113	(b) (6)	2	0.98
114	(b) (6)	2	0.97
115	(b) (6)	2	0.93
116	(b) (6)	2	0.93
117	(b) (6)	2	0.94
118	(b) (6)	2	0.95
119	(b) (6)	2	0.97
120	(b) (6)	2	0.97

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

sub	seq	RAUCT12	RAUC12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	1	1.11	1.09	0.61	2.50	1.10	0.91
(b) (6)	2	1.05	1.05	0.85	1.00	1.01	0.99
(b) (6)	2	1.09	1.09	0.98	2.50	1.08	0.92
(b) (6)	1	0.92	0.91	1.15	9.00	1.02	0.98
(b) (6)	1	1.09	1.09	1.24	18.0	1.01	0.99
(b) (6)	2	0.97	0.97	1.61	1.00	1.04	0.96
(b) (6)	1	0.91	0.96	0.99	1.00	0.71	1.40
(b) (6)	1	0.92	0.93	0.73	1.00	1.27	0.79
(b) (6)	2	1.14	1.11	0.84	1.00	1.21	0.82
(b) (6)	2	0.79	0.79	0.92	1.00	0.98	1.02
(b) (6)	2	1.11	1.08	1.13	1.00	1.15	0.87
(b) (6)	1	1.07	1.06	1.00	1.00	1.04	0.96
(b) (6)	1	1.11	1.10	0.74	1.00	1.12	0.90
(b) (6)	1	1.22	1.21	1.40	1.00	1.13	0.88

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	2	1.13	1.14	1.07	1.00	0.97	1.04
	2	1.06	1.05	0.85	1.00	1.14	0.88
	2	1.15	1.15	1.21	0.40	1.03	0.97
	2	0.77	0.78	0.57	1.00	0.92	1.09
	1	1.08	1.07	1.13	1.00	1.02	0.98
	2	0.89	0.90	0.79	1.00	0.86	1.16
	1	1.02	0.94	0.82	1.00	1.38	0.72
	1	0.95	0.95	0.72	1.00	1.01	0.99
	1	1.24	1.24	1.19	1.00	0.99	1.01
	2	1.28	1.29	1.10	1.00	0.93	1.07
	1	0.67	0.67	0.87	0.40	0.88	1.14
	1	1.22	1.18	1.28	0.78	1.20	0.83
	2	1.02	1.05	1.80	0.04	0.88	1.14
	2	1.71	1.69	1.47	1.00	0.82	1.21
	2	1.45	1.44	1.70	1.00	1.02	0.98
	2	1.21	1.22	0.98	1.00	0.94	1.07
	1	1.08	1.07	0.78	1.00	1.05	0.95
	2	1.21	1.19	1.18	1.00	1.11	0.90
	1	1.09	1.09	0.70	1.00	1.02	0.98
	1	1.11	1.10	0.87	1.33	1.04	0.96
	1	0.97	0.97	1.04	1.00	1.02	0.98
	2	0.92	0.92	0.87	1.00	1.02	0.98
	2	1.34	1.33	1.32	1.00	0.77	1.30
	1	0.85	0.90	1.09	1.00	0.79	1.26
	2	1.27	1.22	0.96	2.50	1.31	0.76
	1	1.05	1.03	0.63	1.00	0.82	1.22
	1	1.21	1.20	0.92	1.00	1.09	0.92
	2	1.11	1.12	1.05	1.00	0.93	1.08
	2	1.11	1.10	1.02	1.00	1.08	0.93
	2	1.08	1.11	0.86	2.50	0.88	1.14
	1	1.17	1.17	1.01	1.00	1.04	0.96
	2	1.09	1.09	1.41	1.00	1.01	0.99
	1	0.93	0.93	0.76	1.00	1.01	0.99
	2	0.91	0.92	1.02	1.00	0.93	1.08
	1	1.19	1.21	1.12	1.67	0.92	1.09
	2	1.05	1.04	0.88	1.00	1.10	0.91
	2	1.05	1.06	0.98	1.00	0.94	1.07
	2	1.27	1.27	1.85	1.00	0.96	1.04
	1	0.98	0.98	0.75	0.80	1.02	0.98
	1	1.29	1.28	1.16	2.50	1.11	0.90

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	2	1.07	1.05	0.77	2.50	1.15	0.87
	2	1.01	1.00	1.04	1.00	1.03	0.97
	1	1.19	1.17	1.16	1.00	1.13	0.88
	2	1.04	1.03	1.12	1.00	1.13	0.88
	1	1.17	1.16	1.15	2.50	1.10	0.91
	1	1.24	1.24	0.60	1.00	0.90	1.11

5.9.1.6 Firm Reviewer Ratio (SA)

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	(b) (6)	1	1	1	1	763.25	797.15	268.1	T	749.52	783.42	268.1	0.98202	0.98278	1
2		1	1	2	2	689.90	728.13	438.2	R	679.22	717.45	438.2	0.98452	0.98533	1
3		1	2	1	2	683.46	702.64	295.6	R	671.53	689.66	295.6	0.98255	0.98153	1
4		1	2	2	1	714.86	735.13	249.8	T	702.25	721.51	249.8	0.98235	0.98147	1
5		1	2	1	2	692.93	713.08	549.6	R	680.08	699.69	549.6	0.98147	0.98122	1
6		1	2	2	1	757.39	775.09	536.1	T	741.25	758.68	536.1	0.97870	0.97883	1
7		1	1	1	1	775.79	803.36	151.6	T	762.49	790.06	151.6	0.98286	0.98345	1
8		1	1	2	2	842.62	879.64	131.3	R	828.23	862.88	131.3	0.98293	0.98095	1
9		1	1	1	1	868.45	890.71	143.9	T	851.04	873.29	143.9	0.97995	0.98045	1
10		1	1	2	2	794.42	816.16	115.8	R	779.16	800.90	115.8	0.98079	0.98130	1
11		1	2	1	2	1875.02	1954.29	298.4	R	1838.72	1917.99	298.4	0.98064	0.98143	1
12		1	2	2	1	1825.26	1893.22	479.0	T	1794.24	1857.30	479.0	0.98301	0.98103	1
13		1	1	1	1	567.28	618.55	468.1	T	558.33	598.63	468.1	0.98422	0.96780	1
14		1	1	2	2	621.89	641.09	473.9	R	610.41	629.61	473.9	0.98154	0.98209	1
15		1	1	1	1	495.27	520.08	221.7	T	487.28	514.48	221.7	0.98388	0.98924	1
16		1	1	2	2	535.82	558.49	302.6	R	527.38	550.05	302.6	0.98425	0.98489	1
17		1	2	1	2	580.94	614.97	356.2	R	572.09	606.11	356.2	0.98476	0.98560	1
18		1	2	2	1	659.91	684.61	298.0	T	648.80	673.50	298.0	0.98318	0.98378	1
19		1	2	1	2	928.08	948.78	480.4	R	909.56	929.75	480.4	0.98004	0.97994	1
20		1	2	2	1	731.47	750.54	443.1	T	715.37	735.78	443.1	0.97798	0.98034	1
21		1	2	1	2	398.97	435.98	238.2	R	394.13	431.14	238.2	0.98786	0.98889	1
22		1	2	2	1	443.81	472.75	268.0	T	437.67	466.64	268.0	0.98616	0.98707	1
23		1	1	1	1	650.25	666.81	428.5	T	638.27	654.82	428.5	0.98157	0.98203	1

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
24	(b) (6)	1	1	2	2	609.82	627.05	426.4	R	598.50	614.82	426.4	0.98144	0.98050	1
25		1	1	1	1	561.90	577.96	248.0	T	552.19	568.25	248.0	0.98272	0.98320	1
26		1	1	2	2	506.58	526.54	334.1	R	497.92	517.03	334.1	0.98291	0.98194	1
27		1	1	1	1	787.09	821.50	586.0	T	774.61	809.03	586.0	0.98415	0.98481	1
28		1	1	2	2	644.61	678.70	418.1	R	636.47	670.56	418.1	0.98737	0.98800	1
29		1	2	1	2	545.93	580.81	322.1	R	537.72	572.61	322.1	0.98497	0.98587	1
30		1	2	2	1	616.24	661.01	345.9	T	607.85	652.62	345.9	0.98638	0.98730	1
31		1	2	1	2	531.06	553.01	185.1	R	521.18	544.27	185.1	0.98139	0.98418	1
32		1	2	2	1	564.60	582.30	157.8	T	552.45	570.15	157.8	0.97848	0.97914	1
33		1	2	1	2	802.32	863.10	741.3	R	791.13	851.90	741.3	0.98605	0.98703	1
34		1	2	2	1	923.17	991.89	894.0	T	908.45	977.16	894.0	0.98405	0.98515	1
35		1	2	1	2	719.97	755.26	253.7	R	708.86	743.03	253.7	0.98456	0.98381	1
36		1	2	2	1	550.92	588.34	143.8	T	543.27	580.68	143.8	0.98610	0.98698	1
37		1	1	1	1	552.15	579.23	516.5	T	544.39	571.46	516.5	0.98594	0.98659	1
38		1	1	2	2	509.30	539.79	458.5	R	501.94	532.44	458.5	0.98555	0.98637	1
39		1	2	1	2	967.71	996.67	492.4	R	947.22	975.45	492.4	0.97882	0.97871	1
40		1	2	2	1	856.94	894.91	386.6	T	842.61	879.16	386.6	0.98327	0.98240	1
41		2	1	1	1	541.61	591.82	236.2	T	533.89	584.10	236.2	0.98575	0.98696	1
42		2	1	2	2	528.67	630.44	287.8	R	523.65	617.46	287.8	0.99051	0.97940	1
43		2	1	1	1	445.07	467.98	218.6	T	437.47	460.39	218.6	0.98294	0.98378	1
44		2	1	2	2	470.18	494.29	303.3	R	463.04	487.16	303.3	0.98482	0.98556	1
45		2	1	1	1	715.20	746.33	533.7	T	704.66	735.79	533.7	0.98527	0.98588	1
46		2	1	2	2	575.86	602.40	450.1	R	566.55	591.55	450.1	0.98383	0.98200	1
47		2	2	1	2	527.41	548.70	302.3	R	518.86	537.81	302.3	0.98380	0.98016	1
48	2	2	2	1	674.72	707.30	331.7	T	663.60	696.18	331.7	0.98352	0.98428	1	

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
49	(b) (6)	2	1	1	1	1090.22	1155.28	372.1	T	1073.06	1137.31	372.1	0.98426	0.98445	1
50		2	1	2	2	1628.66	1723.58	426.8	R	1599.11	1694.03	426.8	0.98186	0.98286	1
51		2	1	1	1	567.15	599.14	206.8	T	558.95	590.95	206.8	0.98555	0.98632	1
52		2	1	2	2	466.11	508.04	161.5	R	459.73	501.67	161.5	0.98632	0.98745	1
53		2	2	1	2	1003.73	1061.05	140.9	R	987.32	1044.63	140.9	0.98364	0.98453	1
54		2	2	2	1	1026.37	1113.51	253.4	T	1013.89	1095.79	253.4	0.98783	0.98408	1
55		2	2	1	2	411.88	435.26	172.1	R	404.74	429.85	172.1	0.98266	0.98757	1
56		2	2	2	1	705.92	736.80	252.3	T	693.67	724.54	252.3	0.98264	0.98337	1
57		2	2	1	2	676.05	710.37	230.4	R	664.56	698.88	230.4	0.98300	0.98382	1
58		2	2	2	1	982.57	1025.51	390.9	T	965.32	1008.25	390.9	0.98244	0.98318	1
59		2	2	1	2	630.98	655.57	473.4	R	620.16	644.40	473.4	0.98286	0.98296	1
60		2	2	2	1	765.52	799.71	462.3	T	753.10	787.29	462.3	0.98377	0.98447	1
61		2	1	1	1	1203.36	1254.88	372.9	T	1183.63	1235.15	372.9	0.98361	0.98428	1
62		2	1	2	2	1117.34	1177.93	479.1	R	1099.90	1157.23	479.1	0.98439	0.98243	1
63		2	2	1	2	548.66	579.70	483.4	R	539.62	565.87	483.4	0.98353	0.97613	1
64		2	2	2	1	664.16	687.98	571.3	T	653.42	677.24	571.3	0.98382	0.98438	1
65		2	1	1	1	943.91	977.32	280.3	T	927.43	959.67	280.3	0.98254	0.98194	1
66		2	1	2	2	866.72	897.70	402.2	R	851.96	881.71	402.2	0.98296	0.98219	1
67		2	1	1	1	529.04	549.38	403.8	T	520.53	540.47	403.8	0.98391	0.98379	1
68		2	1	2	2	477.74	498.15	463.0	R	469.73	490.13	463.0	0.98324	0.98388	1
69		2	1	1	1	600.84	623.40	398.4	T	589.61	614.28	398.4	0.98130	0.98537	1
70		2	1	2	2	618.55	645.34	383.6	R	606.23	635.85	383.6	0.98008	0.98530	1
71		2	2	1	2	717.47	734.88	577.5	R	704.60	722.00	577.5	0.98206	0.98248	1
72		2	2	2	1	660.25	677.54	501.7	T	647.33	666.18	501.7	0.98043	0.98324	1
73		2	2	1	2	569.77	586.05	234.1	R	557.97	574.25	234.1	0.97928	0.97986	1

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
74	(b) (6)	2	2	2	1	762.92	780.69	309.7	T	747.91	767.38	309.7	0.98032	0.98295	1
75		2	1	1	1	406.22	462.44	263.2	T	400.78	.	263.2	0.98660	.	1
76		2	1	2	2	480.20	515.65	240.7	R	474.23	509.68	240.7	0.98756	0.98842	1
77		2	2	1	2	482.23	517.92	309.9	R	475.21	506.94	309.9	0.98544	0.97881	1
78		2	2	2	1	611.53	632.35	297.3	T	601.22	621.23	297.3	0.98315	0.98242	1
79		3	1	1	1	593.33	616.59	146.5	T	583.13	606.39	146.5	0.98280	0.98345	1
80		3	1	2	2	564.80	597.58	234.4	R	554.69	590.32	234.4	0.98210	0.98785	1
81		3	1	1	1	989.20	1017.42	456.4	T	968.79	996.26	456.4	0.97937	0.97920	1
82		3	1	2	2	817.35	846.84	495.8	R	801.08	829.72	495.8	0.98010	0.97979	1
83		3	2	1	2	707.44	756.07	458.0	R	696.31	743.44	458.0	0.98426	0.98329	1
84		3	2	2	1	787.30	847.16	483.1	T	776.65	836.51	483.1	0.98648	0.98743	1
85		3	2	1	2	520.39	543.91	290.6	R	512.45	535.98	290.6	0.98475	0.98541	1
86		3	2	2	1	576.69	598.79	297.5	T	567.12	587.66	297.5	0.98340	0.98141	1
87		3	2	1	2	744.26	774.26	527.3	R	731.89	760.41	527.3	0.98339	0.98211	1
88		3	2	2	1	803.31	855.69	454.7	T	790.17	834.90	454.7	0.98364	0.97570	1
89		3	1	1	1	912.99	948.32	753.6	T	897.16	927.97	753.6	0.98265	0.97854	1
90		3	1	2	2	778.75	809.80	744.6	R	764.43	795.49	744.6	0.98162	0.98232	1
91		3	2	1	2	691.82	737.02	476.6	R	681.21	724.18	476.6	0.98466	0.98258	1
92		3	2	2	1	753.73	801.35	671.3	T	741.32	787.34	671.3	0.98353	0.98252	1
93		3	1	1	1	435.61	455.96	266.8	T	428.06	448.15	266.8	0.98267	0.98287	1
94		3	1	2	2	470.06	491.53	348.8	R	461.76	481.45	348.8	0.98235	0.97948	1
95		3	2	1	2	704.20	734.09	420.1	R	693.43	723.33	420.1	0.98472	0.98534	1
96		3	2	2	1	639.48	674.13	430.5	T	629.19	661.08	430.5	0.98390	0.98063	1
97		3	1	1	1	649.03	695.34	485.1	T	638.44	677.17	485.1	0.98368	0.97387	1
98	3	1	2	2	546.44	574.89	433.1	R	536.93	563.09	433.1	0.98260	0.97947	1	

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
99	(b) (6)	3	2	1	2	629.70	650.64	260.5	R	617.48	638.42	260.5	0.98059	0.98121	1
100		3	2	2	1	663.62	679.58	230.2	T	651.60	666.15	230.2	0.98189	0.98023	1
101		3	2	1	2	775.47	803.35	488.5	R	762.49	790.36	488.5	0.98325	0.98384	1
102		3	2	2	1	811.10	849.54	476.7	T	797.36	833.44	476.7	0.98306	0.98105	1
103		3	2	1	2	924.48	972.43	397.4	R	909.40	954.95	397.4	0.98369	0.98202	1
104		3	2	2	1	1172.10	1237.86	737.1	T	1153.92	1216.82	737.1	0.98449	0.98300	1
105		3	1	1	1	752.62	767.46	387.8	T	736.88	751.72	387.8	0.97909	0.97949	1
106		3	1	2	2	769.45	784.20	519.3	R	753.71	768.47	519.3	0.97955	0.97994	1
107		3	1	1	1	1003.25	1029.55	621.1	T	985.35	1011.64	621.1	0.98215	0.98261	1
108		3	1	2	2	779.88	806.21	536.3	R	767.12	793.45	536.3	0.98363	0.98417	1
109		3	2	1	2	634.41	683.69	339.6	R	625.96	674.79	339.6	0.98668	0.98698	1
110		3	2	2	1	681.19	716.53	262.5	T	670.95	705.37	262.5	0.98497	0.98443	1
111		3	2	1	2	443.96	476.64	318.8	R	437.88	470.56	318.8	0.98631	0.98725	1
112		3	2	2	1	447.62	476.24	332.3	T	441.77	467.15	332.3	0.98694	0.98092	1
113		3	1	1	1	830.03	863.83	313.0	T	814.47	848.27	313.0	0.98125	0.98199	1
114		3	1	2	2	699.31	740.45	269.9	R	687.23	720.92	269.9	0.98273	0.97363	1
115		3	2	1	2	949.78	1002.89	407.7	R	936.07	989.19	407.7	0.98557	0.98633	1
116		3	2	2	1	991.98	1032.62	458.0	T	975.67	1016.31	458.0	0.98356	0.98421	1
117		3	1	1	1	753.24	770.44	487.5	T	739.32	756.53	487.5	0.98152	0.98193	1
118		3	1	2	2	645.21	665.07	423.2	R	634.15	654.01	423.2	0.98286	0.98337	1
119	3	1	1	1	767.40	798.17	248.3	T	754.10	784.87	248.3	0.98267	0.98334	1	
120	3	1	2	2	619.62	641.48	414.5	R	609.00	629.89	414.5	0.98287	0.98193	1	

5.9.2 Fasting Study MGR001-1007

5.9.2.1 Fasting Study Data (FP)

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
1	(b) (6)	1	2	1	R	0.000	16.980	60.240	85.39	117.80	147.50	155.90	168.90	228.60	280.7	287.60	303.50	302.70	271.90	188.50	134.50
2		1	2	2	T	0.000	31.150	49.430	87.20	145.50	190.10	199.70	248.10	236.40	278.1	247.20	290.40	286.60	223.90	186.30	146.70
3		1	2	1	R	0.000	21.730	50.280	106.60	124.60	156.80	262.90	271.40	290.30	317.7	332.90	300.40	267.30	166.30	136.30	80.72
4		1	2	2	T	0.000	19.780	59.660	109.30	153.70	245.20	268.10	326.40	338.20	365.5	330.30	314.00	269.80	162.70	149.00	84.57
5		1	1	1	T	0.000	12.530	38.510	58.21	108.60	110.60	153.30	228.50	197.00	224.5	232.30	225.50	205.40	123.50	88.49	60.98
6		1	1	2	R	0.000	27.060	95.410	108.00	146.90	175.00	226.30	283.90	278.40	295.7	287.40	295.30	259.70	176.20	130.40	77.91
7		1	1	1	T	0.000	8.108	54.260	105.10	144.20	184.40	216.40	277.00	265.80	275.1	350.90	308.70	303.10	220.70	150.50	88.58
8		1	1	2	R	0.000	26.370	132.600	138.40	278.60	322.70	434.10	376.50	431.70	409.3	400.20	398.10	340.60	241.40	159.90	99.01
9		1	2	1	R	0.000	7.801	40.060	59.80	104.30	132.50	168.60	242.60	276.20	347.6	321.60	343.70	302.50	173.60	129.70	97.08
10		1	2	2	T	0.000	12.360	30.830	53.48	71.89	86.37	122.40	113.30	145.40	164.1	161.00	189.30	160.90	124.80	97.74	59.82
11		1	1	1	T	0.000	8.903	22.500	66.86	87.33	100.40	191.30	218.60	253.20	269.9	264.60	263.30	242.40	150.90	111.50	70.21
12		1	1	2	R	1.467	14.040	31.000	61.88	87.60	119.30	168.40	193.10	239.10	241.1	230.40	209.80	181.80	98.32	79.96	45.65
13		1	2	1	R	0.000	19.940	41.150	64.42	84.72	111.50	161.30	157.70	189.70	205.1	198.70	232.30	219.30	148.40	96.59	58.19
14		1	2	2	T	0.000	8.204	20.720	46.83	106.00	110.70	130.10	146.80	154.40	173.6	181.70	177.20	182.40	119.50	98.62	66.93
15		1	2	1	R	0.000	103.900	198.700	227.20	317.50	361.90	351.00	388.20	369.30	328.2	312.30	274.80	223.10	140.70	104.30	70.07
16		1	2	2	T	0.000	44.780	98.760	156.60	212.90	219.50	237.00	251.20	271.60	232.5	217.70	183.10	171.20	103.90	83.52	53.62
17		1	2	1	R	0.000	22.350	48.020	84.19	128.40	146.30	202.00	233.40	267.30	257.2	233.30	184.10	161.00	96.95	70.60	45.98
18		1	2	2	T	0.000	4.742	21.370	54.97	76.60	105.80	128.80	153.40	156.60	172.7	147.50	116.30	95.48	66.56	48.38	35.50
19		1	1	1	T	0.000	27.640	69.390	88.71	138.00	187.60	235.80	273.00	269.80	244.1	237.50	198.90	182.30	110.80	78.03	50.34
20		1	1	2	R	0.000	23.770	50.300	103.30	132.30	202.80	179.20	292.00	266.10	255.5	220.10	191.70	158.60	83.98	69.28	36.29
21		1	1	1	T	0.000	11.160	45.150	114.10	131.40	199.60	298.50	357.00	412.40	410.7	434.60	411.80	400.80	285.60	224.90	151.90
22		1	1	2	R	1.244	36.920	64.810	149.20	242.40	233.30	397.90	503.50	507.60	508.7	460.60	417.80	377.20	251.90	185.00	144.30
23		1	1	1	T	0.000	14.650	33.300	74.01	91.07	106.40	117.50	132.30	157.20	146.6	152.50	190.60	189.20	117.90	88.18	58.35
24		1	1	2	R	0.000	13.140	34.250	55.92	91.57	102.20	132.60	131.60	171.90	196.4	174.50	191.20	168.80	121.70	96.11	61.12
25		1	1	1	T	0.000	11.090	24.790	32.34	34.62	56.55	101.70	112.10	136.80	133.8	175.80	135.30	110.00	83.67	52.89	34.10
26		1	1	2	R	0.000	1.821	8.767	15.55	43.45	58.59	58.80	91.74	87.22	124.1	97.89	92.55	62.26	48.06	31.07	15.25

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
27	(b) (6)	1	2	1	R	0.000	14.510	18.350	31.69	75.99	77.68	98.04	146.20	192.30	226.0	263.70	253.40	286.00	220.30	202.60	133.90
28		1	2	2	T	0.000	6.428	35.900	56.21	155.50	185.00	203.30	180.30	239.40	250.1	326.80	355.30	326.00	290.90	260.90	156.10
29		1	1	1	T	0.000	14.340	42.920	95.38	130.10	159.60	179.60	253.00	248.70	218.0	249.30	213.10	208.40	135.80	110.70	70.78
30		1	1	2	R	0.000	54.460	99.790	130.00	217.50	231.20	280.50	300.50	305.70	307.8	304.20	311.20	300.30	198.70	150.40	91.14
31		1	1	1	T	0.000	5.254	25.760	44.17	72.05	106.70	127.50	150.40	145.70	132.4	112.20	84.48	69.04	43.77	34.62	20.95
32		1	1	2	R	0.000	8.906	28.010	44.08	62.51	84.45	103.80	134.50	140.20	135.6	113.40	82.14	63.15	37.80	29.63	15.00
33		1	2	1	R	0.000	12.560	46.240	85.84	112.50	156.30	249.60	268.70	272.60	317.7	310.50	294.80	309.90	214.40	167.40	107.60
34		1	2	2	T	0.000	8.591	27.900	54.11	80.05	85.30	121.20	198.50	190.70	233.3	235.40	237.10	231.10	206.30	166.00	89.39
35		1	2	1	R	0.000	19.300	22.250	49.88	78.72	81.42	123.00	134.80	213.10	222.5	230.70	210.90	194.60	123.10	91.67	58.94
36		1	2	2	T	0.000	13.890	32.490	49.31	75.65	92.28	136.70	177.60	170.60	169.6	164.60	149.50	121.90	79.16	58.90	31.42
37		1	1	1	T	0.000	26.590	101.000	99.61	152.20	214.90	247.10	316.90	334.80	329.9	331.80	288.00	274.90	185.60	138.80	81.04
38		1	1	2	R	0.000	47.440	72.330	121.40	150.30	209.80	246.60	272.70	292.80	308.7	308.50	329.50	288.10	164.10	144.60	81.56
39		1	1	1	T	0.000	22.340	56.380	63.95	89.16	110.40	134.20	171.80	200.00	215.3	213.90	193.70	175.30	117.10	91.17	59.44
40		1	1	2	R	0.000	18.330	40.660	78.24	127.00	135.70	186.40	261.30	272.40	298.9	305.50	303.60	305.20	186.90	150.70	102.90
41		1	1	1	T	1.535	9.654	33.080	70.72	119.70	195.70	201.70	193.50	207.00	186.5	172.80	150.70	121.70	84.89	66.25	41.45
42		1	1	2	R	0.000	28.990		149.60	206.50	232.30	279.90	330.70	355.80	316.5	266.40	215.40	168.70	121.50	93.55	63.01
43		2	2	1	R	0.000	46.770	48.990	75.99	165.50	226.50	198.70	261.80	287.60	325.6	312.80	292.00	256.50	192.60	158.70	89.55
44		2	2	2	T	0.000	46.850	199.700	223.20	221.70	307.40	337.50	340.00	334.80	303.0	313.20	292.80	279.80	205.20	160.10	88.03
45		2	2	1	R	0.000	17.350	90.730	90.51	136.90	188.20	261.80	313.30	298.70	319.0	300.10	251.70	232.80	172.90	139.70	70.68
46		2	2	2	T	0.000	26.410	77.220	121.50	141.20	208.60	242.50	262.80	260.50	236.0	258.20	233.10	218.80	150.60	125.90	67.73
47		2	2	1	R	0.000	17.080	52.850	58.93	143.10	194.10	238.40	181.90	242.50	194.1	188.20	188.20	152.60	103.00	89.51	48.40
48		2	2	2	T	0.000	27.090	33.060	119.40	106.80	207.40	192.50	187.10	184.80	145.2	143.50	115.40	103.50	76.65	59.32	34.92
49		2	1	1	T	0.000	11.760	18.320	65.56	68.27	121.80	146.70	193.50	238.80	332.0	273.10	304.70	305.70	198.30	160.50	109.70
50		2	1	2	R	0.000	13.990	33.370	64.19	89.19	125.80	190.10	205.40	212.00	261.0	243.80	281.60	282.60	198.20	163.70	96.93
51		2	1	1	T	0.000	5.180	28.700	51.66	155.60	133.60	156.00	166.50	140.90	164.8	175.30	181.10	172.60	113.70	99.92	55.25
52		2	1	2	R	0.000	9.874	43.720	84.35	145.20	174.40	216.70	216.90	191.50	168.8	220.00	220.50	209.80	127.60	110.60	56.86
53		2	1	1	T	0.000	41.750	81.150	82.59	110.80	150.10	146.40	181.40	211.70	256.9	273.50	255.10	233.70	148.70	129.40	77.77
54		2	1	2	R	0.000	19.490	44.630	60.92	100.20	139.90	156.20	165.80	196.30	222.2	209.90	207.60	200.10	126.00	106.10	62.98
55		2	2	1	R	0.000	4.521	18.060	55.13	61.39	88.38	134.20	147.10	167.20	188.2	183.30	167.10	164.70	85.97	72.64	43.19

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
56	(b) (6)	2	2	2	T	0.000	26.990	64.610	67.04	94.59	137.50	124.00	158.20	164.20	167.2	161.00	135.70	132.80	81.08	71.50	34.68
57		2	2	1	R	0.000	6.292	32.790	43.94	74.09	108.70	172.60	146.80	160.70	167.7	157.40	135.70	114.00	99.01	74.40	47.74
58		2	2	2	T	0.000	10.910	30.800	51.72	133.00	166.30	163.10	210.20	154.50	173.0	163.60	143.80	116.70	85.99	66.08	41.26
59		2	1	1	T	0.000	16.760	29.340	71.47	128.40	124.90	177.00	239.50	204.10	251.7	213.60	203.00	191.00	131.60	116.40	56.28
60		2	1	2	R	0.000	90.140	140.400	177.00	189.90	147.50	211.40	248.30	268.10	264.0	261.40	239.40	223.30	143.90	117.10	65.89
61		2	1	1	T	0.000	20.890	55.510	141.60	175.90	196.60	207.80	265.90	271.40	253.3	224.30	204.80	177.30	119.00	89.36	55.46
62		2	1	2	R	0.000	56.060	89.490	112.70	145.50	220.70	264.30	299.90	303.40	279.9	257.30	213.10	190.50	115.90	87.15	49.95
63		2	2	1	R	0.000	18.380	41.690	72.23	124.30	152.40	198.30	264.70	317.50	336.6	324.20	322.20	297.20	217.30	163.00	110.70
64		2	2	2	T	0.000	10.490	44.910	73.27	117.40	159.20	222.30	284.00	312.70	310.8	312.10	281.20	271.10	197.60	182.40	114.80
65		2	1	1	T	0.000	15.530	72.030	104.90	158.60	199.50	289.50	345.60	365.70	437.6	385.50	367.10	331.90	187.90	151.00	103.50
66		2	1	2	R	0.000	24.460	79.150	177.00	216.00	293.20	385.00	482.30	528.00	533.8	498.90	446.40	355.10	216.70	161.30	95.86
67		2	2	1	R	0.000	51.400	85.790	146.80	220.10	252.70	371.40	335.10	373.10	423.5	399.50	380.30	336.90	231.10	178.80	99.50
68		2	2	2	T	0.000	38.100	71.100	106.60	182.20	219.10	251.80	314.10	350.40	355.2	358.80	361.30	341.50	233.40	177.60	115.50
69		2	2	1	R	0.000	24.750	54.300	81.52	107.30	165.80	179.30	207.50	187.90	186.0	178.60	153.50	139.70	98.68	75.04	38.78
70		2	2	2	T	0.000	34.700	57.580	89.09	149.20	130.70	170.20	159.80	186.00	162.7	170.30	137.70	127.10	81.15	63.90	37.75
71		2	1	1	T	0.000	3.631	65.470	98.58	127.20	223.90	220.60	209.70	213.20	194.5	189.60	170.60	153.60	96.69	82.53	42.37
72		2	1	2	R	0.000	77.100	233.500	257.80	177.90	330.90	294.90	341.70	342.20	325.2	276.60	241.30	219.50	127.00	103.90	60.61
73		2	2	1	R	0.000	15.520	44.250	75.52	100.50	163.50	178.20	189.00	206.50	249.9	226.60	248.50	226.60	149.90	112.40	65.42
74		2	2	2	T	0.000	7.574	30.780	57.24	74.57	116.50	136.40	175.30	166.40	175.2	199.30	220.20	205.40	133.60	111.40	69.67
75		2	1	1	T	0.000	52.190	75.180	76.48	97.38	159.70	135.40	195.20	217.80	265.5	258.00	232.70	204.10	150.50	119.80	72.38
76		2	1	2	R	0.000	20.220	57.610	78.71	108.30	110.10	172.10	205.70	248.80	277.9	262.10	243.10	216.60	149.40	113.60	69.21
77		2	2	1	R	0.000	12.670	42.650	71.23	100.70	173.80	196.20	247.10	243.10	313.2	326.50	271.20	296.50	182.60	142.10	84.54
78		2	2	2	T	0.000	17.620	35.140	62.99	73.91	96.53	123.70	152.70	190.80	201.2	225.20	255.70	237.00	134.70	118.70	72.69
79		2	1	1	T	0.000	24.840	66.840	111.70	192.10	190.50	212.10	286.80	265.40	273.1	239.40	200.00	160.10	106.60	76.93	44.62
80		2	1	2	R	0.000	34.710	104.000	155.40	182.30	206.20	333.30	324.80	364.70	324.7	366.70	270.50	219.80	126.70	99.78	52.37
81		2	2	1	R	0.000	23.230	56.700	104.90	126.70	170.50	204.40	235.60	259.40	310.0	318.00	303.50	262.50	192.50	155.60	90.81
82		2	2	2	T	0.000	29.590	70.590	88.98	143.10	184.80	211.70	246.10	244.80	269.9	262.70	236.70	207.10	159.50	132.00	74.70
83		2	2	1	R	0.000	28.230	73.040	77.56	120.90	273.80	228.70	272.70	292.80	268.8	306.30	309.20	273.50	193.20	144.50	83.90
84		2	2	2	T	0.000	5.083	26.570	44.16	77.50	98.53	123.70	181.20	253.30	236.3	265.20	255.60	237.10	148.90	114.30	70.22

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
85	(b) (6)	2	1	1	T	0.000	21.720	50.550	81.19	101.80	148.50	197.00	265.60	281.90	343.0	327.40	358.70	339.90	246.90	216.30	112.50
86		2	1	2	R	0.000	27.700	49.610	106.90	126.40	142.10	200.30	233.90	282.40	337.5	331.00	358.20	327.30	261.60	204.00	105.00
87		3	1	1	T	0.000	16.270	39.920	74.83	123.80	128.40	187.40	209.50	273.40	300.2	323.70	309.90	317.30	272.20	180.20	94.43
88		3	1	2	R	0.000	13.380	33.600	75.34	102.00	139.40	181.30	265.90	260.30	345.6	339.40	290.20	229.10	243.90	169.90	95.82
89		3	2	1	R	0.000	34.120	56.310		159.10	188.60	238.00	333.20	334.20	314.1	307.50	280.90	242.90	165.50	115.50	73.89
90		3	2	2	T	0.000		57.050	91.65	116.20	181.90	207.80	291.30	309.80	287.5	319.00	283.20	249.40	157.70	125.50	94.70
91		3	2	1	R	0.000	23.020	65.210	120.80	171.90	229.30	292.70	308.90	331.00	351.6	325.70	282.40	271.80	156.80	121.40	84.76
92		3	2	2	T	0.000	31.970	46.360	78.13	97.36	160.10	190.10	263.80	271.90	251.9	248.30	198.20	183.50	108.30		
93		3	2	1	R	0.000	9.162	25.060	55.00	113.90	120.30	176.80	226.30	227.40	234.5	232.20	162.60	122.00	80.97	69.61	39.22
94		3	2	2	T	0.000	6.198	13.870	54.99	77.10	93.23	129.00	151.90	185.30	197.5	179.30	145.60	115.30	74.65	53.87	30.90
95		3	2	1	R	0.000	34.050	32.260	58.06	75.54	103.30	158.90	185.70	195.60	195.4	200.50	190.60	178.50	139.80	105.10	65.61
96		3	2	2	T	0.000	7.979	24.910	61.04	93.05	110.00	120.90	163.40	168.50	188.2	162.10	164.70	172.30	104.80	79.52	44.55
97		3	1	1	T	0.000	6.859	26.450	47.18	69.73	90.70	129.10	165.60	204.80	209.8	224.20	213.40	204.60	117.00	84.90	59.83
98		3	1	2	R	0.000	4.728	22.870	44.84	71.61	96.61	128.20	162.40	182.50	221.1	234.30	214.50	202.60	141.60	103.00	73.34
99		3	2	1	R	0.000	5.120	15.860	68.00	116.00	116.90	166.20	184.50	187.30	216.9	230.20	207.50	219.30	172.90	135.40	87.57
100		3	2	2	T	0.000	14.710	29.620	67.44	114.70	126.40	163.40	193.40	215.20	229.0	272.10	252.90	234.20	164.30	124.40	78.00
101		3	1	1	T	0.000	13.750	46.830	61.03	100.60	124.30	165.60	227.50	268.00	264.7	237.20	226.40	216.00	138.40	119.00	73.76
102		3	1	2	R	0.000	7.018	24.080	74.59	68.30	106.10	149.00	220.00	242.80	299.9	277.40	251.90	213.00	151.80	125.10	74.79
103		3	1	1	T	0.000	6.832	24.660	40.83	44.99	98.87	136.00	119.00	198.20	205.0	178.60	181.20	200.30	111.10	92.21	55.86
104		3	1	2	R	0.000	5.486	29.260	37.59	60.59	53.78	91.01	92.64	148.30	168.3	196.90	156.10	158.80	83.75	74.24	51.89
105	3	2	1	R	0.000	30.730	61.820	111.30	133.20	196.60	229.40	321.30	318.60	291.0	278.70	258.50	245.50	156.30	129.70	85.60	
106	3	2	2	T	0.000	63.420	47.920	101.20	163.50	156.60	268.30	287.40	284.40	274.8	278.60	248.30	218.50	142.30	110.60	70.66	
107	3	2	1	R	0.000	19.300	58.640	101.00	156.70	194.50	238.00	282.60	259.00	264.4	234.30	198.50	216.90	136.80	106.90	64.70	
108	3	2	2	T	1.054	17.660	146.000	129.10	171.70	182.40	226.00	299.50	313.80	292.2	306.10	264.50	224.00	151.20	114.10	85.66	
109	3	1	1	T	0.000	29.730	43.110	91.90	158.10	166.40	197.70	346.30	368.40	293.6	332.90	295.20	246.60	168.20	116.20	66.36	
110	3	1	2	R	0.000	21.680	37.810	71.94	124.50	155.70	229.00	254.30	263.60	271.1	306.20	282.00	252.70	143.90	97.39	59.76	
111	3	1	1	T	0.000	12.320	26.750	44.08	73.58	87.01	128.70	141.90	152.30	155.2	162.20	151.40	131.00	91.73	66.53	38.31	
112	3	1	2	R	0.000	22.600	44.950	92.08	139.30	138.80	188.20	208.30	227.10	234.2	213.10	184.30	158.20	104.60	76.76	42.80	
113	3	2	1	R	0.000	18.060	38.670	61.30	111.20	117.00	161.60	230.80	234.00	297.5	339.00	341.80	310.80	200.20	139.90	84.39	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
114	(b) (6)	3	2	2	T	0.000	37.090	79.010		177.80	159.30	314.00	304.10	305.40	329.8	328.30	316.70	308.40	185.00	160.70	100.60
115		3	1	1	T	0.000	10.510	57.740			133.50	162.50	199.40	202.40	215.8	226.80	224.50	220.70	154.60	118.30	77.50
116		3	1	2	R	0.000		50.600	77.62	89.41	137.40	176.10	210.50	232.60	241.4	235.80	236.10	207.00	143.40	115.40	74.48
117		3	1	1	T	0.000	17.550	24.430	64.31	85.04	92.62	127.10	189.00	211.00	258.7	277.90	314.00	291.10	215.10	157.80	110.30
118		3	1	2	R	0.000	14.310	27.210	36.98	87.65	92.63	114.00	152.50	158.90	222.9	235.40	282.10	255.10	164.10	135.40	77.72
119		3	1	1	T	0.000	24.010	56.340	85.21	136.50	148.60	181.20	218.40	225.40	221.4	270.90	272.20	253.40	169.70	128.90	77.44
120		3	1	2	R	0.000	17.120	54.960	68.09	118.30	170.70	170.10	241.10	233.90	271.7	248.50	273.30	245.60	148.20	122.80	71.89
121		3	2	1	R	0.000	69.570	105.000	138.50	136.20	199.20	187.30	221.10	271.40	280.6	254.20	229.00	209.90	160.50	133.90	70.67
122		3	2	2	T	0.000	24.420	108.300	99.05	97.53	174.30	150.90	192.30	190.10	164.5	167.40	155.60	140.00	111.00	91.34	65.81
123		3	2	1	R	0.000	17.760	37.670	67.92	96.62	118.10	145.40	198.70	204.70	221.3	230.50	228.60	204.70	112.60	91.95	60.66
124		3	2	2	T	0.000	14.050	39.990	54.63	81.25	91.25	119.20	184.80	176.10	163.8	152.80	137.60	138.50	88.11	65.67	43.97
125		3	2	1	R	0.000	15.070	53.650	71.17	100.50	98.38	169.50	180.40	250.50	240.3	264.80	272.50	238.10	141.00	107.90	72.41
126		3	2	2	T	0.000	25.220	70.350	72.94	86.78	163.50	177.50	163.10	190.90	200.0	184.10	183.30	176.90	121.70	91.02	56.39
127		3	1	1	T	0.000	83.510	140.600	200.30	239.70	240.20	361.30	371.50	394.80	339.2	381.50	315.30	287.40	192.30	142.90	82.07
128		3	1	2	R	0.000	116.200	204.800	285.80	305.30	345.70	310.70	333.50	328.80	339.3	306.10	248.20	207.00	144.70	114.30	60.48

Obs	c17	c18	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
1	49.310	26.300	16.390	16	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
2	57.460	29.050	20.540	16	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
3	35.090	18.310	8.818	16	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
4	40.180	18.320	12.240	16	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
5	33.060	20.010	12.590	16	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
6	33.130	16.940	15.580	16	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
7	40.340	19.550	10.460	16	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
8	35.390	19.300	8.807	16	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.55000	0.75000	1.00000	1.50000	2.00000	3.00000
9	37.230	13.680	6.251	16	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
10	25.740	13.690	8.905	16	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
11	32.800	19.990	14.140	16	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
12	19.570	11.620	8.260	16	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000

Obs	c17	c18	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
13	24.420	12.640	8.315	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
14	32.760	22.520	12.290	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
15	36.100	21.640	13.390	16	19	0	0.033333	0.11667	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
16	29.670	21.270	12.190	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.56667	0.75000	1.00000	1.50000	2.00000	3.00000
17	21.710	13.490	7.643	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
18	19.880	7.496	6.239	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
19	32.080	16.730	12.630	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
20	18.260	12.680	8.876	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
21	55.320	25.700	20.420	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
22	49.600	31.360	17.240	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.53333	0.75000	1.00000	1.50000	2.00000	3.00000
23	24.930	16.000	9.870	16	19	0	0.033333	0.083333	0.21667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
24	23.840	17.380	7.829	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
25	14.780	5.547	2.490	16	19	0	0.050000	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.05000
26	5.907	2.536	1.337	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
27	50.500	17.040	8.005	16	19	0	0.033333	0.10000	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
28	63.520	26.010	11.780	16	19	0	0.033333	0.083333	0.16667	0.28333	0.35000	0.50000	0.75000	1.00000	1.50000	2.00000	3.03333
29	31.240	13.450	10.720	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.05000	3.00000
30	32.440	15.290	9.554	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
31	9.452	5.262	3.773	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
32	5.561	3.353	2.334	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
33	45.650	13.830	11.300	16	19	0	0.033333	0.083333	0.21667	0.25000	0.33333	0.50000	0.75000	1.00000	1.56667	2.00000	3.00000
34	39.780	16.090	10.010	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.05000	1.50000	2.00000	3.11667
35	21.610	10.320	5.852	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
36	15.590	8.031	4.670	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.05000
37	32.700	17.480	14.350	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
38	29.680	15.810	10.430	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
39	28.560	14.160	12.960	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
40	37.210	16.540	10.890	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
41	23.080	8.366	5.557	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000

Obs	c17	c18	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
42	26.590	15.120	10.160	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
43	30.150	11.990	6.878	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
44	36.750	13.240	8.010	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
45	18.890	12.280	7.095	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
46	27.890	11.370	9.683	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
47	17.730	7.701	6.901	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
48	20.030	10.150	7.274	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.53333	0.75000	1.00000	1.50000	2.00000	3.00000
49	45.170	15.260	6.755	16	19	0	0.033333	0.083333	0.16667	0.25000	0.36667	0.50000	0.75000	1.00000	1.65000	2.00000	3.00000
50	37.830	12.300	9.342	16	19	0	0.033333	0.083333	0.16667	0.25000	0.35000	0.53333	0.75000	1.00000	1.50000	2.00000	3.00000
51	23.540	11.710	6.723	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
52	21.580	8.925	5.189	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
53	33.220	15.860	10.360	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
54	24.200	14.030	8.668	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
55	15.630	5.747	4.900	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
56	15.790	6.237	5.049	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
57	18.560	7.698	3.168	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
58	16.730	8.046	5.096	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
59	27.120	12.120	5.932	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
60	20.470	8.501	5.630	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
61	22.080	13.700	8.705	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
62	19.200	10.780	7.579	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
63	41.720	17.990	9.514	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
64	50.170	21.790	14.740	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
65	34.370	19.120	15.570	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
66	34.790	18.920	10.400	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
67	30.740	21.450	12.030	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
68	49.770	27.650	2.374	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
69	12.280	6.196	2.524	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
70	13.750	7.945	3.678	16	19	0	0.033333	0.083333	0.16667	0.25000	0.36667	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000

Obs	c17	c18	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
71	17.860	7.262	4.421	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
72	20.540	5.202	3.799	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
73	22.790	8.543	5.159	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.05000	1.50000	2.00000	3.00000
74	30.820	12.290	7.952	16	19	0	0.033333	0.083333	0.16667	0.25000	0.38333	0.50000	0.75000	1.00000	1.50000	2.00000	3.05000
75	27.210	14.390	7.529	16	19	0	0.050000	0.10000	0.18333	0.26667	0.35000	0.51667	0.76667	1.01667	1.51667	2.01667	3.01667
76	23.230	10.990	5.352	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
77	41.720	28.510	16.620	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
78	35.810	19.970	14.980	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
79	22.090	11.530	6.078	16	19	0	0.033333	0.083333	0.16667	0.28333	0.33333	0.51667	0.75000	1.00000	1.50000	2.00000	3.00000
80	26.800	15.460	7.953	16	19	0	0.033333	0.083333	0.20000	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
81	31.430	13.980	8.420	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
82	31.780	18.460	9.273	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
83	29.970	12.540	9.802	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
84	29.810	13.840	7.560	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
85	59.440	36.830	22.370	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
86	55.340	25.220	15.980	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
87	42.400	21.850	20.920	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
88	32.750	16.820	10.880	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
89	26.660	12.500	4.608	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
90	41.920	23.470	15.370	16	19	0	0.033333	0.11667	0.16667	0.25000	0.36667	0.50000	0.83333	1.00000	1.50000	2.00000	3.00000
91	28.350	15.100	8.288	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
92	21.280	14.310	9.154	14	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
93	11.340	4.812	2.579	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
94	12.530	5.822	3.958	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
95	24.910	12.450	8.359	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
96	22.130	8.909	7.278	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
97	30.840	12.640	11.600	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
98	27.450	12.220	8.032	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
99	34.410	12.430	6.148	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000

Obs	c17	c18	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
100	37.090	14.060	7.071	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
101	32.100	14.730	8.853	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
102	29.070	9.321	7.075	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
103	29.040	12.260	8.475	16	19	0	0.033333	0.083333	0.16667	0.25000	0.36667	0.50000	0.80000	1.00000	1.50000	2.03333	3.00000
104	22.410	9.554	4.993	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
105	33.640	19.740	12.350	16	19	0	0.033333	0.083333	0.16667	0.28333	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
106	37.300	20.610	12.080	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
107	21.690	14.020	10.270	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
108	34.410	18.630	13.060	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
109	28.320	13.210	10.660	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
110	18.840	8.240	7.116	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
111	18.340	7.031	4.791	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
112	16.480	6.810	4.036	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.76667	1.00000	1.50000	2.00000	3.00000
113	41.990	18.770	12.470	16	19	0	0.033333	0.083333	0.16667	0.28333	0.33333	0.50000	0.75000	1.00000	1.58333	2.00000	3.00000
114	50.050	29.070	14.710	16	19	0	0.033333	0.083333	0.16667	0.28333	0.41667	0.58333	0.75000	1.00000	1.50000	2.00000	3.00000
115	36.030	13.740	10.260	16	19	0	0.033333	0.15000	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.11667
116	28.190	11.930	5.998	16	19	0	0.033333	0.11667	0.18333	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
117	46.410	20.280	16.640	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
118	27.600	12.570	8.065	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
119	32.310	14.850	11.500	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
120	25.270	13.570	9.611	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
121	21.600	9.310	5.789	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
122	28.240	10.840	7.247	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
123	26.720	12.950	12.400	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
124	21.670	13.020	8.876	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.78333	1.00000	1.50000	2.00000	3.00000
125	31.730	13.590	8.506	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
126	27.990	13.790	9.375	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
127	44.730	25.130	17.060	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
128	27.750	16.990	9.411	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000

Obs	T13	T14	T15	T16	T17	T18	T19	trt
1	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
2	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
3	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
4	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
5	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
6	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
7	4.00000	6.00000	8.00000	12.0333	24.0000	36.0000	48.000	1
8	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
9	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
10	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
11	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
12	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
13	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
14	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
15	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
16	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
17	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
18	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
19	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
20	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
21	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
22	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
23	4.00000	6.06667	8.00000	12.0000	24.0000	36.0000	48.000	1
24	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
25	4.00000	6.00000	8.03333	12.0167	24.0000	36.0000	48.000	1
26	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
27	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.617	2
28	4.03333	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1

Obs	T13	T14	T15	T16	T17	T18	T19	trt
29	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
30	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
31	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
32	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
33	4.00000	6.10000	8.00000	12.0333	24.0000	36.0000	48.000	2
34	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
35	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
36	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
37	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
38	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
39	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
40	4.00000	6.00000	8.00000	12.0000	24.0000	37.9167	48.000	2
41	4.00000	6.00000	8.00000	12.0500	24.0000	36.0000	48.000	1
42	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
43	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
44	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
45	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
46	4.00000	6.00000	8.00000	12.0000	24.0000	37.9167	48.000	1
47	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
48	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
49	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
50	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.133	2
51	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
52	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
53	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
54	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.017	2
55	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
56	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
57	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2

Obs	T13	T14	T15	T16	T17	T18	T19	trt
58	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
59	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
60	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
61	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
62	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
63	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
64	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
65	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
66	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
67	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
68	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	126.000	1
69	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
70	4.03333	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
71	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
72	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
73	4.00000	6.00000	8.06667	12.0000	24.0000	36.1333	48.000	2
74	4.00000	6.00000	8.00000	12.1333	24.0167	36.0000	48.000	1
75	4.01667	6.01667	8.01667	12.0167	24.0167	36.0167	48.017	1
76	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
77	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
78	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
79	4.00000	6.00000	8.00000	12.0000	24.0000	36.2000	48.000	1
80	4.00000	6.03333	8.00000	12.0000	24.0000	36.1000	48.000	2
81	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
82	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
83	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
84	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
85	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
86	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2

Obs	T13	T14	T15	T16	T17	T18	T19	trt
87	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.133	1
88	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
89	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.067	2
90	4.00000	6.00000	8.00000	12.0833	24.0000	36.1333	48.050	1
91	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
92	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
93	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
94	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
95	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
96	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
97	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
98	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
99	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
100	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
101	4.00000	6.00000	8.00000	12.0000	24.0167	36.0000	48.000	1
102	4.00000	6.00000	8.00000	12.0000	24.0000	36.0667	48.000	2
103	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
104	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
105	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
106	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
107	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
108	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
109	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
110	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
111	4.00000	6.00000	8.01667	12.0000	24.0000	36.0000	48.000	1
112	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
113	4.03333	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
114	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
115	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1

Obs	T13	T14	T15	T16	T17	T18	T19	trt
116	4.00000	6.00000	8.00000	12.0000	24.0000	36.1167	48.100	2
117	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
118	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
119	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
120	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
121	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
122	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
123	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
124	4.00000	6.00000	8.00000	12.0000	24.0000	36.0667	48.000	1
125	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2
126	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
127	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	1
128	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.000	2

5.9.2.2 Fasting Study Output (FP)

Fasting STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	64	(b) (6)
trt	2	1 2
per	2	1 2
seq	2	1 2
GRP	3	1 2 3

Number of Observations Read	128
Number of Observations Used	128

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	67	13.95708114	0.20831464	10.29	<.0001
Error	60	1.21420870	0.02023681		
Corrected Total	127	15.17128984			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.919967	1.792283	0.142256	7.937149

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.07838759	0.07838759	3.87	0.0537
GRP	2	0.02814169	0.01407085	0.70	0.5029
seq	1	0.00899105	0.00899105	0.44	0.5076
seq*GRP	2	0.37337924	0.18668962	9.23	0.0003
sub(seq*GRP)	58	13.39367616	0.23092545	11.41	<.0001
per(GRP)	2	0.03231908	0.01615954	0.80	0.4547
trt	1	0.04218634	0.04218634	2.08	0.1540

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per	1	0.08060138	0.08060138	3.98	0.0505

Source	DF	Type III SS	Mean Square	F Value	Pr > F
GRP	2	0.01821524	0.00910762	0.45	0.6397
seq	1	0.01121862	0.01121862	0.55	0.4594
seq*GRP	2	0.37337924	0.18668962	9.23	0.0003
sub(seq*GRP)	58	13.39367616	0.23092545	11.41	<.0001
per(GRP)	2	0.03527429	0.01763714	0.87	0.4235
trt	1	0.04218634	0.04218634	2.08	0.1540

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01121862	0.01121862	0.05	0.8263
GRP	2	0.01821524	0.00910762	0.04	0.9614

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.03649682	0.02527785	-1.44	0.1540

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	67	14.12760237	0.21085974	10.61	<.0001
Error	60	1.19284793	0.01988080		
Corrected Total	127	15.32045030			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.922140	1.764032	0.140999	7.993012

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.08339252	0.08339252	4.19	0.0449
GRP	2	0.00798566	0.00399283	0.20	0.8186
seq	1	0.00623094	0.00623094	0.31	0.5777
seq*GRP	2	0.34679829	0.17339915	8.72	0.0005
sub(seq*GRP)	58	13.63375609	0.23506476	11.82	<.0001
per(GRP)	2	0.03787016	0.01893508	0.95	0.3916
trt	1	0.01156871	0.01156871	0.58	0.4486

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per	1	0.08574907	0.08574907	4.31	0.0421
GRP	2	0.00392443	0.00196221	0.10	0.9062
seq	1	0.00803820	0.00803820	0.40	0.5273
seq*GRP	2	0.34679829	0.17339915	8.72	0.0005
sub(seq*GRP)	58	13.63375609	0.23506476	11.82	<.0001
per(GRP)	2	0.03930913	0.01965457	0.99	0.3781
trt	1	0.01156871	0.01156871	0.58	0.4486

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00803820	0.00803820	0.03	0.8539
GRP	2	0.00392443	0.00196221	0.01	0.9917

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.01911224	0.02505452	-0.76	0.4486

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	67	8.04229536	0.12003426	6.52	<.0001
Error	60	1.10432375	0.01840540		
Corrected Total	127	9.14661911			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.879264	2.427335	0.135666	5.589114

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.03597317	0.03597317	1.95	0.1673
GRP	2	0.06289482	0.03144741	1.71	0.1898
seq	1	0.05919668	0.05919668	3.22	0.0779
seq*GRP	2	0.10557751	0.05278875	2.87	0.0646
sub(seq*GRP)	58	7.39610710	0.12751909	6.93	<.0001
per(GRP)	2	0.00791626	0.00395813	0.22	0.8071
trt	1	0.37462981	0.37462981	20.35	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per	1	0.03690945	0.03690945	2.01	0.1619
GRP	2	0.07254248	0.03627124	1.97	0.1483
seq	1	0.05570616	0.05570616	3.03	0.0870
seq*GRP	2	0.10557751	0.05278875	2.87	0.0646
sub(seq*GRP)	58	7.39610710	0.12751909	6.93	<.0001
per(GRP)	2	0.01293552	0.00646776	0.35	0.7051
trt	1	0.37462981	0.37462981	20.35	<.0001

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.05570616	0.05570616	0.44	0.5113
GRP	2	0.07254248	0.03627124	0.28	0.7535

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.10876028	0.02410692	-4.51	<.0001

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	trt	AUCRATIO
1	(b) (6)	1	0.93
2		1	0.94
3		1	0.90
4		1	0.96
5		1	0.93
6		1	0.91
7		1	0.91
8		1	0.89
9		1	0.93
10		1	0.89
11		1	0.94
12		1	0.92
13		1	0.98
14		1	0.97
15		1	0.93
16		1	0.93
17		1	0.95
18		1	0.95

Obs	sub	trt	AUCRATIO
19	(b) (6)	1	0.92
20		1	0.89
21		1	0.95
22		1	0.97
23		1	0.94
24		1	0.91
25		1	0.98
26		1	0.95
27		1	0.94
28		1	0.95
29		1	0.95
30		1	0.96
31		1	0.93
32		1	0.94
33		1	0.93
34		1	0.99
35		1	0.97
36		1	0.97
37		1	0.95
38		1	0.96
39		1	0.90
40		1	0.95
41		1	0.95
42		1	0.96
43		1	0.91
44		1	0.90
45		1	0.92
46		1	0.95
47		1	0.96
48		1	0.94
49		1	0.91
50		1	0.97
51		1	0.95
52		1	0.94
53		1	0.93
54		1	0.93
55		1	0.94
56		1	0.96
57		1	0.94
58		1	0.94

Obs	sub	trt	AUCRATIO
59	(b) (6)	1	0.93
60		1	0.94
61		1	0.95
62		1	0.90
63		1	0.93
64		1	0.91
65		2	0.94
66		2	0.96
67		2	0.91
68		2	0.97
69		2	0.98
70		2	0.93
71		2	0.94
72		2	0.92
73		2	0.93
74		2	0.90
75		2	0.95
76		2	0.94
77		2	0.98
78		2	0.98
79		2	0.96
80		2	0.95
81		2	0.96
82		2	0.96
83		2	0.95
84		2	0.96
85		2	0.93
86		2	0.97
87		2	0.96
88		2	0.94
89		2	0.96
90		2	0.97
91		2	0.94
92		2	0.96
93		2	0.98
94		2	0.97
95		2	0.94
96		2	0.97
97		2	0.96
98		2	0.95

Obs	sub	trt	AUCRATIO
99	(b) (6)	2	0.98
100		2	0.98
101		2	0.97
102		2	0.97
103		2	0.91
104		2	0.95
105		2	0.97
106		2	0.96
107		2	0.94
108		2	0.95
109		2	0.98
110		2	0.96
111		2	0.98
112		2	0.94
113		2	0.95
114		2	0.97
115		2	0.97
116		2	0.96
117		2	0.94
118		2	0.93
119		2	0.96
120		2	0.97
121		2	0.94
122		2	0.97
123		2	0.96
124		2	0.94
125		2	0.97
126		2	0.90
127		2	0.95
128		2	0.94

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

sub	seq	RAUCT12	RAUC12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	2	1.03	1.04	0.96	1.00	0.95	1.06
	2	1.07	1.09	1.10	0.75	0.90	1.11
	1	0.81	0.81	0.79	1.33	0.95	1.05
	1	0.88	0.90	0.81	3.64	0.91	1.10
	2	0.64	0.67	0.54	2.00	0.69	1.45
	1	1.40	1.43	1.12	1.00	0.94	1.07

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	2	1.04	1.08	0.79	1.33	0.84	1.19
	2	0.77	0.79	0.70	1.33	0.87	1.15
	2	0.69	0.70	0.65	1.50	1.06	0.95
	1	1.23	1.25	0.93	1.00	1.05	0.96
	1	1.02	1.03	0.85	1.33	0.99	1.01
	1	0.97	1.00	0.97	2.00	0.89	1.12
	1	1.79	1.79	1.42	1.33	1.08	0.92
	2	1.26	1.27	1.24	0.76	0.92	1.09
	1	0.77	0.79	0.81	0.25	0.87	1.16
	1	1.20	1.23	1.07	0.75	0.94	1.06
	2	0.85	0.86	0.75	1.99	0.94	1.07
	2	0.68	0.69	0.77	0.38	0.83	1.20
	1	1.03	1.06	1.02	0.33	0.86	1.17
	1	0.66	0.70	0.70	0.75	0.71	1.42
	1	0.68	0.67	0.58	1.00	1.17	0.86
	2	1.07	1.08	1.04	0.50	0.95	1.05
	2	0.96	0.98	0.82	0.50	0.91	1.09
	2	0.80	0.83	0.86	0.33	0.81	1.24
	1	1.09	1.07	1.17	0.41	1.16	0.86
	1	0.92	0.94	0.82	1.00	0.87	1.15
	1	1.22	1.21	1.23	1.33	1.05	0.96
	2	0.91	0.92	0.89	1.00	0.89	1.12
	2	0.96	0.99	1.22	1.50	0.78	1.29
	1	0.94	0.95	0.94	1.50	0.91	1.09
	1	1.01	1.02	0.89	1.00	0.97	1.03
	2	1.03	1.06	0.93	0.67	0.85	1.17
	1	0.91	0.94	0.82	1.00	0.86	1.16
	2	1.33	1.29	0.85	2.00	0.57	1.76
	2	0.94	0.96	0.90	1.33	0.85	1.18
	1	0.73	0.75	0.65	0.33	0.79	1.26
	2	1.00	1.02	0.88	2.03	0.87	1.15
	1	1.03	1.05	0.96	1.01	0.88	1.13
	2	0.80	0.81	0.78	1.50	1.01	0.99
	1	0.78	0.77	0.78	0.38	1.07	0.94
	2	0.88	0.90	0.85	0.75	0.86	1.17
	2	0.84	0.84	0.86	0.67	1.02	0.98
	1	1.07	1.11	1.00	1.00	0.83	1.21
	1	1.11	1.19	0.94	1.33	0.72	1.39
	2	1.17	1.25	0.95	2.00	0.67	1.50
	2	0.79	0.80	0.77	0.67	0.99	1.01

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	2	0.87	0.89	0.84	1.00	0.77	1.30
	2	0.81	0.81	0.94	0.75	0.92	1.08
	1	0.94	0.99	0.96	1.00	0.78	1.28
	2	1.02	1.02	1.18	1.00	0.91	1.10
	1	1.00	1.02	0.89	0.67	0.87	1.15
	1	1.20	1.24	1.04	0.75	0.83	1.21
	2	0.93	0.94	0.89	1.00	0.93	1.08
	2	1.23	1.23	1.11	1.33	1.05	0.95
	1	1.17	1.19	1.20	0.50	0.87	1.15
	1	0.86	0.87	0.69	1.33	0.90	1.11
	2	1.12	1.13	0.96	0.50	0.96	1.04
	1	1.06	1.09	0.94	1.33	0.84	1.19
	1	1.32	1.37	1.11	1.00	0.86	1.17
	1	1.07	1.08	1.00	1.00	0.98	1.02
	2	0.82	0.83	0.69	0.50	0.91	1.10
	2	0.75	0.75	0.80	0.39	0.97	1.03
	2	0.82	0.84	0.73	0.50	0.84	1.19
	1	1.31	1.36	1.14	3.00	0.87	1.15

5.9.2.3 Firm Reviewer Ratio (FP)

Obs	sub (b) (6)	GRP	seq	per	trt	FDAAREA	FDAAUICI	FDACMAX	treat	FIRMAREA	FIRMAUICI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1		1	2	1	2	4505.08	4788.35	303.5	R	4390.27	4655.35	303.5	0.97451	0.97222	1
2		1	2	2	1	4626.44	5001.02	290.4	T	4514.93	4850.12	290.4	0.97590	0.96983	1
3		1	2	1	2	3465.45	3610.54	332.9	R	3390.94	3536.03	332.9	0.97850	0.97936	1
4		1	2	2	1	3695.22	3918.31	365.5	T	3620.98	3844.07	365.5	0.97991	0.98105	1
5		1	1	1	1	2726.52	3015.11	232.3	T	2687.14	2975.74	232.3	0.98556	0.98694	1
6		1	1	2	2	3382.58	3722.54	295.7	R	3316.79	3541.31	295.7	0.98055	0.95132	1
7		1	1	1	1	3810.68	3986.50	350.9	T	3732.39	3908.21	350.9	0.97946	0.98036	1
8		1	1	2	2	4307.63	4442.00	434.1	R	4203.41	4355.38	434.1	0.97580	0.98050	1
9		1	2	1	2	3606.40	3687.67	347.6	R	3503.16	3584.21	347.6	0.97137	0.97194	1
10		1	2	2	1	2313.58	2481.99	189.3	T	2266.38	2434.78	189.3	0.97960	0.98098	1
11		1	1	1	1	3093.32	3413.32	269.9	T	3041.11	3361.10	269.9	0.98312	0.98470	1
12		1	1	2	2	2204.48	2379.91	241.1	R	2161.35	2336.79	241.1	0.98044	0.98188	1
13		1	2	1	2	2533.63	2687.25	232.3	R	2480.34	2633.96	232.3	0.97897	0.98017	1
14		1	2	2	1	2631.28	2901.42	182.4	T	2587.91	2858.05	182.4	0.98352	0.98505	1
15		1	2	1	2	3350.67	3644.06	388.2	R	3302.79	3596.18	388.2	0.98571	0.98686	1
16		1	2	2	1	2570.81	2877.05	271.6	T	2537.32	2843.55	271.6	0.98697	0.98836	1
17		1	2	1	2	2211.78	2368.32	267.3	R	2174.90	2331.44	267.3	0.98333	0.98443	1
18		1	2	2	1	1534.42	1655.34	172.7	T	1508.14	1617.34	172.7	0.98287	0.97704	1
19		1	1	1	1	2559.11	2874.91	273.0	T	2527.17	2842.97	273.0	0.98752	0.98889	1
20		1	1	2	2	2072.53	2304.62	292.0	R	2040.33	2210.09	292.0	0.98447	0.95898	1
21		1	1	1	1	5455.13	5816.19	434.6	T	5316.93	5604.93	434.6	0.97467	0.96368	1
22		1	1	2	2	5333.85	5636.64	508.7	R	5201.76	5475.68	508.7	0.97523	0.97144	1
23		1	1	1	1	2327.91	2533.02	190.6	T	2281.66	2486.77	190.6	0.98013	0.98174	1
24		1	1	2	2	2388.66	2533.62	196.4	R	2335.20	2460.42	196.4	0.97762	0.97111	1

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
25	(b) (6)	1	1	1	1	1474.58	1508.40	175.8	T	1439.66	1473.48	175.8	0.97631	0.97684	1
26		1	1	2	2	822.87	842.56	124.1	R	803.71	823.40	124.1	0.97672	0.97726	1
27		1	2	1	2	4128.46	4230.83	286.0	R	3993.07	4092.58	286.0	0.96721	0.96732	1
28		1	2	2	1	5191.96	5355.48	355.3	T	5046.34	5209.85	355.3	0.97195	0.97281	1
29		1	1	1	1	2828.47	3026.22	253.0	T	2768.27	2916.13	253.0	0.97872	0.96362	1
30		1	1	2	2	3666.48	3818.97	311.2	R	3572.33	3703.56	311.2	0.97432	0.96978	1
31		1	1	1	1	1040.35	1119.39	150.4	T	1022.71	1101.74	150.4	0.98303	0.98423	1
32		1	1	2	2	864.68	910.69	140.2	R	846.77	892.78	140.2	0.97929	0.98034	1
33		1	2	1	2	3992.04	4162.37	317.7	R	3885.10	4028.73	317.7	0.97321	0.96789	1
34		1	2	2	1	3403.00	3563.73	237.1	T	3321.59	3482.32	237.1	0.97608	0.97716	1
35		1	2	1	2	2360.50	2452.07	230.7	R	2300.82	2386.05	230.7	0.97472	0.97307	1
36		1	2	2	1	1601.07	1688.87	177.6	T	1572.91	1660.71	177.6	0.98241	0.98333	1
37		1	1	1	1	3550.27	3846.15	334.8	T	3477.93	3673.63	334.8	0.97962	0.95514	1
38		1	1	2	2	3455.33	3639.39	329.5	R	3368.44	3522.67	329.5	0.97485	0.96793	1
39		1	1	1	1	2475.51	2770.57	215.3	T	2433.14	2672.98	215.3	0.98288	0.96478	1
40		1	1	2	2	3768.49	3943.68	305.5	R	3664.59	3823.32	305.5	0.97243	0.96948	1
41		1	1	1	1	1878.99	1973.55	207.0	T	1844.72	1930.11	207.0	0.98176	0.97799	1
42		1	1	2	2	2754.99	2956.88	355.8	R	2705.34	2888.86	355.8	0.98198	0.97700	1
43		2	2	1	2	3467.15	3562.88	325.6	R	3366.60	3445.87	325.6	0.97100	0.96716	1
44		2	2	2	1	3713.41	3830.46	340.0	T	3622.65	3717.63	340.0	0.97556	0.97054	1
45		2	2	1	2	3026.55	3142.75	319.0	R	2933.87	3017.55	319.0	0.96938	0.96016	1
46		2	2	2	1	2908.48	3082.05	262.8	T	2839.00	2965.51	262.8	0.97611	0.96219	1
47		2	2	1	2	2095.02	2219.04	242.5	R	2043.36	2130.42	242.5	0.97534	0.96006	1
48		2	2	2	1	1671.92	1833.99	207.4	T	1648.66	1810.72	207.4	0.98609	0.98731	1
49		2	1	1	1	3848.16	3933.96	332.0	T	3736.84	3820.60	332.0	0.97107	0.97118	1

Obs	sub (b) (6)	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
50		2	1	2	2	3540.45	3678.68	282.6	R	3439.04	3561.68	282.6	0.97136	0.96820	1
51		2	1	1	1	2249.44	2364.40	181.1	T	2198.57	2313.54	181.1	0.97739	0.97849	1
52		2	1	2	2	2439.11	2516.32	220.5	R	2373.34	2450.55	220.5	0.97304	0.97386	1
53		2	1	1	1	3095.37	3278.55	273.5	T	3027.05	3210.23	273.5	0.97793	0.97916	1
54		2	1	2	2	2543.68	2703.91	222.2	R	2485.27	2645.50	222.2	0.97704	0.97840	1
55		2	2	1	2	1816.61	1894.70	188.2	R	1765.15	1832.52	188.2	0.97167	0.96718	1
56		2	2	2	1	1651.01	1741.31	167.2	T	1613.69	1677.69	167.2	0.97739	0.96346	1
57		2	2	1	2	1804.64	1846.79	172.6	R	1757.87	1800.88	172.6	0.97409	0.97514	1
58		2	2	2	1	1739.39	1826.67	210.2	T	1702.44	1789.72	210.2	0.97875	0.97977	1
59		2	1	1	1	2552.87	2647.09	251.7	T	2496.64	2590.86	251.7	0.97797	0.97876	1
60		2	1	2	2	2718.83	2800.64	268.1	R	2638.61	2701.73	268.1	0.97049	0.96468	1
61		2	1	1	1	2464.12	2637.28	271.4	T	2416.24	2589.40	271.4	0.98057	0.98184	1
62		2	1	2	2	2431.08	2576.96	303.4	R	2380.71	2497.44	303.4	0.97928	0.96914	1
63		2	2	1	2	4027.78	4166.95	336.6	R	3922.74	4055.88	336.6	0.97392	0.97335	1
64		2	2	2	1	4163.88	4416.86	312.7	T	4070.07	4281.51	312.7	0.97747	0.96936	1
65		2	1	1	1	4101.17	4399.20	437.6	T	3995.30	4245.88	437.6	0.97419	0.96515	1
66		2	1	2	2	4485.70	4657.31	533.8	R	4382.47	4554.08	533.8	0.97699	0.97783	1
67		2	2	1	2	4261.17	4476.69	423.5	R	4148.61	4300.62	423.5	0.97358	0.96067	1
68		2	2	2	1	5678.24	5753.15	361.3	T	5167.78	5250.01	361.3	0.91010	0.91255	1
69		2	2	1	2	1760.38	1794.49	207.5	R	1711.32	1749.61	207.5	0.97213	0.97499	1
70		2	2	2	1	1663.06	1721.64	186.0	T	1623.39	1681.97	186.0	0.97614	0.97696	1
71		2	1	1	1	1978.02	2047.10	223.9	T	1932.28	2001.36	223.9	0.97687	0.97765	1
72		2	1	2	2	2694.52	2741.60	342.2	R	2613.27	2656.21	342.2	0.96985	0.96886	1
73		2	2	1	2	2653.59	2725.61	249.9	R	2578.01	2641.47	249.9	0.97152	0.96913	1
74		2	2	2	1	2655.87	2783.88	220.2	T	2593.57	2709.10	220.2	0.97654	0.97314	1

Obs	sub (b) (6)	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
75		2	1	1	1	2849.67	2971.33	265.5	T	2781.29	2902.94	265.5	0.97600	0.97699	1
76		2	1	2	2	2754.17	2830.37	277.9	R	2678.34	2765.84	277.9	0.97247	0.97720	1
77		2	2	1	2	3760.96	4140.08	326.5	R	3697.75	4076.87	326.5	0.98319	0.98473	1
78		2	2	2	1	3009.01	3346.75	255.7	T	2954.95	3292.69	255.7	0.98204	0.98385	1
79		2	1	1	1	2266.63	2376.81	286.8	T	2227.95	2338.13	286.8	0.98294	0.98373	1
80		2	1	2	2	2915.45	3069.41	366.7	R	2864.14	3018.10	366.7	0.98240	0.98329	1
81		2	2	1	2	3508.59	3635.77	318.0	R	3412.90	3523.80	318.0	0.97273	0.96920	1
82		2	2	2	1	3096.25	3259.84	269.9	T	3032.22	3195.80	269.9	0.97932	0.98036	1
83		2	2	1	2	3426.04	3586.89	309.2	R	3337.52	3464.44	309.2	0.97416	0.96586	1
84		2	2	2	1	2890.42	3012.13	265.2	T	2824.69	2946.40	265.2	0.97726	0.97818	1
85		2	1	1	1	4869.00	5373.17	358.7	T	4789.25	5293.43	358.7	0.98362	0.98516	1
86		2	1	2	2	4551.72	4849.77	358.2	R	4465.67	4763.73	358.2	0.98110	0.98226	1
87		3	1	1	1	4148.42	4634.70	323.7	T	4067.76	.	323.7	0.98056	.	1
88		3	1	2	2	3722.24	3903.75	345.6	R	3622.16	3761.87	345.6	0.97311	0.96366	1
89		3	2	1	2	3108.88	3169.86	334.2	R	3028.31	3089.29	334.2	0.97408	0.97458	1
90		3	2	2	1	3642.72	3948.45	319.0	T	3574.45	3863.77	319.0	0.98126	0.97855	1
91		3	2	1	2	3357.87	3488.65	351.6	R	3267.93	3385.91	351.6	0.97321	0.97055	1
92		3	2	2	1	2661.05	2807.48	271.9	T	2444.74	2602.05	271.9	0.91871	0.92683	1
93		3	2	1	2	1740.68	1774.98	234.5	R	1688.13	1729.93	234.5	0.96981	0.97462	1
94		3	2	2	1	1512.04	1580.56	197.5	T	1480.33	1548.85	197.5	0.97903	0.97993	1
95		3	2	1	2	2505.17	2651.08	200.5	R	2446.65	2562.14	200.5	0.97664	0.96645	1
96		3	2	2	1	2017.33	2154.97	188.2	T	1975.93	2088.92	188.2	0.97948	0.96935	1
97		3	1	1	1	2520.27	2759.72	224.2	T	2472.27	2678.13	224.2	0.98095	0.97044	1
98		3	1	2	2	2667.07	2796.55	234.3	R	2599.51	2722.03	234.3	0.97467	0.97335	1
99		3	2	1	2	3051.28	3133.37	230.2	R	2965.40	3044.57	230.2	0.97185	0.97166	1

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
100	(b) (6)	3	2	2	1	3101.46	3205.29	272.1	T	3031.16	3134.99	272.1	0.97733	0.97807	1
101		3	1	1	1	2924.68	3073.46	268.0	T	2860.38	3009.17	268.0	0.97802	0.97908	1
102		3	1	2	2	2914.65	3018.05	299.9	R	2835.63	2920.01	299.9	0.97289	0.96751	1
103		3	1	1	1	2361.43	2517.43	205.0	T	2312.65	2449.14	205.0	0.97934	0.97287	1
104		3	1	2	2	1959.81	2035.88	196.9	R	1909.98	1983.02	196.9	0.97457	0.97404	1
105		3	2	1	2	3378.96	3612.67	321.3	R	3306.37	3508.79	321.3	0.97852	0.97125	1
106		3	2	2	1	3153.35	3399.37	287.4	T	3104.47	3350.49	287.4	0.98450	0.98562	1
107		3	2	1	2	2701.67	2908.52	282.6	R	2635.85	2773.07	282.6	0.97564	0.95343	1
108		3	2	2	1	3318.98	3569.49	313.8	T	3250.91	3472.74	313.8	0.97949	0.97289	1
109		3	1	1	1	3151.43	3356.16	368.4	T	3088.01	3223.53	368.4	0.97987	0.96048	1
110		3	1	2	2	2701.35	2819.77	306.2	R	2626.58	2723.34	306.2	0.97232	0.96580	1
111		3	1	1	1	1712.70	1792.60	162.2	T	1677.45	1750.36	162.2	0.97942	0.97644	1
112		3	1	2	2	2000.79	2061.58	234.2	R	1953.71	2014.49	234.2	0.97647	0.97716	1
113		3	2	1	2	3718.66	3947.42	341.8	R	3647.13	3875.88	341.8	0.98076	0.98188	1
114		3	2	2	1	4180.19	4459.88	329.8	T	4103.69	4383.39	329.8	0.98170	0.98285	1
115		3	1	1	1	2969.22	3144.35	226.8	T	2904.32	3059.84	226.8	0.97814	0.97312	1
116		3	1	2	2	2802.84	2888.64	241.4	R	2729.40	2822.79	241.4	0.97380	0.97720	1
117		3	1	1	1	3953.78	4260.88	314.0	T	3864.46	4130.80	314.0	0.97741	0.96947	1
118		3	1	2	2	2985.18	3112.80	282.1	R	2902.07	3011.76	282.1	0.97216	0.96754	1
119		3	1	1	1	3165.40	3377.74	272.2	T	3095.89	3272.21	272.2	0.97804	0.96875	1
120		3	1	2	2	2952.26	3125.47	273.3	R	2877.55	3020.94	273.3	0.97469	0.96655	1
121		3	2	1	2	2822.28	2905.49	280.6	R	2736.69	2803.10	280.6	0.96967	0.96476	1
122		3	2	2	1	2305.55	2420.34	192.3	T	2251.37	2352.88	192.3	0.97650	0.97213	1
123		3	2	1	2	2544.40	2815.58	230.5	R	2492.60	2715.84	230.5	0.97964	0.96457	1
124	3	2	2	1	1898.91	2099.58	184.8	T	1869.28	2069.96	184.8	0.98440	0.98589	1	

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
125	(b) (6)	3	2	1	2	2933.41	3073.76	272.5	R	2867.64	3000.16	272.5	0.97758	0.97605	1
126	(b) (6)	3	2	2	1	2400.75	2585.45	200.0	T	2358.85	2543.56	200.0	0.98255	0.98380	1
127	(b) (6)	3	1	1	1	4008.41	4395.47	394.8	T	3949.72	4336.78	394.8	0.98536	0.98665	1
128	(b) (6)	3	1	2	2	3049.78	3235.77	345.7	R	2996.70	3182.69	345.7	0.98260	0.98360	1

5.9.2.4 Fasting Study Data (SA)

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KI
1	(b) (6)	1	2	1	R	0	438.00	485.50	330.00	197.40	163.30	131.20	104.70	92.99	96.42	101.20	67.95	46.590	35.080	25.230	17.270	7.714	2.580	1.757	
2		1	2	2	T	0	292.90	488.00	302.80	231.40	182.30	130.00	109.70	107.50	99.38	94.93	62.07	48.920	33.370	24.360	18.000	7.892	2.734	1.703	
3		1	2	1	R	0	346.50	431.00	298.00	223.60	176.90	161.80	134.90	110.60	88.33	79.60	55.47	47.700	36.150	26.760	15.340	8.195	3.444	1.755	
4		1	2	2	T	0	335.00	554.30	378.70	266.90	212.80	162.00	134.20	117.80	111.30	105.90	71.42	61.100	38.920	32.370	19.110	9.352	4.037	1.997	
5		1	1	1	T	0	195.10	332.30	261.60	200.70	166.00	128.90	117.50	99.05	116.90	113.90	64.30	55.170	35.260	24.700	15.400	7.919	3.653	2.044	
6		1	1	2	R	0	346.00	430.70	282.00	208.80	162.10	126.00	95.01	106.00	147.80	110.40	76.63	54.960	37.100	29.500	17.520	8.817	3.731	2.417	
7		1	1	1	T	0	147.70	568.50	378.40	293.80	223.00	171.30	161.00	133.20	101.00	86.35	60.52	45.170	32.700	24.070	14.750	7.624	2.962	1.805	
8		1	1	2	R	0	422.60	711.90	439.00	291.30	261.60	183.00	142.80	132.80	102.80	84.82	61.30	46.280	33.030	28.390	16.180	8.177	3.263	2.091	
9		1	2	1	R	0	240.60	432.50	352.20	232.40	167.50	133.20	113.10	99.88	96.16	73.19	52.47	39.850	29.940	23.630	15.940	8.168	3.472	1.780	
10		1	2	2	T	0	180.20	293.90	204.00	147.70	106.60	97.25	72.37	77.81	70.77	52.53	42.06	31.380	26.360	20.400	12.990	5.779	2.692	1.519	
11		1	1	1	T	0	165.10	297.30	248.00	177.70	135.20	104.70	90.23	67.74	78.41	70.04	54.66	45.950	33.810	24.240	15.130	9.016	4.175	1.983	
12		1	1	2	R	0	144.90	259.70	173.10	134.20	115.30	88.02	76.14	71.35	62.44	51.99	45.85	35.990	29.000	20.790	14.220	8.139	4.205	2.396	
13		1	2	1	R	0	218.40	322.30	211.40	146.40	119.90	88.73	79.54	64.90	52.07	49.07	40.36	32.400	23.230	17.160	10.850	7.225	3.039	1.877	
14		1	2	2	T	0	134.20	300.60	214.40	165.70	134.90	123.90	99.38	97.73	82.07	64.68	46.24	38.270	25.380	19.190	12.020	7.641	4.088	1.912	
15		1	2	1	R	0	624.20	459.50	303.00	218.10	158.00	124.90	113.60	100.20	84.99	69.82	43.64	31.920	24.110	18.730	10.190	5.255	2.110	1.320	
16		1	2	2	T	0	353.80	425.10	253.50	156.60	121.60	86.04	72.28	67.37	77.24	69.74	40.40	33.990	23.330	16.430	10.100	4.650	2.029	1.083	
17		1	2	1	R	0	160.50	256.80	191.20	138.40	126.50	110.90	86.88	74.99	70.48	80.23	65.92	41.170	26.380	19.120	11.200	4.987	1.920	1.074	
18		1	2	2	T	0	43.85	108.30	104.30	97.58	99.81	85.00	102.70	106.70	94.33	69.88	46.13	34.130	19.370	13.340	9.318	3.976	1.632	0.000	
19		1	1	1	T	0	171.60	241.30	179.10	149.70	143.00	151.50	154.40	144.70	109.40	84.30	50.53	39.850	26.800	18.390	11.020	6.573	2.652	1.523	
20		1	1	2	R	0	185.10	259.70	213.40	160.10	146.30	123.80	122.50	120.80	110.30	85.17	55.39	40.470	26.610	19.300	10.150	5.895	2.728	1.793	
21		1	1	1	T	0	280.90	663.50	567.50	362.50	315.40	259.70	220.30	205.00	153.30	150.90	102.30	85.240	63.830	41.990	29.700	12.600	4.570	2.341	
22		1	1	2	R	0	545.90	654.40	480.00	343.80	246.10	177.50	153.30	140.40	170.30	141.60	90.95	75.890	52.170	35.990	26.510	11.290	4.547	2.142	
23		1	1	1	T	0	240.60	406.60	258.10	214.50	173.80	138.30	107.80	100.70	92.28	78.34	54.91	42.050	26.910	18.540	11.680	4.765	2.073	0.000	
24		1	1	2	R	0	332.90	425.90	292.60	202.90	173.70	131.70	95.51	87.22	80.24	66.20	47.93	35.230	26.520	18.030	11.560	4.848	2.362	1.116	
25		1	1	1	T	0	93.30	111.40	88.01	60.15	45.47	43.91	39.89	39.90	36.64	38.69	22.05	16.470	14.480	8.919	6.400	3.215	1.557	0.000	
26		1	1	2	R	0	39.32	81.59	51.06	42.80	41.51	32.45	33.68	33.49	37.69	31.90	23.68	17.010	13.720	9.444	5.734	2.921	1.407	0.000	
27		1	2	1	R	0	339.30	366.50	269.20	184.50	127.50	87.33	76.19	62.02	51.14	41.26	26.86	26.560	18.740	14.120	11.240	5.228	2.474	1.650	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	K
28	(b) (6)	1	2	2	T	0	117.40	433.00	300.70	209.40	148.30	128.30	92.88	86.94	62.54	57.11	40.52	30.320	22.710	18.080	14.190	7.000	3.358	1.534	
29		1	1	1	T	0	163.10	370.70	235.60	179.50	142.90	110.90	110.10	98.92	83.07	71.06	46.58	35.420	20.460	15.040	8.520	3.722	1.457	0.000	
30		1	1	2	R	0	598.40	563.10	276.80	198.30	146.50	116.80	98.32	84.53	62.10	48.47	35.27	28.440	19.230	13.720	9.380	4.015	1.678	0.000	
31		1	1	1	T	0	42.10	114.80	95.50	91.45	101.60	104.70	123.50	117.50	103.20	93.69	62.16	42.710	24.210	16.390	10.930	5.686	2.583	1.476	
32		1	1	2	R	0	69.48	105.30	85.66	77.40	84.48	86.69	93.86	83.61	106.40	97.49	57.87	38.290	23.880	17.160	11.880	5.570	1.979	1.764	
33		1	2	1	R	0	387.80	537.00	282.30	232.70	186.20	139.90	118.50	99.01	71.28	61.18	42.70	33.280	23.350	17.520	11.680	7.098	2.334	1.665	
34		1	2	2	T	0	256.80	391.70	296.60	191.30	151.40	111.40	97.46	68.21	60.93	48.27	32.38	26.240	19.100	14.810	8.999	5.694	2.273	1.324	
35		1	2	1	R	0	184.80	288.20	164.50	116.00	94.34	69.56	60.66	57.49	42.06	33.71	22.21	18.450	14.500	10.900	8.105	4.684	2.060	1.532	
36		1	2	2	T	0	106.70	165.10	90.35	60.64	44.46	38.69	32.71	25.66	20.41	15.26	11.41	9.552	7.469	6.137	3.864	2.305	1.289	0.000	
37		1	1	1	T	0	281.00	623.10	402.10	274.20	224.40	147.20	118.70	90.06	86.75	71.73	44.03	35.820	23.900	18.680	12.090	4.481	1.557	1.109	
38		1	1	2	R	0	434.90	587.00	365.20	244.00	190.50	130.00	95.20	75.79	60.77	52.00	39.33	28.680	20.500	16.470	9.458	4.313	1.816	1.124	
39		1	1	1	T	0	264.20	483.80	366.40	271.70	232.10	192.80	175.60	182.30	183.60	174.40	145.90	123.900	101.300	67.930	37.190	18.680	6.777	4.685	
40		1	1	2	R	0	395.40	549.80	349.60	252.30	187.30	134.60	111.40	94.92	86.43	83.41	64.02	55.490	41.250	32.180	23.010	12.140	4.359	3.507	
41		2	2	1	R	0	543.80	630.40	354.00	237.70	189.00	118.00	101.50	80.23	107.50	125.40	72.40	56.470	36.320	26.540	20.490	8.875	3.397	1.601	
42		2	2	2	T	0	383.90	703.40	426.00	270.70	219.90	167.90	131.30	148.20	175.80	149.40	90.46	67.910	44.660	33.680	24.550	10.350	3.367	1.832	
43		2	2	1	R	0	196.20	373.70	238.80	162.30	137.90	110.80	107.70	87.89	72.70	67.75	47.13	39.210	26.310	18.310	13.250	5.899	2.976	1.827	
44		2	2	2	T	0	142.50	263.00	197.70	148.30	140.70	133.10	144.30	147.90	112.60	98.98	62.84	47.610	31.710	22.730	14.290	7.593	3.401	1.947	
45		2	2	1	R	0	183.30	297.80	193.50	172.90	154.60	145.50	121.30	117.20	94.77	85.79	65.23	50.490	36.900	26.520	14.330	7.699	3.099	1.672	
46		2	2	2	T	0	80.59	143.20	159.80	145.60	162.60	173.90	177.90	172.30	136.50	124.80	83.76	67.340	49.110	31.590	15.640	8.990	3.667	2.489	
47		2	1	1	T	0	341.30	494.00	356.80	245.80	176.10	132.20	97.93	84.55	86.80	75.93	53.00	39.880	27.340	20.380	12.520	7.685	3.560	2.464	
48		2	1	2	R	0	310.50	458.00	246.00	170.10	136.90	100.80	83.38	65.84	48.80	36.57	30.38	26.250	17.360	13.330	9.315	5.816	3.824	3.784	
49		2	1	1	T	0	54.64	352.60	239.60	182.50	142.50	115.00	106.00	87.19	78.03	68.52	50.21	41.570	30.750	20.950	13.910	8.260	3.241	2.214	
50		2	1	2	R	0	175.70	330.60	216.70	145.10	123.80	93.61	72.08	63.24	49.60	44.28	39.69	32.620	24.550	19.380	11.420	7.612	3.502	2.051	
51		2	1	1	T	0	307.90	660.20	434.90	275.60	203.90	139.50	142.40	154.20	117.70	84.37	46.80	37.550	25.560	18.990	11.750	5.352	2.182	1.260	
52		2	1	2	R	0	393.90	519.20	323.10	217.40	165.60	122.30	103.80	85.06	81.47	74.62	45.26	34.270	21.190	17.070	9.934	5.160	1.913	1.110	
53		2	2	1	R	0	106.70	203.40	142.20	95.34	80.48	60.30	47.70	39.68	32.79	28.27	20.89	18.780	13.260	11.790	7.233	3.258	1.352	0.000	
54		2	2	2	T	0	63.47	192.00	127.70	83.27	69.63	49.02	42.35	37.74	27.25	23.07	18.14	14.970	12.720	10.220	6.024	3.040	1.248	0.000	
55		2	2	1	R	0	103.20	167.00	134.10	107.40	93.19	84.31	73.26	68.86	63.48	51.15	32.81	23.870	14.490	12.040	7.837	3.657	1.084	0.000	
56		2	2	2	T	0	78.49	139.40	124.60	109.60	108.80	90.81	87.37	81.33	68.68	50.79	33.63	23.810	15.780	11.270	8.837	3.322	1.341	0.000	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KI
57	(b) (6)	2	1	1	T	0	168.90	265.80	188.00	128.80	99.91	81.83	68.68	55.09	48.65	35.17	23.68	18.760	12.260	10.590	5.850	4.013	1.971	1.216	
58		2	1	2	R	0	317.40	383.70	246.50	158.20	114.20	86.80	60.94	51.55	38.85	33.20	23.51	19.570	14.880	12.110	6.822	3.495	2.130	1.465	
59		2	1	1	T	0	139.40	294.80	237.30	192.30	166.50	137.30	127.70	110.70	87.96	71.22	50.58	40.800	29.150	19.960	12.840	5.362	2.064	1.119	
60		2	1	2	R	0	311.10	363.60	238.70	184.80	157.60	131.80	109.80	97.65	76.88	66.24	45.12	36.070	27.970	18.320	11.590	4.941	2.525	1.458	
61		2	2	1	R	0	326.10	494.00	321.20	233.90	167.60	129.90	98.49	71.76	72.72	70.75	53.80	47.060	29.700	22.560	14.520	8.578	3.139	2.049	
62		2	2	2	T	0	237.90	563.50	349.50	255.00	208.30	144.30	106.70	83.33	72.11	66.49	48.06	38.060	29.600	25.660	15.120	8.096	3.576	2.607	
63		2	1	1	T	0	257.30	422.20	241.10	172.40	151.40	123.00	104.00	94.46	76.47	59.81	38.85	31.650	21.980	17.360	10.220	4.737	2.258	1.602	
64		2	1	2	R	0	428.90	498.50	341.80	221.90	184.40	136.30	113.20	114.30	98.02	70.36	55.78	39.700	27.870	24.600	13.950	7.245	3.107	1.811	
65		2	2	1	R	0	573.70	602.80	379.80	271.00	205.00	154.60	129.40	102.00	94.16	83.21	56.32	46.010	29.260	24.320	14.310	7.220	3.359	1.782	
66		2	2	2	T	0	567.40	630.90	402.10	294.50	253.00	194.80	161.10	150.50	120.60	102.10	69.44	52.310	35.520	28.840	18.010	7.538	3.207	0.000	
67		2	2	1	R	0	201.00	270.60	151.40	109.80	107.70	90.95	94.60	91.47	80.12	74.16	51.77	41.940	29.530	21.560	12.830	5.537	2.109	1.058	
68		2	2	2	T	0	180.90	254.10	152.70	111.40	95.18	81.37	63.81	60.31	71.52	74.16	51.98	40.700	27.190	19.290	12.210	5.333	2.097	1.233	
69		2	1	1	T	0	22.90	157.20	141.70	127.80	133.70	122.50	106.90	95.22	73.16	54.45	35.34	26.070	15.130	13.590	7.670	4.610	1.919	0.000	
70		2	1	2	R	0	180.60	352.00	237.70	153.20	147.60	114.30	93.36	86.49	74.47	55.87	36.45	28.360	20.030	17.270	10.330	5.565	1.843	1.214	
71		2	2	1	R	0	225.00	331.50	208.70	149.20	116.70	90.86	71.16	55.21	52.25	41.46	26.75	21.410	14.430	11.400	7.093	4.279	1.757	1.235	
72		2	2	2	T	0	92.24	242.50	214.60	150.40	118.30	105.60	92.61	76.90	64.81	54.57	38.29	28.140	17.410	14.750	8.873	4.855	1.979	1.379	
73		2	1	1	T	0	291.80	419.80	256.20	176.00	137.50	100.00	76.87	67.20	50.88	64.52	35.50	25.650	18.880	14.570	9.608	3.700	1.174	0.000	
74		2	1	2	R	0	405.90	414.20	243.40	164.40	111.50	85.08	60.86	49.42	51.04	50.83	34.43	26.070	19.430	13.290	9.096	4.418	1.469	1.138	
75		2	2	1	R	0	499.20	623.80	386.80	268.90	230.70	169.50	144.10	131.30	117.10	88.31	63.78	51.890	36.300	26.830	16.750	8.535	3.468	2.327	
76		2	2	2	T	0	286.50	354.10	240.00	156.40	133.50	107.40	83.71	81.93	67.85	61.10	46.99	35.270	26.040	21.580	11.820	5.160	2.302	1.401	
77		2	1	1	T	0	166.70	244.90	188.80	153.90	140.80	126.20	127.20	136.20	101.20	84.90	51.48	39.650	25.480	18.800	10.370	4.553	1.821	1.023	
78		2	1	2	R	0	409.20	465.70	251.30	212.00	160.80	145.80	109.20	133.30	128.90	106.00	68.66	48.770	31.940	22.250	14.440	6.766	2.261	1.461	
79		2	2	1	R	0	448.50	535.20	291.30	199.70	169.00	146.60	123.50	99.88	77.30	66.55	49.76	36.950	24.930	19.180	13.720	6.240	3.011	1.741	
80		2	2	2	T	0	206.90	391.90	237.40	167.90	143.00	113.90	111.90	104.80	86.10	58.97	43.38	33.250	25.110	17.460	10.980	5.253	3.423	1.653	
81		2	2	1	R	0	251.90	354.50	221.40	146.70	124.90	87.42	68.45	58.55	49.41	42.90	32.69	24.690	18.680	13.930	8.030	4.954	2.911	1.698	
82		2	2	2	T	0	111.00	299.40	208.00	156.20	124.40	87.47	71.90	73.94	59.11	49.00	32.24	25.220	18.070	13.030	7.332	4.616	2.078	1.474	
83		2	1	1	T	0	393.80	972.50	577.90	423.80	347.20	271.50	225.50	177.60	137.80	105.60	68.05	50.450	33.320	25.250	14.480	8.255	3.971	2.445	
84		2	1	2	R	0	735.70	796.50	526.20	360.00	286.60	227.50	152.70	133.70	104.00	83.73	56.46	41.060	31.650	22.840	11.970	6.915	3.525	1.884	
85		3	1	1	T	0	260.50	494.80	357.70	260.30	196.80	142.00	117.00	88.90	68.60	65.46	56.54	46.170	35.540	24.100	16.300	9.172	3.305	2.072	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KI
86	(b) (6)	3	1	2	R	0	428.50	518.20	307.10	216.50	165.20	140.70	119.50	81.48	69.78	66.40	50.47	39.570	33.690	24.900	17.660	7.940	3.149	1.452	
87		3	1	1	T	0	381.20	351.00	236.70	136.70	118.00				45.97	42.19	32.54	22.800	16.190	12.450	8.660	5.231	1.820	1.092	
88		3	1	2	R	0	382.90	311.90	219.90		121.60	88.31	72.69	62.31	55.05	37.92	27.10	21.380	15.160	12.950	9.488	4.249	1.921	1.442	
89		3	2	1	R	0	501.10	653.30	410.30	261.80	191.60	140.10	109.80	89.32	76.43	58.30	49.30	42.220	32.510	22.100	15.000	7.790	3.209	1.558	
90		3	2	2	T	0	397.80	472.20	282.00	192.20	161.60	114.80	81.59	74.74	73.43	60.97	44.01	35.450	26.910			5.692	1.994	1.346	
91		3	2	1	R	0	122.10	231.50	192.30	221.00	189.80	197.10	201.10	164.50	143.80	153.40	174.00	117.500	59.810	44.920	28.300	14.090	6.451	4.384	
92		3	2	2	T	0	62.59	127.20	126.10	117.50	109.90	117.50	136.90	146.40	124.40	105.40	72.28	49.810	32.380	23.610	15.540	9.432	4.423	2.899	
93		3	2	1	R	0	337.60	306.20	208.20	136.60	103.70	78.92	57.34	45.64	41.40	37.42	27.98	22.060	20.250	14.180	9.347	3.822	1.596	0.000	
94		3	2	2	T	0	117.00	230.30	174.80	124.00	90.04	66.11	52.04	45.89	38.38	32.70	24.62	21.250	17.330	11.530	8.024	3.702	1.381	0.000	
95		3	1	1	T	0	145.60	263.30	186.50	134.30	116.90	84.89	76.51	75.77	60.84	52.30	43.19	34.690	25.880	20.290	12.890	8.616	4.533	3.531	
96		3	1	2	R	0	145.60	283.90	205.50	161.40	115.70	83.96	70.57	66.46	53.47	45.46	37.77	29.910	29.110	19.020	13.350	8.132	5.095	3.854	
97		3	2	1	R	0	201.00	371.80	266.00	185.60	136.90	96.05	78.07	78.28	80.71	71.39	50.66	40.170	27.000	19.430	12.360	6.137	2.650	1.518	
98		3	2	2	T	0	215.00	422.00	274.10	194.50	133.50	97.44	92.50	100.70	89.95	83.44	51.70	38.130	28.000	20.610	11.660	6.603	2.511	1.498	
99		3	1	1	T	0	154.80	273.60	206.10	141.90	119.80	100.20	81.10	74.79	64.80	50.13	34.72	25.020	20.550	14.550	7.949	5.143	2.568	1.530	
100		3	1	2	R	0	146.70	298.00	197.70	122.70	96.94	77.23	56.89	52.96	43.47	35.89	25.27	18.690	15.920	12.720	7.937	5.491	2.650	1.495	
101		3	1	1	T	0	88.98	266.30	221.40	163.60	143.10	119.40	106.40	103.50	96.01	77.89	53.42	44.150	27.490	19.380	11.420	7.055	2.545	1.527	
102		3	1	2	R	0	129.70	286.20	175.10	120.30	97.57	83.36	67.05	70.25	71.05	57.42	41.90	30.830	21.080	15.070	10.530	5.812	2.358	1.426	
103		3	2	1	R	0	553.50	488.30	285.80	167.30	160.10	125.30	114.60	103.60	102.60	69.72	47.67	34.160	24.240	17.780	12.080	5.745	2.145	1.530	
104		3	2	2	T	0	471.80	419.50	308.50	220.30	186.30	174.20	154.90	138.90	111.60	85.64	58.29	41.570	28.460	20.410	12.280	6.644	2.402	1.624	
105		3	2	1	R	0	339.00	468.20	314.60	230.40	201.60	153.80	124.00	113.30	100.00	82.39	64.39	53.990	41.840	28.620	18.540	9.728	3.699	2.440	
106		3	2	2	T	0	245.60	567.30	380.10	252.50	196.60	157.20	133.90	109.30	102.20	90.00	68.98	54.720	44.620	31.620	24.880	10.210	5.048	3.770	
107		3	1	1	T	0	309.00	450.00	355.20	264.70	207.10	165.60	139.50	119.10	94.07	130.30	75.27	53.450	39.230	26.740	16.510	6.269	1.726	1.150	
108		3	1	2	R	0	340.10	404.70	306.10	226.00	169.00	151.60	116.70	98.55	87.46	71.23	77.44	52.530	35.860	22.730	15.920	6.510	2.301	1.377	
109		3	1	1	T	0	108.10	203.40	156.80	138.90	130.00	130.60	118.00	103.80	83.68	71.37	42.10	28.460	17.540	13.670	7.736	4.096	1.184	0.000	
110		3	1	2	R	0	177.70	299.60	209.80	180.60	144.50	150.00	143.80	133.00	106.30	82.05	45.57	35.260	20.320	15.870	8.924	3.947	1.395	0.000	
111		3	1	1	T	0	306.80	431.70	339.80	227.80	172.40	135.60	123.10	101.60	93.98	82.67	68.69	50.350	34.380	26.610	16.130	9.642	4.684	3.252	
112		3	1	2	R	0	281.00	351.40	226.80	188.90	133.10	116.40	97.66	80.35	76.20	66.22	54.85	42.320	29.950	24.870	15.130	8.630	4.488	2.946	
113		3	1	1	T	0	285.40	354.90	240.30	163.80	129.30	108.00	93.43	83.45	63.53	62.79	42.05	33.380	25.020	19.950	12.480	7.813	3.586	2.236	
114		3	1	2	R	0	205.40	366.20	218.70	168.20	133.70	105.40	96.61	83.07	70.20	53.42	38.97	31.790	25.790	20.750	13.300	7.497	3.909	2.692	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	K
115	(b) (6)	3	2	1	R	0	359.90	472.60	308.50	229.60	183.10	128.90	100.90	102.60	94.24	56.68	36.67	29.020	20.160	15.630	9.573	4.943	1.612	0.000	
116		3	2	2	T	0	91.52	339.90	245.90	158.10	130.10	92.62	65.60	55.69	55.72	79.06	61.06	32.050	20.730	14.180	10.450	4.491	1.698	0.000	
117		3	2	1	R	0	272.10	300.10	227.30	144.30	122.40	93.74	86.14	76.93	61.53	50.17	35.61	27.810	18.620	14.930	9.021	5.799	1.956	1.322	
118		3	2	2	T	0	118.00	175.40	117.20	124.10	110.20	99.73	92.08	75.05	71.46	56.01	34.74	27.610	17.210	12.820	8.586	4.589	1.775	1.373	
119		3	2	1	R	0	238.70	348.60	230.70	150.10	116.70	92.55	73.29	56.92	44.50	37.97	27.70	21.310	16.140	10.810	7.026	3.580	1.554	0.000	
120		3	2	2	T	0	101.20	280.80	206.90	135.80	118.70	91.52	70.69	62.95	52.23	39.29	27.27	20.730	15.530	11.270	6.595	3.224	1.509	0.000	
121		3	1	1	T	0	419.50	861.30	559.20	399.60	336.50	269.40	244.90	238.20	225.40	176.90	128.60	113.300	83.720	67.950	35.110	17.180	4.855	2.260	
122		3	1	2	R	0	374.20	582.70	407.70	298.10	247.20	192.30	182.30	188.30	176.30	142.80	106.60	78.450	90.980	57.150	30.490	13.400	4.355	2.343	

Obs	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19
1	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
2	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
3	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
4	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
5	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
6	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
7	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0333	24.0000	36.0000	48.0000
8	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.55000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
9	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
10	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
11	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
12	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
13	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
14	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
15	19	0	0.033333	0.11667	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
16	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.56667	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
17	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
18	18	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
19	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000

Obs	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T
107	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
108	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
109	18	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.01667	12.0000	24.0000	36.0000	48.0000
110	18	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.76667	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
111	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
112	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
113	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
114	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
115	18	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
116	18	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
117	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
118	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.78333	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0667	48.0000
119	18	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
120	18	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
121	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
122	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4.00000	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000

5.9.2.5 Fasting Study Output (SA)

Fasting STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	61	(b) (6)
trt	2	1 2
per	2	1 2
seq	2	1 2
GRP	3	1 2 3

Number of Observations Read	122
Number of Observations Used	122

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	64	14.60372229	0.22818316	11.79	<.0001
Error	57	1.10329166	0.01935599		
Corrected Total	121	15.70701394			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.929758	2.129981	0.139126	6.531788

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.09661660	0.09661660	4.99	0.0294
GRP	2	0.10854660	0.05427330	2.80	0.0689
seq	1	0.20049829	0.20049829	10.36	0.0021
seq*GRP	2	0.17687418	0.08843709	4.57	0.0144
sub(seq*GRP)	55	13.95766740	0.25377577	13.11	<.0001
per(GRP)	2	0.06328707	0.03164353	1.63	0.2040
trt	1	0.00023214	0.00023214	0.01	0.9132

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per	1	0.10409697	0.10409697	5.38	0.0240

Source	DF	Type III SS	Mean Square	F Value	Pr > F
GRP	2	0.09226542	0.04613271	2.38	0.1014
seq	1	0.21571541	0.21571541	11.14	0.0015
seq*GRP	2	0.17687418	0.08843709	4.57	0.0144
sub(seq*GRP)	55	13.95766740	0.25377577	13.11	<.0001
per(GRP)	2	0.06222235	0.03111118	1.61	0.2094
trt	1	0.00023214	0.00023214	0.01	0.9132

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.21571541	0.21571541	0.85	0.3606
GRP	2	0.09226542	0.04613271	0.18	0.8343

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.00276873	0.02528191	0.11	0.9132

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	64	14.04238424	0.21941225	12.33	<.0001
Error	57	1.01465210	0.01780091		
Corrected Total	121	15.05703633			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.932613	2.028448	0.133420	6.577447

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.07434078	0.07434078	4.18	0.0456
GRP	2	0.10625304	0.05312652	2.98	0.0585
seq	1	0.22945208	0.22945208	12.89	0.0007
seq*GRP	2	0.15849192	0.07924596	4.45	0.0160
sub(seq*GRP)	55	13.40516300	0.24373024	13.69	<.0001
per(GRP)	2	0.06866237	0.03433118	1.93	0.1547
trt	1	0.00002104	0.00002104	0.00	0.9727

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per	1	0.08150407	0.08150407	4.58	0.0367
GRP	2	0.08991839	0.04495920	2.53	0.0889
seq	1	0.24535341	0.24535341	13.78	0.0005
seq*GRP	2	0.15849192	0.07924596	4.45	0.0160
sub(seq*GRP)	55	13.40516300	0.24373024	13.69	<.0001
per(GRP)	2	0.06839022	0.03419511	1.92	0.1558
trt	1	0.00002104	0.00002104	0.00	0.9727

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.24535341	0.24535341	1.01	0.3201
GRP	2	0.08991839	0.04495920	0.18	0.8321

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.00083357	0.02424506	-0.03	0.9727

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	64	24.21059450	0.37829054	10.43	<.0001
Error	57	2.06797194	0.03628021		
Corrected Total	121	26.27856644			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.921306	3.236484	0.190474	5.885202

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.15459723	0.15459723	4.26	0.0436
GRP	2	0.08502472	0.04251236	1.17	0.3172
seq	1	0.12693979	0.12693979	3.50	0.0665
seq*GRP	2	0.27019504	0.13509752	3.72	0.0302
sub(seq*GRP)	55	22.89487827	0.41627051	11.47	<.0001
per(GRP)	2	0.03459219	0.01729609	0.48	0.6233
trt	1	0.64436726	0.64436726	17.76	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per	1	0.17657097	0.17657097	4.87	0.0314
GRP	2	0.10228534	0.05114267	1.41	0.2526
seq	1	0.11118972	0.11118972	3.06	0.0854
seq*GRP	2	0.27019504	0.13509752	3.72	0.0302
sub(seq*GRP)	55	22.89487827	0.41627051	11.47	<.0001
per(GRP)	2	0.05934890	0.02967445	0.82	0.4465
trt	1	0.64436726	0.64436726	17.76	<.0001

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.11118972	0.11118972	0.27	0.6073
GRP	2	0.10228534	0.05114267	0.12	0.8846

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.14587098	0.03461283	-4.21	<.0001

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	trt	AUCRATIO
1	(b) (6)	1	0.97
2		1	0.97
3		1	0.96
4		1	0.97
5		1	0.96
6		1	0.96
7		1	0.95
8		1	0.97
9		1	0.96
10		1	0.97
11		1	0.98
12		1	0.96
13		1	0.92
14		1	0.97
15		1	0.97
16		1	0.96
17		1	0.96
18		1	0.89

Obs	sub	trt	AUCRATIO
19	(b) (6)	1	0.98
20		1	0.96
21		1	0.98
22		1	0.96
23		1	0.96
24		1	0.94
25		1	0.95
26		1	0.98
27		1	0.94
28		1	0.96
29		1	0.94
30		1	0.98
31		1	0.94
32		1	0.95
33		1	0.96
34		1	0.97
35		1	0.94
36		1	0.95
37		1	0.98
38		1	0.97
39		1	0.98
40		1	0.95
41		1	0.94
42		1	0.96
43		1	0.96
44		1	0.97
45		1	0.98
46		1	0.94
47		1	0.95
48		1	0.88
49		1	0.97
50		1	0.94
51		1	0.97
52		1	0.97
53		1	0.94
54		1	0.98
55		1	0.97
56		1	0.93
57		1	0.94
58		1	0.96

Obs	sub	trt	AUCRATIO
59	(b) (6)	1	0.95
60		1	0.95
61		1	0.99
62		2	0.97
63		2	0.97
64		2	0.96
65		2	0.96
66		2	0.97
67		2	0.94
68		2	0.94
69		2	0.97
70		2	0.98
71		2	0.95
72		2	0.98
73		2	0.97
74		2	0.93
75		2	0.95
76		2	0.96
77		2	0.95
78		2	0.96
79		2	0.93
80		2	0.97
81		2	0.94
82		2	0.98
83		2	0.95
84		2	0.97
85		2	0.80
86		2	0.94
87		2	0.97
88		2	0.95
89		2	0.97
90		2	0.93
91		2	0.96
92		2	0.96
93		2	0.96
94		2	0.97
95		2	0.98
96		2	0.97
97		2	0.95
98		2	0.96

Obs	sub	trt	AUCRATIO
99	(b) (6)	2	0.96
100		2	0.98
101		2	0.96
102		2	0.93
103		2	0.96
104		2	0.98
105		2	0.95
106		2	0.97
107		2	0.95
108		2	0.96
109		2	0.86
110		2	0.96
111		2	0.94
112		2	0.96
113		2	0.97
114		2	0.96
115		2	0.98
116		2	0.97
117		2	0.93
118		2	0.92
119		2	0.97
120		2	0.96
121		2	0.95
122		2	0.98

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

sub	seq	RAUCT12	RAUC12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	2	1.00	1.00	1.01	1.00	1.02	0.98
	2	1.19	1.19	1.29	1.00	1.03	0.97
	1	0.91	0.91	0.77	1.00	1.00	1.00
	1	0.93	0.92	0.80	1.00	1.03	0.97
	2	0.76	0.77	0.68	1.00	0.97	1.03
	1	1.15	1.12	1.14	1.00	1.14	0.87
	2	1.17	1.16	0.93	1.00	1.00	1.00
	2	0.88	0.87	0.68	2.50	1.07	0.94
	2	0.81	0.83	0.42	1.00	1.11	0.90
	1	1.03	1.01	0.93	1.00	1.15	0.87
	1	1.13	1.13	1.01	1.00	1.02	0.98
	1	1.03	1.04	0.95	1.00	1.19	0.84

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	1	1.10	1.10	1.37	1.00	0.94	1.06
	2	1.25	1.23	1.18	0.83	1.13	0.89
	1	1.03	1.02	0.62	2.50	1.08	0.92
	1	1.05	1.04	1.16	0.50	1.01	0.99
	2	0.80	0.80	0.73	1.00	0.96	1.04
	2	0.48	0.51	0.57	1.00	1.08	0.92
	1	1.16	1.15	1.06	1.00	1.13	0.88
	1	1.76	1.73	0.88	1.00	1.09	0.92
	2	1.23	1.23	1.12	1.00	1.03	0.97
	2	1.23	1.22	0.70	1.00	1.01	0.99
	2	1.23	1.24	0.60	9.00	0.87	1.15
	1	1.37	1.16	1.08	1.00	1.82	0.55
	1	1.20	1.19	1.07	1.00	1.09	0.92
	1	1.20	1.20	1.27	1.00	1.00	1.00
	2	0.87	0.87	0.94	1.00	0.95	1.05
	2	1.04	1.05	0.83	1.00	0.93	1.08
	1	0.93	0.92	0.69	1.00	1.06	0.94
	1	1.05	1.04	0.81	1.00	1.20	0.83
	2	1.02	1.03	1.14	1.00	0.89	1.13
	1	0.76	0.77	0.85	1.00	0.90	1.11
	2	1.14	1.15	1.05	1.00	1.31	0.76
	2	0.93	0.94	0.94	1.00	0.92	1.08
	1	0.83	0.85	0.45	1.00	1.03	0.97
	2	1.19	1.18	0.73	1.00	1.06	0.94
	1	1.02	1.01	1.01	1.20	1.45	0.69
	2	0.66	0.66	0.57	1.00	1.06	0.95
	1	0.78	0.78	0.53	1.00	0.99	1.01
	2	0.89	0.89	0.73	1.00	0.88	1.13
	2	0.96	0.95	0.84	1.00	1.08	0.93
	1	1.19	1.19	1.22	1.00	0.98	1.03
	1	1.04	1.05	0.95	1.00	0.85	1.17
	1	1.06	1.04	1.00	1.00	1.13	0.88
	2	0.91	0.90	0.72	1.00	1.21	0.83
	2	0.58	0.59	0.63	12.0	0.91	1.10
	2	0.86	0.87	0.68	2.50	0.97	1.04
	1	1.02	0.99	0.93	1.00	1.08	0.93
	2	1.05	1.05	1.14	1.00	1.00	1.00
	1	1.16	1.15	0.92	1.00	0.98	1.02
	1	1.27	1.26	0.93	1.00	1.02	0.98
	2	1.15	1.14	0.85	1.00	0.99	1.01

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	2	1.12	1.15	1.21	1.00	0.90	1.11
	1	1.11	1.10	1.11	1.00	1.11	0.90
	1	0.85	0.85	0.68	1.00	0.99	1.01
	1	1.16	1.16	1.23	1.00	0.99	1.01
	1	1.00	0.98	0.97	1.00	1.09	0.92
	2	0.92	0.93	0.72	1.00	0.98	1.03
	2	0.92	0.92	0.58	1.00	0.94	1.06
	2	0.96	0.96	0.81	1.00	1.03	0.97
	1	1.22	1.21	1.48	1.00	1.08	0.93

5.9.2.6 Firm Reviewer Ratio (SA)

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	(b) (6)	1	2	1	2	883.38	909.90	485.50	R	864.88	889.23	485.50	0.97905	0.97728	1
2		1	2	2	1	884.75	909.87	488.00	T	865.95	889.77	488.00	0.97876	0.97790	1
3		1	2	1	2	874.04	902.61	431.00	R	859.43	888.00	431.00	0.98328	0.98381	1
4		1	2	2	1	1041.41	1072.88	554.30	T	1022.02	1053.49	554.30	0.98138	0.98193	1
5		1	1	1	1	892.81	928.71	332.30	T	877.02	912.92	332.30	0.98232	0.98300	1
6		1	1	2	2	977.75	1020.39	430.70	R	959.75	1002.38	430.70	0.98158	0.98235	1
7		1	1	1	1	891.12	920.98	568.50	T	876.17	904.18	568.50	0.98323	0.98176	1
8		1	1	2	2	961.45	997.01	711.90	R	944.43	979.99	711.90	0.98230	0.98293	1
9		1	2	1	2	825.86	854.60	432.50	R	811.94	840.68	432.50	0.98314	0.98371	1
10		1	2	2	1	629.79	655.09	293.90	T	618.17	643.47	293.90	0.98155	0.98226	1
11		1	1	1	1	795.74	830.39	297.30	T	783.56	814.99	297.30	0.98470	0.98145	1
12		1	1	2	2	694.18	742.08	259.70	R	684.81	732.71	259.70	0.98650	0.98737	1
13		1	2	1	2	609.07	645.81	322.30	R	600.53	635.20	322.30	0.98599	0.98356	1
14		1	2	2	1	711.38	748.74	300.60	T	701.88	737.22	300.60	0.98666	0.98462	1
15		1	2	1	2	685.78	708.26	624.20	R	674.35	696.84	624.20	0.98334	0.98387	1
16		1	2	2	1	601.07	618.33	425.10	T	589.26	606.52	425.10	0.98036	0.98091	1
17		1	2	1	2	652.17	668.30	256.80	R	639.22	655.36	256.80	0.98015	0.98063	1
18		1	2	2	1	529.45	551.46	108.30	T	519.06	541.54	108.30	0.98037	0.98200	1
19		1	1	1	1	737.93	764.64	241.30	T	726.36	753.06	241.30	0.98431	0.98486	1
20		1	1	2	2	717.83	753.86	259.70	R	707.42	743.46	259.70	0.98550	0.98620	1
21		1	1	1	1	1490.22	1522.75	663.50	T	1458.73	1490.69	663.50	0.97887	0.97895	1
22		1	1	2	2	1318.71	1349.10	654.40	R	1290.66	1320.79	654.40	0.97873	0.97902	1
23		1	1	1	1	692.73	719.77	406.60	T	679.47	708.25	406.60	0.98086	0.98398	1
24		1	1	2	2	672.66	689.98	425.90	R	660.31	678.55	425.90	0.98164	0.98343	1

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
25	(b) (6)	1	1	1	1	312.17	337.60	111.40	T	306.92	333.34	111.40	0.98319	0.98737	1
26		1	1	2	2	284.93	306.60	81.59	R	280.36	304.40	81.59	0.98397	0.99282	1
27		1	2	1	2	549.97	580.08	366.50	R	540.60	570.71	366.50	0.98297	0.98385	1
28		1	2	2	1	688.10	712.94	433.00	T	676.00	700.99	433.00	0.98242	0.98324	1
29		1	1	1	1	574.75	592.96	370.70	T	563.86	583.66	370.70	0.98106	0.98431	1
30		1	1	2	2	559.23	581.92	598.40	R	548.46	571.86	598.40	0.98074	0.98271	1
31		1	1	1	1	675.64	701.71	123.50	T	664.41	690.48	123.50	0.98338	0.98400	1
32		1	1	2	2	644.02	675.35	106.40	R	631.04	658.59	106.40	0.97985	0.97520	1
33		1	2	1	2	713.90	742.60	537.00	R	701.07	727.45	537.00	0.98203	0.97961	1
34		1	2	2	1	568.32	592.15	391.70	T	559.81	582.27	391.70	0.98502	0.98331	1
35		1	2	1	2	426.15	457.75	288.20	R	419.90	450.24	288.20	0.98532	0.98361	1
36		1	2	2	1	206.64	231.21	165.10	T	204.04	228.61	165.10	0.98742	0.98876	1
37		1	1	1	1	706.37	722.56	623.10	T	690.58	705.19	623.10	0.97764	0.97596	1
38		1	1	2	2	609.24	627.83	587.00	R	598.32	616.91	587.00	0.98207	0.98260	1
39		1	1	1	1	1869.73	1947.50	483.80	T	1833.99	1889.81	483.80	0.98088	0.97038	1
40		1	1	2	2	1061.64	1125.13	549.80	R	1041.46	1100.17	549.80	0.98099	0.97781	1
41		2	2	1	2	995.62	1017.94	630.40	R	971.67	994.11	630.40	0.97595	0.97659	1
42		2	2	2	1	1226.45	1251.12	703.40	T	1197.31	1221.19	703.40	0.97624	0.97607	1
43		2	2	1	2	690.84	723.91	373.70	R	678.83	710.29	373.70	0.98262	0.98117	1
44		2	2	2	1	848.90	883.88	263.00	T	834.83	869.82	263.00	0.98343	0.98409	1
45		2	2	1	2	842.24	869.52	297.80	R	827.91	855.19	297.80	0.98299	0.98352	1
46		2	2	2	1	1035.29	1081.88	177.90	T	1018.46	1065.05	177.90	0.98374	0.98444	1
47		2	1	1	1	784.53	836.89	494.00	T	773.97	826.34	494.00	0.98655	0.98739	1
48		2	1	2	2	572.97	719.04	458.00	R	567.24	.	458.00	0.99001	.	1
49		2	1	1	1	751.82	793.02	352.60	T	740.39	779.49	352.60	0.98479	0.98294	1

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
50	(b) (6)	2	1	2	2	627.13	668.65	330.60	R	618.54	660.06	330.60	0.98630	0.98716	1
51		2	1	1	1	789.34	809.24	660.20	T	774.26	794.17	660.20	0.98090	0.98137	1
52		2	1	2	2	658.08	675.69	519.20	R	646.04	663.65	519.20	0.98170	0.98218	1
53		2	2	1	2	340.85	358.93	203.40	R	334.21	353.56	203.40	0.98052	0.98503	1
54		2	2	2	1	296.46	313.95	192.00	T	291.19	310.22	192.00	0.98222	0.98813	1
55		2	2	1	2	425.81	438.87	167.00	R	416.95	429.92	167.00	0.97919	0.97962	1
56		2	2	2	1	442.69	460.09	139.40	T	433.35	450.41	139.40	0.97888	0.97897	1
57		2	1	1	1	403.24	430.14	265.80	T	398.07	424.98	265.80	0.98718	0.98799	1
58		2	1	2	2	433.60	468.00	383.70	R	427.51	461.92	383.70	0.98596	0.98699	1
59		2	1	1	1	710.02	726.24	294.80	T	696.17	711.65	294.80	0.98050	0.97990	1
60		2	1	2	2	673.03	698.42	363.60	R	661.40	686.80	363.60	0.98273	0.98336	1
61		2	2	1	2	802.27	838.01	494.00	R	788.67	822.68	494.00	0.98305	0.98171	1
62		2	2	2	1	815.80	867.16	563.50	T	802.74	845.01	563.50	0.98400	0.97446	1
63		2	1	1	1	620.07	650.58	422.20	T	609.58	640.09	422.20	0.98308	0.98387	1
64		2	1	2	2	814.03	845.20	498.50	R	800.41	831.58	498.50	0.98327	0.98389	1
65		2	2	1	2	865.18	895.66	602.80	R	850.63	881.11	602.80	0.98318	0.98375	1
66		2	2	2	1	988.79	1030.69	630.90	T	969.92	1014.52	630.90	0.98091	0.98432	1
67		2	2	1	2	673.38	688.41	270.60	R	659.16	674.19	270.60	0.97888	0.97934	1
68		2	2	2	1	625.72	644.66	254.10	T	612.67	630.53	254.10	0.97914	0.97809	1
69		2	1	1	1	489.64	519.29	157.20	T	482.13	510.96	157.20	0.98464	0.98395	1
70		2	1	2	2	590.42	609.77	352.00	R	579.52	597.25	352.00	0.98154	0.97947	1
71		2	2	1	2	449.96	474.13	331.50	R	443.25	464.45	331.50	0.98509	0.97958	1
72		2	2	2	1	535.87	561.31	242.50	T	527.48	549.93	242.50	0.98435	0.97972	1
73		2	1	1	1	518.61	531.89	419.80	T	505.83	519.10	419.80	0.97534	0.97596	1
74		2	1	2	2	510.07	528.68	414.20	R	500.18	516.87	414.20	0.98062	0.97767	1

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
75	(b) (6)	2	2	1	2	977.93	1018.86	623.80	R	961.72	999.72	623.80	0.98343	0.98122	1
76	(b) (6)	2	2	2	1	648.27	671.60	354.10	T	636.02	659.35	354.10	0.98110	0.98176	1
77	(b) (6)	2	1	1	1	678.04	693.67	244.90	T	664.89	680.52	244.90	0.98061	0.98105	1
78	(b) (6)	2	1	2	2	868.41	890.42	465.70	R	850.67	871.69	465.70	0.97957	0.97897	1
79	(b) (6)	2	2	1	2	747.65	777.83	535.20	R	734.58	763.50	535.20	0.98252	0.98158	1
80	(b) (6)	2	2	2	1	662.40	694.88	391.90	T	652.29	684.76	391.90	0.98472	0.98544	1
81	(b) (6)	2	2	1	2	512.26	551.50	354.50	R	505.95	545.19	354.50	0.98769	0.98856	1
82	(b) (6)	2	2	2	1	493.84	525.37	299.40	T	487.05	518.57	299.40	0.98624	0.98707	1
83	(b) (6)	2	1	1	1	1099.09	1147.44	972.50	T	1083.11	1131.46	972.50	0.98546	0.98607	1
84	(b) (6)	2	1	2	2	926.15	962.49	796.50	R	912.90	949.25	796.50	0.98570	0.98624	1
85	(b) (6)	3	1	1	1	857.60	892.21	494.80	T	843.17	876.63	494.80	0.98318	0.98254	1
86	(b) (6)	3	1	2	2	826.08	846.78	518.20	R	809.12	829.56	518.20	0.97947	0.97967	1
87	(b) (6)	3	1	1	1	522.08	540.11	381.20	T	507.30	524.46	381.20	0.97169	0.97102	1
88	(b) (6)	3	1	2	2	494.04	520.96	382.90	R	485.04	509.69	382.90	0.98178	0.97836	1
89	(b) (6)	3	2	1	2	821.75	846.09	653.30	R	807.49	831.27	653.30	0.98265	0.98249	1
90	(b) (6)	3	2	2	1	746.22	763.60	472.20	T	692.07	708.94	472.20	0.92743	0.92841	1
91	(b) (6)	3	2	1	2	1522.49	1605.00	231.50	R	1493.78	1576.29	231.50	0.98114	0.98211	1
92	(b) (6)	3	2	2	1	890.54	950.58	146.40	T	878.26	938.29	146.40	0.98621	0.98708	1
93	(b) (6)	3	2	1	2	447.16	467.94	337.60	R	438.09	459.76	337.60	0.97972	0.98251	1
94	(b) (6)	3	2	2	1	386.74	405.36	230.30	T	379.41	398.03	230.30	0.98105	0.98192	1
95	(b) (6)	3	1	1	1	689.79	783.39	263.30	T	682.47	765.28	263.30	0.98940	0.97688	1
96	(b) (6)	3	1	2	2	677.48	787.73	283.90	R	670.77	769.35	283.90	0.99009	0.97666	1
97	(b) (6)	3	2	1	2	687.32	712.87	371.80	R	675.46	701.01	371.80	0.98274	0.98336	1
98	(b) (6)	3	2	2	1	719.93	745.17	422.00	T	707.42	732.66	422.00	0.98263	0.98321	1
99	(b) (6)	3	1	1	1	530.21	562.77	273.60	T	523.45	556.01	273.60	0.98725	0.98799	1

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
100	(b) (6)	3	1	2	2	457.22	488.51	298.00	R	451.27	480.58	298.00	0.98700	0.98378	1
101		3	1	1	1	718.47	744.44	266.30	T	706.79	731.21	266.30	0.98374	0.98223	1
102		3	1	2	2	566.71	591.51	286.20	R	557.42	581.45	286.20	0.98360	0.98299	1
103		3	2	1	2	713.91	739.46	553.50	R	700.75	724.99	553.50	0.98157	0.98043	1
104		3	2	2	1	817.44	844.94	471.80	T	804.33	829.93	471.80	0.98396	0.98223	1
105		3	2	1	2	972.28	1013.80	468.20	R	955.87	995.13	468.20	0.98312	0.98158	1
106		3	2	2	1	1091.07	1162.15	567.30	T	1070.47	1138.17	567.30	0.98111	0.97937	1
107		3	1	1	1	928.26	943.13	450.00	T	904.81	918.27	450.00	0.97473	0.97364	1
108		3	1	2	2	838.98	858.69	404.70	R	821.25	840.36	404.70	0.97887	0.97865	1
109		3	1	1	1	529.06	543.48	203.40	T	518.93	532.88	203.40	0.98085	0.98050	1
110		3	1	2	2	623.71	640.51	299.60	R	611.37	629.42	299.60	0.98022	0.98268	1
111		3	1	1	1	929.80	1000.42	431.70	T	917.74	988.36	431.70	0.98703	0.98795	1
112		3	1	2	2	801.95	865.50	351.40	R	791.26	854.81	351.40	0.98667	0.98765	1
113		3	1	1	1	693.45	738.65	354.90	T	683.85	729.04	354.90	0.98615	0.98700	1
114		3	1	2	2	694.26	753.60	366.20	R	685.08	744.42	366.20	0.98678	0.98782	1
115		3	2	1	2	607.40	628.29	472.60	R	596.17	616.36	472.60	0.98151	0.98101	1
116		3	2	2	1	560.95	583.52	339.90	T	548.50	571.06	339.90	0.97780	0.97865	1
117		3	2	1	2	548.43	571.60	300.10	R	539.55	560.52	300.10	0.98380	0.98062	1
118		3	2	2	1	503.02	528.57	175.40	T	494.77	517.38	175.40	0.98361	0.97882	1
119		3	2	1	2	422.05	445.35	348.60	R	415.46	440.18	348.60	0.98440	0.98839	1
120		3	2	2	1	406.00	428.02	280.80	T	399.65	424.20	280.80	0.98436	0.99108	1
121		3	1	1	1	1877.61	1906.18	861.30	T	1834.98	1861.36	861.30	0.97729	0.97648	1
122	3	1	2	2	1544.38	1576.25	582.70	R	1507.95	1539.82	582.70	0.97641	0.97689	1	

5.9.3 Fasting Study MGR001-1005

5.9.3.1 Fasting Study Data (FP)

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
1	(b) (6)	1	2	1	R	0	30.110	73.740	78.60	115.20	147.20	180.80	187.20	166.50	137.20	119.80	87.59	67.16	36.76	27.31	13.70
2	(b) (6)	1	2	2	T	0	160.600	170.700	206.00	278.20	312.10	374.00	349.60	318.00	279.40	235.00	182.20	136.90	85.65	60.58	35.69
3	(b) (6)	1	1	1	T	0	4.055	29.360	51.84	78.66	81.65	111.30	129.00	141.70	168.40	170.70	156.70	140.90	84.83	72.64	39.05
4	(b) (6)	1	1	2	R	0	8.981	35.280	53.60	79.00	100.30	123.00	135.70	167.10	167.40	181.50	171.40	146.70	90.59	80.22	41.01
5	(b) (6)	1	2	1	R	0	43.020	71.320	133.90	169.70	192.00	239.40	232.90	223.00	198.50	177.80	143.40	124.00	82.68	56.59	32.24
6	(b) (6)	1	2	2	T	0	21.630	92.030	119.50	153.60	170.40	223.00	223.30	212.50	207.60	186.30	129.50	121.30	70.62	45.47	23.75
7	(b) (6)	1	1	1	T	0	20.180	30.540	62.71	88.85	104.10	141.50	190.90	208.10	250.60	278.30	230.70	225.60	143.10	119.60	70.91
8	(b) (6)	1	1	2	R	0	7.259	28.150	63.43	101.00	99.07	111.00	171.80	160.80	189.80	190.80	191.00	166.80	110.30	98.08	56.08
9	(b) (6)	1	2	1	R	0	7.579	18.490	37.40	34.47	50.77	70.58	98.95	116.00	123.60	123.10	119.20	106.50	71.73	51.10	30.99
10	(b) (6)	1	2	2	T	0	14.470	23.140	50.94	61.08	72.43	101.20	148.50	129.50	155.90	166.90	152.70	143.20	98.72	69.40	46.06
11	(b) (6)	1	1	1	T	0	43.700	91.400	79.74	124.70	144.70	186.00	185.50	207.00	171.30	188.40	187.20	154.50	92.25	68.05	51.79
12	(b) (6)	1	1	2	R	0	37.230	63.190	93.66	137.30	130.60	133.80	163.60	167.50	158.00	181.60	157.50	132.40	76.59	60.38	39.17
13	(b) (6)	1	1	1	T	0	2.344	25.890	42.01	66.47	86.34	102.90	130.20	148.30	139.50	142.70	130.50	104.70	62.76	49.73	35.48
14	(b) (6)	1	1	2	R	0	6.447	28.230	37.84	69.83	79.63	102.00	131.00	126.80	117.40	130.80	131.60	115.90	68.08	52.41	33.22
15	(b) (6)	1	1	1	T	0	11.480	47.160	94.83	198.40	198.80	232.60	298.30	238.90	259.30	246.90	188.30	162.20	116.00	96.68	52.33
16	(b) (6)	1	1	2	R	0	11.330	78.670	77.59	110.50	145.60	185.70	226.30	237.90	254.70	214.30	184.10	161.10	91.30	75.94	46.86
17	(b) (6)	1	1	1	T	0	16.750	63.010	108.40	139.90	158.30	193.90	222.80	254.00	272.50	261.40	221.70	183.30	131.80	100.80	53.00
18	(b) (6)	1	1	2	R	0	38.750	85.710	128.40	169.70	191.90	254.60	321.60	312.70	305.70	288.80	236.20	202.40	131.90	99.35	56.40
19	(b) (6)	1	2	1	R	0	68.150	96.010	122.80	151.90	177.00	210.60	230.80	234.90	206.00	185.50	154.70	146.20	84.02	61.26	35.10
20	(b) (6)	1	2	2	T	0	49.750	133.100	166.40	241.90	229.30	279.20	278.20	269.70	262.20	248.90	177.20	160.90	104.00	79.08	36.93
21	(b) (6)	1	2	1	R	0	2.380	8.987	33.91	69.51	55.56	70.20	83.04	72.68	81.45	76.13	54.76	47.62	28.46	19.95	10.02
22	(b) (6)	1	2	2	T	0	4.997	18.480	40.77	63.10	84.29	101.30	130.50	132.90	146.30	130.00	106.20	92.68	63.33	43.81	22.96
23	(b) (6)	1	2	1	R	0	11.600	64.180	62.47	117.50	131.80	161.90	153.70	156.80	151.70	149.40	101.30	95.99	51.75	35.86	18.76
24	(b) (6)	1	2	2	T	0	46.050	128.500	147.40	214.20	234.10	281.60	276.30	304.10	259.70	236.80	181.80	157.60	93.05	69.17	44.07
25	(b) (6)	1	1	1	T	0	28.110	121.000	167.30	198.30	240.10	294.40	333.60	271.30	251.40	217.70	184.80	141.90	86.57	64.66	32.38
26	(b) (6)	1	1	2	R	0	27.130	101.600	122.10	197.10	177.20	213.90	263.20	272.10	255.20	220.10	185.50	142.80	69.92	56.77	27.09

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
27	(b) (6)	1	2	1	R	0	10.370	28.400	55.04	77.16	78.50	111.00	127.90	139.50	130.30	111.10	89.52	78.11	49.65	36.28	17.98
28		1	2	2	T	0	5.416	21.830	52.92	80.53	103.30	126.10	160.10	167.60	169.00	130.50	114.60	91.28	63.18	44.24	25.62
29		1	2	1	R	0	34.270	90.640	166.60	189.70	218.40	229.20	239.30	224.00	168.50	135.20	102.30	77.61	56.62	34.63	18.72
30		1	2	2	T	0	68.280	175.000	223.10	252.30	283.00	305.10	333.90	321.00	236.80	191.80	153.80	112.90	68.02	47.78	29.27
31		1	2	1	R	0	14.080	43.280	86.15	91.10	123.70	132.50	158.80	188.10	197.60	231.50	205.30	175.70	126.40	89.39	52.24
32		1	2	2	T	0	29.490	40.340	83.59	78.84	109.90	135.40	181.70	215.50	248.10	258.70	230.10	215.20	151.20	125.40	69.66
33		1	1	1	T	0	47.490	91.820	132.10	201.70	249.10	271.40	286.40	275.60	230.60	205.00	166.90	134.40	78.62	59.11	32.17
34		1	1	2	R	0	44.790	95.250	180.10	235.90	292.60	312.20	309.50	340.00	297.90	269.00	200.40	168.10	97.97	74.24	37.30
35		1	1	1	T	0	31.070	73.160	79.39	158.10	186.50	196.40	177.80	179.70	165.40	156.00	138.80	122.50	71.50	57.44	30.42
36		1	1	2	R	0	28.560	128.300	98.52	121.10	137.50	153.70	193.60	183.70	182.00	157.20	136.30	109.10	61.42	48.19	25.19
37		1	1	1	T	0	28.600	220.500	199.50	189.40	267.10	210.90	235.60	232.30	225.20	182.60	144.80	129.70	74.92	54.63	32.19
38		1	1	2	R	0	25.010	47.220	79.19	125.00	137.90	192.40	177.00	196.30	176.30	162.60	142.40	130.00	72.55	48.00	30.16
39		1	1	1	T	0	19.880	60.120	92.34	108.10	128.40	180.20	221.20	243.70	229.10	252.60	206.10	190.20	82.11	74.25	48.66
40		1	1	2	R	0	28.790	46.400	94.49	129.40	150.70	208.70	266.70	265.90	251.10	249.50	200.80	155.50	101.00	67.59	41.83
41		1	1	1	T	0	39.400	126.700	139.40	209.40	181.00	270.30	303.00	367.40	329.10	294.00	272.10	196.40	119.60	85.23	55.33
42		1	1	2	R	0	25.870	75.120	108.20	171.80	186.30	229.90	275.80	278.10	252.70	230.40	170.30	134.50	71.88	52.23	36.48
43		1	2	1	R	0	47.250	83.220	99.69	162.40	175.70	248.00	197.70	213.30	183.70	174.00	158.00	135.30	81.15	59.49	34.75
44		1	2	2	T	0	37.850	56.240	85.73	104.90	135.60	168.90	222.40	209.60	192.40	204.80	175.70	145.60	85.34	57.03	35.34
45		2	2	1	R	0	31.460	96.860	110.40	168.90	191.20	227.70	258.80	259.60	243.80	242.80	201.90	171.00	104.30	69.11	46.11
46		2	2	2	T	0	37.920	79.990	127.50	139.60	177.80	209.10	258.00	237.60	287.10	251.00	222.90	198.80	116.90	85.28	54.00
47		2	2	1	R	0	29.770	57.310	99.64	141.20	174.90	219.20	240.80	242.90	237.20	236.50	186.80	176.20	89.80	65.77	36.32
48		2	2	2	T	0	44.560	87.050	123.30	137.20	164.80	229.00	281.60	321.30	342.20	312.10	276.80	263.30	137.10	94.66	57.52
49		2	2	1	R	0	5.386	28.530	51.86	75.95	103.70	123.10	152.00	169.00	154.10	139.30	115.10	103.60	60.55	46.80	27.37
50		2	2	2	T	0	10.630	31.270	62.84	72.37	79.62	120.00	133.70	152.50	178.00	159.00	138.90	113.00	76.68	55.59	34.25
51		2	2	1	R	0	5.259	25.350	54.13	78.88	97.10	115.90	138.50	144.30	168.00	156.50	123.60	102.40	67.54	54.12	31.36
52		2	2	2	T	0	13.480	43.580	82.43	100.80	148.60	161.20	185.50	174.00	225.10	174.70	147.60	125.70	81.02	63.89	38.68
53		2	1	1	T	0	152.300	94.310	134.20	182.60	198.80	226.20	294.60	271.90	243.20	210.10	157.40	131.90	75.62	61.12	35.32
54		2	1	2	R	0	17.120	68.960	103.70	136.70	141.60	148.30	190.60	186.00	180.80	166.90	116.30	94.13	52.93	39.90	23.14
55		2	1	1	T	0	35.120	72.560	121.70	139.30	196.90	257.30	290.60	303.40	274.90	234.70	191.30	160.90	100.00	76.42	43.79

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
56	(b) (6)	2	1	2	R	0	23.540	60.370	82.72	135.00	165.10	181.90	244.70	265.40	236.70	204.00	164.80	140.20	78.77	55.47	30.66
57		2	2	1	R	0	41.670	142.900	111.50	166.80	237.30	284.10	256.10	229.10	204.30	158.30	129.00	109.00	69.67	55.43	31.01
58		2	2	2	T	0	29.560	179.800	160.60	251.90	272.70	301.00	297.90	277.60	237.20	200.40	169.80	139.10	81.36	64.23	37.61
59		2	1	1	T	0	10.850	28.980	73.31	123.30	137.40	182.60	192.40	186.60	182.60	156.40	147.80	123.60	79.49	52.35	27.73
60		2	1	2	R	0	19.090	32.070	52.22	71.12	115.20	163.80	166.90	179.90	169.50	158.70	128.60	101.00	66.14	47.01	27.16
61		2	1	1	T	0	10.810	28.020	75.83	70.50	110.50	114.00	138.70	153.00	146.10	153.60	107.60	118.10	66.82	46.11	34.98
62		2	1	2	R	0	13.250	36.220	49.51	57.32	82.99	121.60	125.10	135.40	154.10	137.40	118.20	116.20	55.13	46.96	28.18
63		2	1	1	T	0	20.550	46.650	98.72	115.90	169.30	190.50	233.80	249.40	230.20	189.50	171.10	134.90	85.14	61.01	34.68
64		2	1	2	R	0	18.950	22.970	66.36	82.04	124.10	109.20	138.00	110.00	145.60	129.80	105.40	84.85	57.48	47.23	26.67
65		2	1	1	T	0	15.780	47.430	73.82	109.60	139.00	136.60	159.30	172.50	159.70	135.90	110.60	93.01	62.51	50.68	29.23
66		2	1	2	R	0	10.770	49.070	47.22	107.50	100.00	136.10	161.80	146.10	136.10	134.30	108.40	78.73	55.78	42.23	26.10
67		2	2	1	R	0	9.672	41.790	67.74	113.90	104.10	164.50	214.00	250.60	206.70	187.80	160.70	129.70	82.36	62.22	37.08
68		2	2	2	T	0	44.360	109.500	185.40	240.80	318.80	373.00	374.00	363.60	331.90	308.90	247.20	227.00	136.50	105.40	57.68
69		2	2	1	R	0	19.500	72.450	104.70	177.00	186.40	248.10	259.30	229.90	211.10	198.20	149.40	118.60	65.42	53.50	25.50
70		2	2	2	T	0	34.730	150.700	169.70	174.20	286.60	266.10	261.10	227.70	209.00	191.80	161.60	124.10	83.46	60.69	34.41
71		2	1	1	T	0	4.478	25.400	95.88	102.50	179.20	173.70	223.30	215.30	217.70	204.40	166.30	145.70	86.75	61.77	42.93
72		2	1	2	R	0	10.360	22.570	70.89	77.27	92.98	131.00	140.30	163.30	188.20	167.50	147.50	102.30	75.13	55.36	31.59
73		2	1	1	T	0	14.890	59.390	144.70	138.00	217.40	223.40	284.00	273.20	266.60	274.30	241.70	200.00	125.40	88.98	49.90
74		2	1	2	R	0	25.160	50.510	85.37	119.10	131.60	160.40	189.20	180.60	186.50	182.60	151.20	135.70	79.27	63.57	35.16
75		2	2	1	R	0	18.060	62.220	94.64	121.00	166.00	197.70	260.60	304.90	267.80	246.20	205.40	168.20	107.10	74.68	38.82
76		2	2	2	T	0	13.400	63.120	109.00	202.80	184.10	294.60	254.30	303.70	343.50	334.60	257.30	240.00	154.00	94.24	67.30
77		2	1	1	T	0	7.768	31.420	51.96	73.68	91.09	121.40	176.80	194.20	188.70	188.00	181.00	153.30	101.80	69.87	52.96
78		2	1	2	R	0	13.210	36.260	68.99	85.16	154.70	197.20	169.60	186.10	185.30	178.80	155.10	153.90	102.80	69.41	38.78
79	2	2	1	R	0	9.622	40.560	76.71	101.30	130.90	157.20	163.30	153.00	126.30	103.80	71.51	58.62	29.88	22.05	12.13	
80	2	2	2	T	0	16.430	61.030	90.26	133.40	157.90	187.90	198.00	176.70	142.80	122.30	90.05	74.69	48.56	37.75	18.70	
81	2	2	1	R	0	117.400	206.800	223.50	288.50	324.50	355.80	393.80	361.10	307.10	276.60	211.40	170.70	94.68	64.86	36.23	
82	2	2	2	T	0	136.900	249.400	310.20	411.90	460.60	455.00	430.90	407.10	307.70	272.30	187.10	148.90	81.73	64.97	37.93	
83	2	1	1	T	0	24.810	70.890	97.18	136.80	157.20	151.00	186.80	213.80	179.30	177.70	157.00	136.20	90.45	74.11	51.24	
84	2	1	2	R	0	30.520	58.210	85.71	106.70	135.80	175.30	190.20	186.20	167.40	165.00	140.00	119.70	71.17	51.80	27.73	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
85	(b) (6)	2	1	1	T	0	21.100	146.700	115.90	154.80	206.10	204.80	229.50	223.60	175.70	143.90	104.80	84.08	47.64	35.17	17.88
86		2	1	2	R	0	60.040	60.79	82.50	112.70	138.80	160.90	148.00	126.20	96.08	69.20	53.34	33.39	21.58	11.75	
87		3	2	1	R	0	32.610	61.020	97.98	100.20	147.30	161.70	168.00	156.30	121.10	91.83	73.48	58.21	33.67	26.90	15.23
88		3	2	2	T	0	32.570	80.720	104.70	143.40	158.70	188.90	189.50	205.60	149.50	130.90	96.73	72.03	47.58	31.70	18.44
89		3	2	1	R	0	18.550	58.090	98.79	130.70	158.00	177.00	192.80	198.20	169.10	164.00	135.30	115.30	77.53	54.70	32.00
90		3	2	2	T	0	30.960	94.670	106.40	159.50	179.50	196.50	219.70	212.30	219.10	198.50	157.80	140.70	81.96	63.25	41.28
91		3	1	1	T	0	12.140	53.060	85.36	110.50	128.30	152.90	197.80	214.60	193.10	184.50	150.00	119.70	68.67	61.38	35.29
92		3	1	2	R	0	25.070	56.680	100.70	133.30	150.70	203.80	230.40	206.50	192.20	183.70	136.90	104.80	58.48	37.80	22.57
93		3	2	1	R	0	8.718	33.030	58.65	92.19	108.20	169.60	215.00	221.80	235.10	221.10	176.50	140.30	75.24	57.01	29.88
94		3	2	2	T	0	20.490	49.260	116.90	145.20	181.40	205.70	189.70	221.90	250.20	220.50	174.00	149.40	88.71	63.62	33.07
95		3	2	1	R	0	12.780	44.640	72.46	103.60	126.90	142.20	176.80	189.00	202.90	213.30	182.40	163.30	99.24	81.28	49.99
96		3	2	2	T	0	18.190	41.990	100.40	110.80	104.20	134.60	164.80	204.10	229.20	229.10	196.60	180.90	116.10	87.25	57.27
97		3	1	1	T	0	25.370	71.020	159.10	268.60	311.70	357.60	357.00	347.10	355.30	339.10	269.50	219.40	119.00	92.21	47.89
98		3	1	2	R	0	25.830	62.260	140.30	218.50	235.50	283.40	271.40	265.70	242.50	226.10	165.00	139.00	77.27	58.90	28.46
99		3	1	1	T	0	71.650	123.400	176.20	237.40	268.50	312.20	324.50	304.80	272.10	230.00	185.20	154.00	82.12	56.45	34.81
100		3	1	2	R	0	65.090	88.960	128.00	178.10	242.50	275.00	273.20	277.20	234.70	221.80	166.90	137.80	77.29	57.07	32.17
101		3	2	1	R	0	16.640	52.910	69.51	136.40	129.00	143.60	186.80	207.20	217.20	220.20	187.70	167.00	87.06	67.66	39.06
102		3	2	2	T	0	16.790	55.000	101.50	126.60	150.70	193.80	201.80	229.50	222.10	216.20	187.80	159.00	88.24	72.83	45.08
103		3	2	1	R	0	21.790	36.490	76.03	111.90	178.70	169.50	200.70	214.30	218.10	190.70	149.20	123.40	74.93	50.28	26.18
104		3	2	2	T	0	25.570	57.480	117.30	131.60	148.00	200.90	221.10	245.90	248.80	237.70	193.60	166.60	100.60	84.94	48.98
105	3	2	1	R	0	13.510	44.760	85.40	106.00	134.80	162.20	198.20	216.60	242.80	232.50	166.40	132.40	76.63	55.66	30.60	
106	3	2	2	T	0	21.590	31.560	74.74	102.80	138.40	178.00	201.20	229.30	191.90	203.00	170.60	131.90	86.58	61.14	33.22	
107	3	1	1	T	0	21.170	104.600	92.72	131.70	155.70	211.90	234.30	252.70	228.50	234.40	199.10	164.10	96.58	71.30	36.99	
108	3	1	2	R	0	25.380	34.280	75.02	101.10	117.80	135.80	180.80	229.40	200.80	197.70	165.10	125.70	69.26	55.92	30.10	
109	3	1	1	T	0	73.640	98.020	135.50	170.00	224.10	211.70	219.00	189.60	198.60	170.40	132.60	115.00	58.38	43.68	24.62	
110	3	1	2	R	0	105.400	154.30	161.60	185.60	212.20	229.90	189.90	197.00	144.70	121.10	60.56	44.56	29.66			
111	3	2	1	R	0	51.790	153.500	148.40	240.70	259.20	316.50	275.80	262.30	231.80	199.70	167.60	147.70	81.78	62.06	32.53	
112	3	2	2	T	0	30.090	86.680	93.02	126.00	168.60	283.30	256.10	272.60	240.90	224.40	185.60	164.90	87.53	70.61	39.25	
113	3	2	1	R	0	14.780	59.210	108.60	142.00	147.70	182.50	202.20	213.30	219.40	189.70	168.90	149.80	101.10	65.96	41.00	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
114	(b) (6)	3	2	2	T	0	21.680	102.500	123.90	150.30	203.40	236.80	215.80	256.70	259.50	249.90	224.90	199.10	128.30	88.72	57.75
115		3	1	1	T	0	31.960	56.470	89.94	128.90	156.50	224.20	247.70	246.70	250.00	202.50	164.60	119.50	69.93	53.07	30.20
116		3	1	2	R	0	45.730	69.750	89.96	137.90	162.40	168.00	179.60	206.20	160.00	146.30	107.80	83.26	50.52	39.46	19.17
117		3	1	1	T	0	63.130	102.200	95.73	160.30	146.70	170.80	205.40	213.00	203.50	177.30	160.40	144.70	88.22	69.67	41.72
118		3	1	2	R	0	25.570	68.300	91.33	102.20	142.90	177.20	195.70	183.90	184.30	170.60	142.70	119.90	65.44	54.91	27.46
119		3	2	1	R	0	19.000	53.610	115.10	129.20	173.40	192.80	259.30	264.00	272.40	265.50	211.90	189.50	118.30	82.98	45.89
120		3	2	2	T	0	43.740	60.510	98.67	169.70	194.60	297.50	344.00	400.80	375.90	342.60	295.30	244.60	153.40	118.10	62.93
121		3	2	1	R	0	106.500	159.300	221.60	253.60	311.60	360.20	353.80	310.00	320.30	272.50	220.00	176.30	100.50	66.85	42.77
122		3	2	2	T	0	64.140	103.500	196.10	254.60	274.30	332.40	342.50	348.40	277.90	238.10	207.90	162.70	93.03	72.30	40.46
123		3	1	1	T	0	31.670	119.400	162.50	252.40	243.90	297.20	321.60	310.00	266.80	225.30	147.10	119.20	74.00	57.23	30.54
124		3	1	2	R	0	59.930	118.300	175.70	212.90	263.40	319.30	323.40	329.20	272.80	245.50	181.20	151.40	84.20	62.41	33.51
125		3	2	1	R	0	26.470	57.760	89.56	122.20	180.50	219.60	261.40	279.70	270.10	235.70	183.10	148.60	87.14	55.92	33.97
126		3	2	2	T	0	40.240	73.540	90.24	129.60	158.00	242.80	267.10	290.40	266.80	266.00	208.30	173.20	101.00	67.21	41.89

Obs	c17	c18	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
1	4.255	3.152	2.728	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
2	14.930	9.300	7.286	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.55000	0.75000	1.00000	1.50000	2.05000	3.00000
3	18.740	10.750	4.600	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
4	17.360	10.430	3.251	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
5	10.080	6.842	4.637	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
6	8.459	4.497	2.845	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
7	25.490	12.780	6.605	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
8	16.930	6.097	2.059	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
9	10.950	4.337	2.162	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
10	18.320	8.446	3.483	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
11	19.210	10.400	6.297	16	19	0	0.033333	0.10000	0.20000	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
12	14.530	6.885	3.772	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
13	12.800	5.819	4.389	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
14	11.790	5.666	2.790	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000

Obs	c17	c18	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
15	17.620	7.442	4.558	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
16	15.550	7.204	3.960	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
17	26.750	10.060	7.265	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.53333	2.00000	3.03333
18	22.980	8.439	5.745	16	19	0	0.033333	0.083333	0.21667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
19	12.400	6.726	5.404	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
20	15.870	10.030	5.164	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
21	3.088	1.279	0.000	15	18	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.03333	1.50000	2.00000	3.00000
22	8.827	3.912	1.758	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
23	4.667	1.676	1.069	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
24	11.530	4.181	2.333	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
25	12.290	6.055	4.007	16	19	0	0.033333	0.083333	0.20000	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
26	9.812	3.961	2.463	16	19	0	0.033333	0.083333	0.18333	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.01667
27	5.459	2.377	2.008	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
28	8.663	4.566	2.813	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
29	7.557	3.529	2.326	16	19	0	0.033333	0.11667	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
30	12.370	6.481	4.062	16	19	0	0.033333	0.10000	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
31	20.570	10.560	4.941	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
32	27.390	17.740	8.400	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
33	14.070	9.184	4.188	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
34	14.170	6.190	6.368	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
35	12.810	4.966	3.293	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
36	8.895	4.029	2.189	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
37	11.800	6.864	5.541	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.76667	1.00000	1.50000	2.00000	3.00000
38	9.742	5.000	3.739	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
39	22.790	10.100	5.619	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
40	18.720	7.078	4.809	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
41	25.110	16.340	10.880	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
42	13.070	8.446	5.873	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
43	11.050	7.794	3.799	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.51667	2.00000	3.00000

Obs	c17	c18	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
44	13.920	8.356	5.568	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
45	17.640	9.013	5.381	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
46	23.210	12.150	9.287	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
47	14.140	8.212	5.360	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
48	24.820	16.210	8.644	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
49	7.819	2.483	1.525	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
50	13.770	5.409	3.564	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
51	11.120	5.184	2.914	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
52	15.470	7.975	5.061	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
53	13.240	7.637	6.635	16	19	0	0.033333	0.083333	0.16667	0.25000	0.36667	0.50000	0.78333	1.00000	1.50000	2.00000	3.10000
54	9.047	4.953	3.462	16	19	0	0.033333	0.083333	0.16667	0.28333	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
55	19.350	8.960	7.626	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
56	12.210	6.626	3.778	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
57	11.790	7.110	4.432	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
58	14.920	7.346	5.905	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
59	12.130	5.754	3.745	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
60	7.216	3.797	2.009	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.55000	2.00000	3.00000
61	16.000	6.120	4.871	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
62	12.840	5.547	3.667	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
63	14.330	8.614	6.363	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
64	11.350	5.889	3.733	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
65	12.010	5.140	2.890	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
66	8.569	2.636	2.086	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
67	10.880	3.996	2.181	16	19	0	0.033333	0.083333	0.18333	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
68	25.590	9.784	3.705	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.01667	1.50000	2.00000	3.00000
69	10.430	4.281	3.398	16	19	0	0.033333	0.083333	0.20000	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
70	13.530	6.409	5.988	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
71	17.820	10.350	9.119	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
72	12.220	7.502	4.697	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000

Obs	c17	c18	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
73	18.130	8.717	4.085	16	19	0	0.033333	0.083333	0.250000	0.283333	0.383333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
74	13.580	4.771	2.360	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.81667	1.000000	1.500000	2.000000	3.000000
75	16.900	7.615	4.618	16	19	0	0.033333	0.083333	0.183333	0.250000	0.333333	0.500000	0.750000	1.06667	1.500000	2.000000	3.000000
76	24.610	11.200	8.781	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
77	23.050	13.390	7.547	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
78	15.790	8.562	3.609	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
79	4.299	2.263	2.032	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
80	8.381	3.970	3.248	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
81	11.930	5.938	3.605	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
82	13.520	8.380	5.441	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
83	21.120	9.080	7.346	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.033333	3.000000
84	11.730	4.678	4.351	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.01667	3.000000
85	6.847	3.391	1.920	16	19	0	0.033333	0.083333	0.16667	0.300000	0.350000	0.550000	0.800000	1.000000	1.533333	2.000000	3.000000
86	5.281	2.136	1.365	16	19	0	0.033333	0.11667	0.16667	0.250000	0.333333	0.500000	0.800000	1.000000	1.500000	2.000000	3.000000
87	5.692	3.886	1.901	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
88	8.674	5.183	3.470	16	19	0	0.033333	0.100000	0.16667	0.250000	0.333333	0.500000	0.81667	1.000000	1.500000	2.000000	3.000000
89	11.890	6.121	5.407	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
90	17.120		7.905	15	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
91	12.510	7.610	4.768	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
92	7.688	4.528	2.794	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
93	10.490	5.006	3.510	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
94	13.750	5.694	3.999	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
95	19.040	8.001	3.794	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
96	27.450	11.150	6.493	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
97	21.960	14.140	8.122	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
98	11.850	5.202	3.655	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
99	16.570	8.115	8.262	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
100	14.590	8.506	5.151	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000
101	15.100	7.485	4.629	16	19	0	0.033333	0.083333	0.16667	0.250000	0.333333	0.500000	0.750000	1.000000	1.500000	2.000000	3.000000

Obs	c17	c18	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
102	20.640	8.186	6.538	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
103	10.100	4.174	2.148	16	19	0	0.033333	0.083333	0.16667	0.25000	0.36667	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
104	21.680	7.961	6.097	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
105	12.830	6.203	3.807	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
106	16.340	10.170	7.610	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
107	14.380	6.604	3.454	16	19	0	0.033333	0.083333	0.16667	0.25000	0.41667	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
108	10.100	3.385	2.601	16	19	0	0.050000	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
109	8.898	4.805	3.768	16	19	0	0.033333	0.083333	0.16667	0.25000	0.38333	0.50000	0.75000	1.00000	1.55000	2.00000	3.00000
110	8.715	4.905	2.748	16	19	0	0.033333	0.10000	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.66667	2.00000	3.00000
111	10.730	4.175	1.257	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
112	15.010	7.110	5.401	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.53333	0.75000	1.00000	1.50000	2.00000	3.00000
113	15.040	6.419	3.953	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
114	24.730	11.630	7.226	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
115	11.260	5.842	4.197	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
116	6.590	3.428	1.891	16	19	0	0.033333	0.083333	0.16667	0.25000	0.40000	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
117	14.560	9.052	5.678	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
118	9.194	5.541	3.164	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
119	19.470	6.450	3.822	16	19	0	0.033333	0.083333	0.18333	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
120	30.010	11.440	7.104	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
121	18.030	9.646	5.261	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
122	18.450	11.390	6.982	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
123	12.630	8.237	6.301	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
124	13.590	6.507	5.172	16	19	0	0.033333	0.10000	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.13333
125	14.440	9.312	7.184	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000
126	20.720	12.590	7.750	16	19	0	0.033333	0.083333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000

Obs	T13	T14	T15	T16	T17	T18	T19	trt
1	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
2	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1

Obs	T13	T14	T15	T16	T17	T18	T19	trt
3	4	6.00000	8.00000	12.0000	24.0000	36.0000	50.1833	1
4	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
5	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
6	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
7	4	6.00000	8.00000	12.0000	24.0000	36.0833	48.0000	1
8	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
9	4	6.00000	8.00000	12.0000	24.0000	36.0167	48.0000	2
10	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
11	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
12	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
13	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
14	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
15	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
16	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
17	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
18	4	6.00000	8.00000	12.0000	24.0333	36.0000	48.0000	2
19	4	6.00000	8.00000	12.0333	24.0000	36.1333	48.0000	2
20	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
21	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
22	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
23	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
24	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
25	4	6.00000	8.00000	12.0000	24.0500	36.0000	48.0000	1
26	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
27	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
28	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
29	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
30	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
31	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2

Obs	T13	T14	T15	T16	T17	T18	T19	trt
32	4	6.01667	8.03333	12.0000	24.0000	36.0000	48.0000	1
33	4	6.00000	8.05000	12.0000	24.0000	36.0000	48.0500	1
34	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
35	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
36	4	6.01667	8.00000	12.0000	24.0000	36.0000	48.0000	2
37	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
38	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
39	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
40	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
41	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
42	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
43	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
44	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
45	4	6.00000	8.03333	12.0000	24.0000	36.0000	48.0000	2
46	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
47	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
48	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
49	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
50	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
51	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
52	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
53	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.4167	1
54	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
55	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
56	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0500	2
57	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
58	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
59	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
60	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2

Obs	T13	T14	T15	T16	T17	T18	T19	trt
61	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
62	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
63	4	6.00000	8.00000	12.0000	24.0000	36.0000	49.3167	1
64	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
65	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
66	4	6.00000	8.00000	12.0000	24.0167	36.0000	48.0000	2
67	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0333	2
68	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
69	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
70	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
71	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
72	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
73	4	6.00000	8.00000	12.0667	24.0167	36.0000	48.0000	1
74	4	6.00000	8.00000	12.0167	24.0000	36.0000	48.0000	2
75	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
76	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
77	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
78	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
79	4	6.00000	8.00000	12.0500	24.0000	36.0000	48.0000	2
80	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
81	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
82	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
83	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
84	4	6.03333	8.01667	12.0000	24.0000	36.0000	48.0000	2
85	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
86	4	6.05000	8.00000	12.0000	24.0500	36.0000	48.0000	2
87	4	6.00000	8.01667	12.0000	24.0000	36.0000	48.0000	2
88	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
89	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2

Obs	T13	T14	T15	T16	T17	T18	T19	trt
90	4	6.00000	8.00000	12.0000	24.0000	36.0000	53.3833	1
91	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
92	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
93	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
94	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
95	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
96	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
97	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
98	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
99	4	6.00000	8.00000	12.0500	24.0000	36.0000	48.0000	1
100	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
101	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
102	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
103	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
104	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
105	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
106	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
107	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
108	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
109	4	6.05000	8.00000	12.0000	24.0000	36.0000	48.0000	1
110	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
111	4	6.00000	8.00000	12.0167	24.0000	36.0000	48.0000	2
112	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
113	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
114	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
115	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
116	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
117	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
118	4	6.00000	8.01667	12.0000	24.0000	36.0000	48.0000	2

Obs	T13	T14	T15	T16	T17	T18	T19	trt
119	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
120	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
121	4	6.00000	8.00000	12.1667	24.0000	36.0000	48.0000	2
122	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1
123	4	6.03333	8.00000	12.0000	24.0000	36.0000	48.0000	1
124	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
125	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	2
126	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000	1

5.9.3.2 Fasting Study Output (FP)

Group 1

Fasting STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	22	(b) (6)
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	44
Number of Observations Used	44

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	23	4.13843624	0.17993201	6.59	<.0001
Error	20	0.54630594	0.02731530		
Corrected Total	43	4.68474219			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.883386	2.222410	0.165273	7.436676

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.76657129	0.76657129	28.06	<.0001
sub(seq)	20	2.67061619	0.13353081	4.89	0.0004
per	1	0.11830861	0.11830861	4.33	0.0505
trt	1	0.58294016	0.58294016	21.34	0.0002

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.76657129	0.76657129	28.06	<.0001
sub(seq)	20	2.67061619	0.13353081	4.89	0.0004
per	1	0.16969907	0.16969907	6.21	0.0216
trt	1	0.58294016	0.58294016	21.34	0.0002

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.76657129	0.76657129	5.74	0.0265

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.23116267	0.05003901	4.62	0.0002

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	23	4.25283988	0.18490608	6.53	<.0001
Error	20	0.56616303	0.02830815		
Corrected Total	43	4.81900291			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.882514	2.250370	0.168250	7.476559

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.77266493	0.77266493	27.29	<.0001
sub(seq)	20	2.74982792	0.13749140	4.86	0.0004
per	1	0.10557687	0.10557687	3.73	0.0678
trt	1	0.62477016	0.62477016	22.07	0.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.77266493	0.77266493	27.29	<.0001
sub(seq)	20	2.74982792	0.13749140	4.86	0.0004
per	1	0.15637059	0.15637059	5.52	0.0291
trt	1	0.62477016	0.62477016	22.07	0.0001

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.77266493	0.77266493	5.62	0.0279

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.23931276	0.05094030	4.70	0.0001

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	23	3.93487923	0.17108171	6.41	<.0001
Error	20	0.53361802	0.02668090		
Corrected Total	43	4.46849726			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.880582	3.022637	0.163343	5.403987

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.21377844	0.21377844	8.01	0.0103
sub(seq)	20	3.26983595	0.16349180	6.13	<.0001
per	1	0.06436475	0.06436475	2.41	0.1361
trt	1	0.38690009	0.38690009	14.50	0.0011

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.21377844	0.21377844	8.01	0.0103
sub(seq)	20	3.26983595	0.16349180	6.13	<.0001
per	1	0.09560352	0.09560352	3.58	0.0729
trt	1	0.38690009	0.38690009	14.50	0.0011

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.21377844	0.21377844	1.31	0.2663

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.18832377	0.04945452	3.81	0.0011

Group 2

Fasting STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	21	(b) (6)
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	42
Number of Observations Used	42

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	22	3.82374646	0.17380666	19.92	<.0001
Error	19	0.16580206	0.00872642		
Corrected Total	41	3.98954852			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.958441	1.259825	0.093415	7.414943

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.26849626	0.26849626	30.77	<.0001
sub(seq)	19	2.82306816	0.14858253	17.03	<.0001
per	1	0.00326437	0.00326437	0.37	0.5480
trt	1	0.72891767	0.72891767	83.53	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.26849626	0.26849626	30.77	<.0001
sub(seq)	19	2.82306816	0.14858253	17.03	<.0001
per	1	0.00026943	0.00026943	0.03	0.8624
trt	1	0.72891767	0.72891767	83.53	<.0001

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.26849626	0.26849626	1.81	0.1947

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.26377738	0.02886134	9.14	<.0001

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	22	3.95719567	0.17987253	22.31	<.0001
Error	19	0.15317779	0.00806199		
Corrected Total	41	4.11037345			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.962734	1.203482	0.089789	7.460734

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.25262779	0.25262779	31.34	<.0001
sub(seq)	19	2.87480858	0.15130571	18.77	<.0001
per	1	0.00430378	0.00430378	0.53	0.4739
trt	1	0.82545553	0.82545553	102.39	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.25262779	0.25262779	31.34	<.0001
sub(seq)	19	2.87480858	0.15130571	18.77	<.0001
per	1	0.00049571	0.00049571	0.06	0.8068
trt	1	0.82545553	0.82545553	102.39	<.0001

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.25262779	0.25262779	1.67	0.2118

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.28070177	0.02774083	10.12	<.0001

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	22	3.18100172	0.14459099	10.82	<.0001
Error	19	0.25399996	0.01336842		
Corrected Total	41	3.43500167			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.926055	2.128153	0.115622	5.432968

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.75472774	0.75472774	56.46	<.0001
sub(seq)	19	2.02751974	0.10671157	7.98	<.0001
per	1	0.00492042	0.00492042	0.37	0.5512
trt	1	0.39383381	0.39383381	29.46	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.75472774	0.75472774	56.46	<.0001
sub(seq)	19	2.02751974	0.10671157	7.98	<.0001
per	1	0.00161461	0.00161461	0.12	0.7320
trt	1	0.39383381	0.39383381	29.46	<.0001

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.75472774	0.75472774	7.07	0.0155

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.19388973	0.03572221	5.43	<.0001

Group 3

Fasting STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	20	(b) (6)
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	40
Number of Observations Used	40

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	2.21700500	0.10557167	8.60	<.0001
Error	18	0.22105412	0.01228078		
Corrected Total	39	2.43805913			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.909332	1.477488	0.110819	7.500480

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.13158208	0.13158208	10.71	0.0042
sub(seq)	18	1.73591680	0.09643982	7.85	<.0001
per	1	0.01275478	0.01275478	1.04	0.3217
trt	1	0.33675135	0.33675135	27.42	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.13158208	0.13158208	10.71	0.0042
sub(seq)	18	1.73591680	0.09643982	7.85	<.0001
per	1	0.00002922	0.00002922	0.00	0.9616
trt	1	0.33675135	0.33675135	27.42	<.0001

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.13158208	0.13158208	1.36	0.2580

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.18729193	0.03576658	5.24	<.0001

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	2.30126528	0.10958406	9.21	<.0001
Error	18	0.21413917	0.01189662		
Corrected Total	39	2.51540445			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.914869	1.445071	0.109072	7.547839

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.13345660	0.13345660	11.22	0.0036
sub(seq)	18	1.73762256	0.09653459	8.11	<.0001
per	1	0.01537198	0.01537198	1.29	0.2706
trt	1	0.41481414	0.41481414	34.87	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.13345660	0.13345660	11.22	0.0036
sub(seq)	18	1.73762256	0.09653459	8.11	<.0001
per	1	0.00005378	0.00005378	0.00	0.9471
trt	1	0.41481414	0.41481414	34.87	<.0001

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.13345660	0.13345660	1.38	0.2550

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.20786969	0.03520272	5.90	<.0001

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	1.35137728	0.06435130	8.33	<.0001
Error	18	0.13902851	0.00772381		
Corrected Total	39	1.49040579			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.906718	1.589338	0.087885	5.529674

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00212016	0.00212016	0.27	0.6067
sub(seq)	18	1.28145024	0.07119168	9.22	<.0001
per	1	0.00320790	0.00320790	0.42	0.5274
trt	1	0.06459898	0.06459898	8.36	0.0097

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00212016	0.00212016	0.27	0.6067
sub(seq)	18	1.28145024	0.07119168	9.22	<.0001
per	1	0.00002173	0.00002173	0.00	0.9583
trt	1	0.06459898	0.06459898	8.36	0.0097

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00212016	0.00212016	0.03	0.8649

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.08203085	0.02836482	2.89	0.0097

AUCT/AUCI Ratio for Individual Subjects

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	trt	AUCRATIO
1	(b) (6)	1	0.93
2		1	0.96
3		1	0.97
4		1	0.96
5		1	0.97
6		1	0.95
7		1	0.95
8		1	0.97
9		1	0.95
10		1	0.96
11		1	0.98
12		1	0.99
13		1	0.96
14		1	0.96
15		1	0.96
16		1	0.95
17		1	0.96
18		1	0.97
19		1	0.94
20		1	0.96
21		1	0.92
22		1	0.94
23		1	0.93
24		1	0.95
25		1	0.96
26		1	0.95
27		1	0.93
28		1	0.94
29		1	0.94
30		1	0.96
31		1	0.95
32		1	0.93
33		1	0.97
34		1	0.98
35		1	0.94
36		1	0.90
37		1	0.98
38		1	0.95

Obs	sub	trt	AUCRATIO
39	(b) (6)	1	0.94
40		1	0.94
41		1	0.96
42		1	0.94
43		1	0.97
44		1	0.94
45		1	0.92
46		1	0.95
47		1	0.96
48		1	0.96
49		1	0.94
50		1	0.91
51		1	0.95
52		1	0.96
53		1	0.91
54		1	0.97
55		1	0.95
56		1	0.95
57		1	0.95
58		1	0.96
59		1	0.95
60		1	0.97
61		1	0.94
62		1	0.93
63		1	0.93
64		2	0.93
65		2	0.97
66		2	0.95
67		2	0.99
68		2	0.98
69		2	0.97
70		2	0.97
71		2	0.97
72		2	0.97
73		2	0.94
74		2	0.98
75		2	0.99
76		2	0.98
77		2	0.97
78		2	0.97

Obs	sub	trt	AUCRATIO
79	(b) (6)	2	0.97
80		2	0.95
81		2	0.98
82		2	0.96
83		2	0.96
84		2	0.94
85		2	0.96
86		2	0.96
87		2	0.95
88		2	0.98
89		2	0.97
90		2	0.95
91		2	0.96
92		2	0.95
93		2	0.98
94		2	0.95
95		2	0.95
96		2	0.98
97		2	0.98
98		2	0.96
99		2	0.94
100		2	0.98
101		2	0.96
102		2	0.97
103		2	0.95
104		2	0.97
105		2	0.95
106		2	0.97
107		2	0.96
108		2	0.93
109		2	0.96
110		2	0.97
111		2	0.97
112		2	0.97
113		2	0.95
114		2	0.96
115		2	0.98
116		2	0.96
117		2	0.98
118		2	0.97

Obs	sub	trt	AUCRATIO
119	(b) (6)	2	0.99
120	(b) (6)	2	0.97
121	(b) (6)	2	0.97
122	(b) (6)	2	0.96
123	(b) (6)	2	0.98
124	(b) (6)	2	0.96
125	(b) (6)	2	0.95
126	(b) (6)	2	0.92

T/R ratios for individual Subjects

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	2	2.28	2.30	2.00	0.73	1.02	0.98
(b) (6)	1	0.97	0.99	0.94	1.00	0.82	1.23
(b) (6)	2	0.87	0.86	0.93	1.50	1.13	0.89
(b) (6)	1	1.34	1.38	1.46	0.67	0.71	1.40
(b) (6)	2	1.43	1.43	1.35	1.33	0.96	1.05
(b) (6)	1	1.22	1.25	1.14	0.50	0.89	1.12
(b) (6)	1	1.02	1.05	1.13	0.33	0.86	1.16
(b) (6)	1	1.13	1.13	1.17	0.50	1.00	1.00
(b) (6)	1	0.96	0.98	0.85	2.04	0.88	1.13
(b) (6)	2	1.21	1.19	1.19	0.50	1.02	0.98
(b) (6)	2	2.10	2.10	1.76	2.00	0.74	1.35
(b) (6)	2	1.90	1.91	1.88	2.00	1.02	0.98
(b) (6)	1	1.12	1.14	1.23	0.75	0.86	1.16
(b) (6)	2	1.30	1.31	1.21	1.50	0.98	1.02
(b) (6)	2	1.45	1.47	1.40	1.00	0.94	1.07
(b) (6)	2	1.28	1.30	1.12	1.00	0.88	1.14
(b) (6)	1	0.85	0.84	0.84	0.75	1.07	0.94
(b) (6)	1	1.13	1.14	1.01	0.67	0.94	1.07
(b) (6)	1	1.15	1.17	1.36	0.33	0.84	1.19
(b) (6)	1	1.07	1.07	0.95	2.67	0.98	1.02
(b) (6)	1	1.52	1.55	1.32	1.00	0.90	1.11
(b) (6)	2	1.06	1.08	0.90	1.50	0.87	1.15
(b) (6)	2	1.16	1.19	1.11	1.50	0.83	1.20
(b) (6)	2	1.49	1.50	1.41	1.50	0.97	1.03
(b) (6)	2	1.23	1.26	1.05	1.50	0.79	1.27
(b) (6)	2	1.26	1.28	1.34	1.00	0.86	1.17
(b) (6)	1	1.45	1.49	1.55	1.04	0.87	1.15

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	1	1.29	1.33	1.14	1.00	0.87	1.14
	2	1.21	1.22	1.06	1.00	0.99	1.01
	1	1.17	1.19	1.07	0.75	0.80	1.25
	1	1.11	1.12	1.00	1.33	0.99	1.01
	1	1.48	1.51	1.71	0.67	0.82	1.22
	1	1.17	1.18	1.07	1.33	0.89	1.12
	2	1.74	1.74	1.49	0.75	0.97	1.03
	2	1.16	1.20	1.11	0.44	0.86	1.16
	1	1.30	1.36	1.19	0.50	0.84	1.20
	1	1.48	1.48	1.50	0.92	0.90	1.11
	2	1.39	1.42	1.13	1.41	0.96	1.04
	1	1.16	1.20	0.98	2.00	0.83	1.21
	2	1.40	1.41	1.21	1.00	1.00	1.00
	2	1.03	1.05	1.17	0.44	0.83	1.21
	1	1.37	1.39	1.12	1.33	1.03	0.97
	1	1.50	1.50	1.43	1.00	1.00	1.00
	2	1.29	1.33	1.22	1.33	0.83	1.20
	2	1.30	1.33	1.11	0.75	0.88	1.14
	1	1.24	1.26	0.93	1.33	0.96	1.05
	2	1.10	1.10	1.06	1.00	1.01	0.99
	2	1.16	1.18	1.07	0.75	0.86	1.16
	1	1.60	1.64	1.26	1.00	0.83	1.21
	1	1.10	1.14	1.17	0.75	0.83	1.20
	2	1.09	1.10	1.04	0.50	0.95	1.06
	2	1.49	1.53	1.14	1.00	0.86	1.16
	2	1.08	1.15	0.94	0.67	0.70	1.43
	1	1.28	1.29	1.10	1.00	0.94	1.07
	1	0.95	0.97	0.97	0.38	0.81	1.23
	2	1.13	1.18	0.90	1.07	0.63	1.60
	2	1.37	1.39	1.18	1.00	0.89	1.13
	1	1.45	1.48	1.21	1.50	0.87	1.16
	1	1.29	1.31	1.09	1.33	0.92	1.08
	2	1.39	1.41	1.47	0.67	0.88	1.14
	2	0.97	0.99	0.97	2.00	0.83	1.21
	1	0.92	0.95	0.98	0.75	0.81	1.23
	2	1.17	1.16	1.04	1.00	1.09	0.92

5.9.3.3 Firm Reviewer Ratio (FP)

Obs	sub (b) (6)	GRP	seq	per	trt	FDAAREA	FDAAUICI	FDACMAX	treat	FIRMAREA	FIRMAUICI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1		1	2	1	2	904.71	968.38	187.20	R	885.23	.	187.20	0.97847	.	1
2		1	2	2	1	2060.03	2226.88	374.00	T	2026.42	2166.73	374.00	0.98369	0.97299	1
3		1	1	1	1	1810.27	1893.70	170.70	T	1772.80	1856.23	170.70	0.97930	0.98021	1
4		1	1	2	2	1862.71	1910.79	181.50	R	1817.15	1860.21	181.50	0.97554	0.97353	1
5		1	2	1	2	1633.51	1723.19	239.40	R	1596.15	1664.85	239.40	0.97713	0.96615	1
6		1	2	2	1	1428.23	1477.02	223.30	T	1396.55	1445.34	223.30	0.97782	0.97855	1
7		1	1	1	1	2798.82	2900.36	278.30	T	2724.22	2825.75	278.30	0.97334	0.97428	1
8		1	1	2	2	2086.00	2108.59	191.00	R	2012.84	2036.29	191.00	0.96493	0.96571	1
9		1	2	1	2	1271.07	1300.18	123.60	R	1236.13	1265.23	123.60	0.97251	0.97312	1
10		1	2	2	1	1814.14	1863.19	166.90	T	1769.20	1818.26	166.90	0.97523	0.97588	1
11		1	1	1	1	2046.91	2155.87	207.00	T	1998.79	2107.75	207.00	0.97649	0.97768	1
12		1	1	2	2	1671.52	1729.79	181.60	R	1630.55	1688.82	181.60	0.97549	0.97631	1
13		1	1	1	1	1403.89	1478.52	148.30	T	1369.05	1435.56	148.30	0.97518	0.97094	1
14		1	1	2	2	1370.24	1411.25	131.60	R	1333.98	1380.44	131.60	0.97354	0.97817	1
15		1	1	1	1	2280.73	2347.56	298.30	T	2219.40	2273.14	298.30	0.97311	0.96830	1
16		1	1	2	2	2020.00	2078.08	254.70	R	1965.22	2023.30	254.70	0.97288	0.97364	1
17		1	1	1	1	2542.16	2667.79	272.50	T	2491.82	2617.45	272.50	0.98020	0.98113	1
18		1	1	2	2	2639.36	2727.11	321.60	R	2578.36	2654.24	321.60	0.97689	0.97328	1
19		1	2	1	2	1755.88	1860.03	234.90	R	1716.44	1798.05	234.90	0.97753	0.96667	1
20		1	2	2	1	2121.28	2218.70	279.20	T	2079.76	2177.18	279.20	0.98043	0.98129	1
21		1	2	1	2	544.60	557.97	83.04	R	529.89	544.81	83.04	0.97299	0.97640	1
22		1	2	2	1	1145.25	1170.01	146.30	T	1118.14	1144.28	146.30	0.97632	0.97801	1
23		1	2	1	2	1044.06	1057.40	161.90	R	1011.02	1022.35	161.90	0.96835	0.96685	1
24		1	2	2	1	1986.01	2014.49	304.10	T	1922.77	1948.68	304.10	0.96816	0.96733	1

Obs	sub (b) (6)	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
25		1	1	1	1	1872.52	1941.41	333.60	T	1833.17	1902.05	333.60	0.97898	0.97973	1
26		1	1	2	2	1668.20	1704.69	272.10	R	1627.02	1663.50	272.10	0.97531	0.97584	1
27		1	2	1	2	943.79	976.32	139.50	R	918.85	940.06	139.50	0.97358	0.96287	1
28		1	2	2	1	1228.42	1274.87	169.00	T	1199.69	1246.14	169.00	0.97661	0.97746	1
29		1	2	1	2	1172.07	1211.85	239.30	R	1150.09	1189.87	239.30	0.98125	0.98186	1
30		1	2	2	1	1705.15	1779.33	333.90	T	1674.67	1748.85	333.90	0.98212	0.98287	1
31		1	2	1	2	2254.92	2331.51	231.50	R	2202.87	2286.01	231.50	0.97692	0.98049	1
32		1	2	2	1	2886.56	3035.22	258.70	T	2820.84	2969.50	258.70	0.97723	0.97835	1
33		1	1	1	1	1833.70	1910.60	286.40	T	1799.94	1876.84	286.40	0.98159	0.98233	1
34		1	1	2	2	2152.21	2276.84	340.00	R	2105.34	.	340.00	0.97822	.	1
35		1	1	1	1	1516.03	1567.90	196.40	T	1481.77	1533.65	196.40	0.97740	0.97815	1
36		1	1	2	2	1341.05	1373.40	193.60	R	1308.49	1345.97	193.60	0.97572	0.98003	1
37		1	1	1	1	1688.82	1803.07	267.10	T	1654.27	1742.80	267.10	0.97954	0.96658	1
38		1	1	2	2	1473.61	1538.35	196.30	R	1437.06	1489.89	196.30	0.97520	0.96850	1
39		1	1	1	1	2221.86	2314.36	252.60	T	2170.02	2262.52	252.60	0.97667	0.97760	1
40		1	1	2	2	2076.22	2153.56	266.70	R	2033.69	2105.56	266.70	0.97952	0.97771	1
41		1	1	1	1	2783.58	3029.51	367.40	T	2738.89	2984.82	367.40	0.98395	0.98525	1
42		1	1	2	2	1830.76	1949.89	278.10	R	1792.37	1911.51	278.10	0.97903	0.98031	1
43		1	2	1	2	1683.72	1748.94	248.00	R	1642.14	1695.98	248.00	0.97530	0.96972	1
44		1	2	2	1	1776.66	1887.02	222.40	T	1741.39	1851.76	222.40	0.98015	0.98131	1
45		2	2	1	2	2164.73	2255.47	259.60	R	2118.09	2208.83	259.60	0.97845	0.97932	1
46		2	2	2	1	2503.14	2691.13	287.10	T	2455.24	2622.06	287.10	0.98086	0.97434	1
47		2	2	1	2	1958.88	2061.24	242.90	R	1916.13	2018.49	242.90	0.97818	0.97926	1
48		2	2	2	1	2928.05	3097.77	342.20	T	2869.59	3039.31	342.20	0.98003	0.98113	1
49		2	2	1	2	1218.02	1236.68	169.00	R	1179.20	1195.99	169.00	0.96813	0.96710	1

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
50	(b) (6)	2	2	2	1	1501.67	1557.05	178.00	T	1467.13	1518.42	178.00	0.97700	0.97519	1
51		2	2	1	2	1378.04	1422.35	168.00	R	1343.60	1387.91	168.00	0.97501	0.97578	1
52		2	2	2	1	1737.10	1826.89	225.10	T	1700.53	1790.32	225.10	0.97895	0.97998	1
53		2	1	1	1	1833.93	1978.84	294.60	T	1796.90	.	294.60	0.97981	.	1
54		2	1	2	2	1263.23	1329.16	190.60	R	1237.66	1303.59	190.60	0.97976	0.98076	1
55		2	1	1	1	2203.87	2356.05	303.40	T	2162.55	2284.33	303.40	0.98125	0.96956	1
56		2	1	2	2	1707.02	1772.89	265.40	R	1671.81	1737.67	265.40	0.97937	0.98014	1
57		2	2	1	2	1593.72	1677.58	284.10	R	1562.12	1645.98	284.10	0.98017	0.98116	1
58		2	2	2	1	1929.23	2042.37	301.00	T	1890.88	1982.84	301.00	0.98012	0.97085	1
59		2	1	1	1	1508.81	1575.37	192.40	T	1479.61	1546.16	192.40	0.98065	0.98146	1
60		2	1	2	2	1290.13	1318.64	179.90	R	1252.84	1281.35	179.90	0.97110	0.97172	1
61		2	1	1	1	1463.60	1548.62	153.60	T	1430.68	1507.71	153.60	0.97751	0.97359	1
62		2	1	2	2	1321.45	1384.70	154.10	R	1291.45	1347.04	154.10	0.97729	0.97280	1
63		2	1	1	1	1819.47	1961.24	249.40	T	1786.72	1928.49	249.40	0.98200	0.98330	1
64		2	1	2	2	1230.80	1299.14	145.60	R	1206.46	1274.80	145.60	0.98022	0.98126	1
65		2	1	1	1	1335.38	1379.90	172.50	T	1305.98	1350.50	172.50	0.97798	0.97869	1
66		2	1	2	2	1142.20	1170.77	161.80	R	1110.24	1134.59	161.80	0.97203	0.96910	1
67		2	2	1	2	1651.65	1679.22	250.60	R	1602.27	1627.06	250.60	0.97010	0.96893	1
68		2	2	2	1	2875.11	2923.45	374.00	T	2808.54	2854.55	374.00	0.97685	0.97643	1
69		2	2	1	2	1527.16	1585.94	259.30	R	1493.85	1540.65	259.30	0.97819	0.97144	1
70		2	2	2	1	1777.64	1897.54	286.60	T	1742.80	1811.77	286.60	0.98040	0.95480	1
71		2	1	1	1	1955.57	2166.37	223.30	T	1919.89	2088.10	223.30	0.98175	0.96387	1
72		2	1	2	2	1504.09	1594.92	188.20	R	1473.85	1564.68	188.20	0.97990	0.98104	1
73		2	1	1	1	2415.73	2475.11	284.00	T	2357.42	2423.17	284.00	0.97587	0.97901	1
74	2	1	2	2	1635.94	1666.88	189.20	R	1593.15	1624.09	189.20	0.97384	0.97433	1	

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
75	(b) (6)	2	2	1	2	2110.50	2187.64	304.90	R	2067.89	2145.03	304.90	0.97981	0.98052	1
76		2	2	2	1	2944.13	3096.91	343.50	T	2874.82	3016.58	343.50	0.97646	0.97406	1
77		2	1	1	1	2132.34	2274.11	194.20	T	2091.72	2233.48	194.20	0.98095	0.98214	1
78		2	1	2	2	1839.07	1895.06	197.20	R	1798.14	1854.12	197.20	0.97774	0.97840	1
79		2	2	1	2	780.02	820.61	163.30	R	763.54	.	163.30	0.97887	.	1
80		2	2	2	1	1090.92	1155.89	198.00	T	1071.02	1136.00	198.00	0.98176	0.98279	1
81		2	2	1	2	2148.17	2204.94	393.80	R	2098.84	2155.61	393.80	0.97704	0.97763	1
82		2	2	2	1	2221.04	2324.62	460.60	T	2175.66	2279.24	460.60	0.97957	0.98048	1
83		2	1	1	1	2007.46	2139.60	213.80	T	1963.53	2080.62	213.80	0.97812	0.97243	1
84		2	1	2	2	1463.36	1543.99	190.20	R	1432.43	1482.70	190.20	0.97886	0.96030	1
85		2	1	1	1	1145.37	1176.52	229.50	T	1121.60	1152.75	229.50	0.97924	0.97979	1
86		2	1	2	2	762.55	784.78	160.90	R	748.28	770.52	160.90	0.98129	0.98182	1
87		3	2	1	2	861.25	895.68	168.00	R	843.87	878.31	168.00	0.97983	0.98060	1
88		3	2	2	1	1112.51	1187.86	205.60	T	1095.28	1170.63	205.60	0.98452	0.98550	1
89		3	2	1	2	1542.45	1650.63	198.20	R	1510.19	1578.34	198.20	0.97908	0.95621	1
90		3	2	2	1	2009.24	2189.11	219.70	T	1960.75	.	219.70	0.97587	.	1
91		3	1	1	1	1636.50	1724.50	214.60	T	1598.64	1686.64	214.60	0.97686	0.97804	1
92		3	1	2	2	1322.91	1372.24	230.40	R	1294.13	1343.46	230.40	0.97824	0.97903	1
93		3	2	1	2	1638.81	1697.60	235.10	R	1599.40	1646.90	235.10	0.97595	0.97014	1
94		3	2	2	1	1800.88	1867.35	250.20	T	1761.89	1828.37	250.20	0.97835	0.97912	1
95		3	2	1	2	2057.01	2109.94	213.30	R	2003.51	2059.96	213.30	0.97399	0.97631	1
96		3	2	2	1	2388.60	2493.44	229.20	T	2339.01	2438.83	229.20	0.97924	0.97810	1
97		3	1	1	1	2784.57	2953.68	357.60	T	2734.64	2903.76	357.60	0.98207	0.98310	1
98		3	1	2	2	1740.89	1803.72	283.40	R	1704.29	1767.12	283.40	0.97897	0.97971	1
99		3	1	1	1	2023.32	2220.28	324.50	T	1989.61	.	324.50	0.98334	.	1

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
100	(b) (6)	3	1	2	2	1842.51	1944.93	277.20	R	1810.17	1912.59	277.20	0.98245	0.98337	1
101		3	2	1	2	1892.15	1970.38	220.20	R	1847.76	1926.00	220.20	0.97654	0.97748	1
102		3	2	2	1	2059.35	2176.15	229.50	T	2016.16	2117.57	229.50	0.97903	0.97308	1
103		3	2	1	2	1486.92	1517.66	218.10	R	1453.06	1483.80	218.10	0.97723	0.97769	1
104		3	2	2	1	2219.79	2320.67	248.80	T	2170.12	2257.75	248.80	0.97762	0.97289	1
105		3	2	1	2	1677.97	1743.42	242.80	R	1643.13	1708.58	242.80	0.97924	0.98002	1
106		3	2	2	1	1811.24	1997.79	229.30	T	1783.82	1970.37	229.30	0.98486	0.98627	1
107		3	1	1	1	1950.97	2003.50	252.70	T	1906.09	1964.21	252.70	0.97699	0.98039	1
108		3	1	2	2	1518.81	1555.79	229.40	R	1477.09	1508.82	229.40	0.97254	0.96981	1
109		3	1	1	1	1398.25	1470.63	224.10	T	1367.66	1424.54	224.10	0.97812	0.96866	1
110		3	1	2	2	1473.11	1515.87	229.90	R	1432.76	1475.52	229.90	0.97261	0.97338	1
111		3	2	1	2	1762.10	1776.19	316.50	R	1714.05	1728.14	316.50	0.97273	0.97295	1
112		3	2	2	1	1990.61	2087.38	283.30	T	1945.42	2024.59	283.30	0.97730	0.96992	1
113		3	2	1	2	1867.35	1927.63	219.40	R	1823.11	1878.90	219.40	0.97631	0.97472	1
114		3	2	2	1	2560.72	2684.77	259.50	T	2508.65	2632.71	259.50	0.97967	0.98061	1
115		3	1	1	1	1635.84	1712.42	250.00	T	1601.65	1663.70	250.00	0.97910	0.97155	1
116		3	1	2	2	1128.82	1158.67	206.20	R	1102.62	1132.47	206.20	0.97679	0.97739	1
117		3	1	1	1	1864.72	1970.22	213.00	T	1821.90	1927.40	213.00	0.97704	0.97827	1
118		3	1	2	2	1448.47	1502.80	195.70	R	1412.87	1467.19	195.70	0.97542	0.97631	1
119		3	2	1	2	2267.87	2321.44	272.40	R	2213.86	2263.57	272.40	0.97619	0.97507	1
120		3	2	2	1	3162.49	3276.02	400.80	T	3096.96	3210.49	400.80	0.97928	0.98000	1
121		3	2	1	2	2333.78	2424.76	360.20	R	2289.85	2380.83	360.20	0.98117	0.98188	1
122		3	2	2	1	2263.03	2408.66	348.40	T	2224.74	2370.37	348.40	0.98308	0.98410	1
123		3	1	1	1	1814.44	1960.90	321.60	T	1782.71	.	321.60	0.98251	.	1
124	3	1	2	2	1976.55	2074.41	329.20	R	1936.98	2014.01	329.20	0.97998	0.97088	1	

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
125	(b) (6)	3	2	1	2	1920.90	2089.95	279.70	R	1888.31	2057.36	279.70	0.98303	0.98441	1
126		3	2	2	1	2256.88	2424.14	290.40	T	2221.21	2388.46	290.40	0.98419	0.98528	1

5.9.3.4 Fasting Study Data (SA)

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE
1	(b) (6)	1	2	1	R	0	198.50	223.20	125.90	112.10	102.60	101.00	89.26	88.55	76.91	61.38	46.11	34.48	25.14	18.420	11.970	5.219	2.372	1.159	
2		1	2	2	T	0	750.70	529.50	354.60	256.10	192.50	148.90	108.90	96.09	86.97	85.47	63.56	50.40	36.25	25.640	15.790	7.629	3.481	1.889	
3		1	1	1	T	0	142.20	538.60	290.70	215.50	187.10	146.50	150.70	160.20	129.80	132.80	94.01	76.89	48.30	38.580	21.300	10.030	4.304	2.141	
4		1	1	2	R	0	391.90	474.80	285.70	206.60	183.50	146.90	129.30	120.30	98.73	91.43	65.38	47.09	40.74	30.840	15.440	9.178	3.984	1.784	
5		1	2	1	R	0	528.30	458.70	283.40	201.10	149.90	116.90	83.14	66.32	53.02	45.54	34.21	30.36	27.01	18.350	13.650	5.382	2.524	1.205	
6		1	2	2	T	0	314.10	425.80	244.70	164.40	123.80	96.06	70.98	61.34	44.13	40.25	29.59	25.96	22.06	13.940	10.490	4.129	1.581	0.000	
7		1	1	1	T	0	396.00	532.90	361.20	239.40	177.60	118.10	82.71	65.19	53.88	48.39	33.43	31.10	22.86	17.540	12.380	4.956	3.090	1.493	
8		1	1	2	R	0	252.90	417.30	263.30	189.90	128.20	86.67	79.22	55.70	42.63	41.62	37.53	27.94	19.05	15.800	10.290	4.899	1.908	0.000	
9		1	2	1	R	0	198.00	238.20	151.10	99.86	75.51	65.58	59.16	54.93	45.29	33.80	27.77	20.41	16.10	12.990	8.754	4.920	2.438	1.469	
10		1	2	2	T	0	295.70	405.90	260.60	168.40	127.70	102.80	87.84	74.03	74.54	61.07	42.47	36.00	25.92	19.720	14.920	7.505	4.058	2.199	
11		1	1	1	T	0	490.50	545.30	262.80	263.20	184.80	142.30	104.70	91.06	65.77	60.58	48.42	79.92	47.26	31.380	21.300	9.745	5.339	2.688	
12		1	1	2	R	0	486.00	450.40	304.30	209.40	160.30	116.10	98.12	93.92	115.50	102.00	68.25	45.37	35.88	26.100	17.820	9.026	4.123	2.399	
13		1	1	1	T	0	59.71	318.80	238.20	173.90	146.80	107.00	98.99	85.83	76.42	71.88	53.60	42.67	31.78	23.200	17.620	9.949	4.420	2.397	
14		1	1	2	R	0	124.60	328.20	271.10	191.00	144.80	102.60	81.94	66.84	49.02	45.03	37.40	29.27	23.37	16.750	11.910	7.408	2.991	1.871	
15		1	1	1	T	0	239.60	489.50	334.90	217.60	181.30	125.50	91.99	80.28	61.82	54.81	40.50	32.80	25.06	21.640	14.180	7.105	3.585	2.180	
16		1	1	2	R	0	342.00	547.90	347.70	219.90	175.70	127.50	95.68	79.70	75.86	62.75	47.08	38.55	26.37	20.920	15.360	7.870	3.667	1.901	
17		1	1	1	T	0	334.30	570.40	331.40	247.40	218.80	150.70	134.10	98.94	88.31	86.63	67.12	51.69	38.35	29.200	21.200	10.780	4.072	2.593	
18		1	1	2	R	0	633.80	622.90	266.20	262.80	194.50	140.10	108.90	91.20	83.96	78.65	53.83	47.77	35.60	26.500	17.070	10.540	3.994	2.566	
19		1	2	1	R	0	437.40	493.70	290.80	220.00	164.90	146.40	125.00	109.20	85.00	65.03	51.55	45.31	31.05	21.160	14.990	6.575	3.293	1.455	
20		1	2	2	T	0	518.10	711.70	496.50	330.10	236.30	177.90	161.00	140.20	108.10	98.72	72.57	61.31	47.42	33.240	22.030	10.250	4.992	2.448	
21		1	2	1	R	0	56.83	75.92	66.25	61.78	50.29	50.39	49.38	47.59	39.06	29.16	18.78	14.60	10.01	6.926	4.472	2.001	0.000	0.000	
22		1	2	2	T	0	147.40	198.60	144.40	111.70	90.69	79.72	74.92	61.57	50.85	37.44	25.65	18.79	12.91	9.498	6.319	2.932	1.357	0.000	
23		1	2	1	R	0	204.00	321.90	161.70	122.60	88.98	65.02	42.54	35.14	30.01	28.23	21.52	20.29	26.55	18.180	12.960	6.492	3.682	2.312	
24		1	2	2	T	0	272.30	489.70	310.60	186.50	128.30	90.25	66.65	57.08	49.53	37.38	32.95	25.86	25.73	15.960	13.420	6.428	3.387	1.939	
25		1	1	1	T	0	274.70	474.10	228.90	205.70	160.20	118.20	105.60	94.63	79.21	65.36	44.27	29.95	20.44	16.690	8.745	5.555	2.729	1.918	
26		1	1	2	R	0	304.10	345.20	227.50	155.80	126.40	96.18	72.87	72.45	68.46	54.56	38.37	26.38	15.48	13.270	7.783	5.015	2.016	1.618	
27		1	2	1	R	0	163.00	230.10	151.90	113.60	84.59	83.35	73.72	73.70	57.07	48.04	35.51	32.46	22.40	14.820	10.010	4.187	1.789	0.000	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE
28	(b) (6)	1	2	2	T	0	148.10	258.40	186.80	131.80	117.50	105.30	95.46	85.36	76.62	64.30	47.95	42.11	28.39	19.980	13.760	4.724	2.593	1.057	
29		1	2	1	R	0	287.80	298.00	223.00	158.30	160.10	155.50	149.90	133.90	95.52	77.11	50.09	42.40	27.35	20.510	13.190	6.116	1.987	1.408	
30		1	2	2	T	0	498.20	455.80	356.90	252.40	217.10	200.20	182.30	168.30	113.80	98.49	73.76	56.32	38.03	28.710	18.420	7.500	3.167	1.942	
31		1	2	1	R	0	359.00	423.90	274.50	185.70	146.00	104.30	68.87	56.83	54.54	54.58	40.20	30.44	25.53	19.650	15.440	7.865	3.548	1.983	
32		1	2	2	T	0	452.00	514.80	404.80	226.70	192.00	141.40	117.10	108.00	80.83	75.13	53.52	41.75	34.79	27.340	19.370	9.834	4.758	2.729	
33		1	1	1	T	0	353.60	416.90	275.30	225.90	184.40	156.10	152.10	147.00	124.40	104.40	78.46	60.95	40.18	30.560	20.690	10.830	4.753	2.538	
34		1	1	2	R	0	435.70	549.50	344.00	222.70	173.80	127.10	125.90	125.60	102.30	89.45	62.63	50.47	33.61	29.210	18.600	9.753	4.755	2.883	
35		1	1	1	T	0	191.60	363.30	224.40	165.50	124.70	95.15	76.53	58.80	49.84	39.40	27.90	23.74	17.09	13.980	8.202	4.168	2.352	1.513	
36		1	1	2	R	0	237.10	372.20	226.90	142.30	113.10	92.57	64.80	56.05	41.96	33.89	23.69	19.01	13.00	12.460	7.002	3.842	2.264	1.320	
37		1	1	1	T	0	205.50	321.50	211.20	143.80	148.90	127.00	129.80	129.30	122.10	112.10	89.58	73.50	52.05	37.350	28.010	13.520	6.686	3.828	
38		1	1	2	R	0	271.50	357.20	218.40	165.90	141.50	114.30	108.80	121.40	91.22	94.96	89.67	71.37	44.97	30.750	21.600	13.370	5.350	2.821	
39		1	1	1	T	0	408.20	539.60	313.60	217.80	196.20	145.90	114.50	112.30	81.84	82.64	56.20	46.69	35.93	23.370	16.390	9.027	3.721	2.115	
40		1	1	2	R	0	516.20	548.60	301.80	204.40	162.80	126.10	98.14	90.08	73.76	60.94	42.94	34.28	28.41	19.870	12.480	6.242	2.815	1.854	
41		1	1	1	T	0	563.40	918.80	533.30	401.00	306.50	261.70	207.40	208.00	178.60	141.60	120.10	87.13	64.64	48.930	33.480	13.180	6.520	2.972	
42		1	1	2	R	0	413.70	474.40	297.90	208.30	178.80	156.90	147.60	124.30	114.30	90.36	62.42	48.45	33.21	26.310	18.520	8.962	3.692	2.405	
43		1	2	1	R	0	532.30	474.20	295.20	203.50	154.40	123.00	89.86	89.86	103.50	81.30	56.45	48.04	38.87	26.640	18.260	8.559	3.334	2.177	
44		1	2	2	T	0	374.40	519.70	369.50	227.60	183.10	145.80	123.10	106.90	78.51	65.90	50.43	39.35	32.73	22.400	15.200	7.890	3.015	2.100	
45		2	2	1	R	0	643.50	811.00	472.40	362.90	311.40	252.60	252.80	208.00	161.30	124.10	76.49	53.44	34.06	25.210	15.200	7.568	3.665	1.919	
46		2	2	2	T	0	676.10	808.90	578.60	393.50	325.20	257.30	195.90	159.00	126.40	106.20	76.08	52.26	33.09	23.280	16.100	7.902	3.926	2.499	
47		2	2	1	R	0	460.80	433.90	286.60	194.70	155.70	107.70	86.08	81.64	65.36	55.09	37.12	28.65	19.75	16.900	10.800	5.915	2.563	2.318	
48		2	2	2	T	0	707.60	690.80	436.80	284.00	205.40	141.20	107.00	82.88	69.32	69.99	43.89	38.82	25.42	19.110	15.000	8.174	4.448	2.788	
49		2	2	1	R	0	220.20	520.60	413.00	316.80	257.20	213.80	189.90	207.80	163.80	160.20	111.10	69.71	40.46	29.980	16.150	5.142	2.064	1.286	
50		2	2	2	T	0	287.10	408.50	301.90	203.20	164.70	136.70	96.54	97.57	80.69	56.92	44.88	33.30	26.42	16.600	10.120	4.510	1.910	1.440	
51		2	2	1	R	0	198.70	295.90	234.50	148.40	126.10	92.35	66.41	53.76	59.35	69.32	41.95	26.35	18.95	14.150	9.869	4.704	1.606	1.042	
52		2	2	2	T	0	309.70	386.10	329.60	210.70	156.20	109.60	84.20	63.45	75.86	82.50	42.52	28.52	20.52	14.700	10.190	4.831	2.132	1.242	
53		2	1	1	T	0	455.90	496.20	338.80	246.80	201.80	166.90	144.10	125.50	101.20	87.19	66.93	56.65	48.91	32.960	20.560	7.538	2.988	1.827	
54		2	1	2	R	0	275.50	402.50	245.70	168.00	141.80	108.50	92.90	76.41	65.75	63.93	43.98	35.95	29.34	22.220	15.340	5.512	2.079	1.226	
55		2	1	1	T	0	480.00	580.40	415.00	295.20	246.80	204.40	179.20	152.10	119.70	124.70	75.09	55.48	37.16	30.580	19.550	8.446	3.317	2.461	
56		2	1	2	R	0	507.40	462.90	266.10	209.40	179.80	146.80	132.00	114.50	91.90	83.08	52.60	38.84	26.76	20.520	13.880	6.049	2.690	1.689	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE
57	(b) (6)	2	2	1	R	0	111.60	378.70	229.80	160.50	128.60	95.95	78.06	67.78	72.68	55.13	34.21	27.68	24.95	18.850	12.120	6.859	3.110	1.883	
58		2	2	2	T	0	144.70	405.80	292.20	220.10	179.20	134.30	112.60	95.58	76.40	86.08	56.39	40.67	26.38	21.500	13.820	7.874	3.623	2.224	
59		2	1	1	T	0	216.50	303.10	207.50	158.50	126.90	105.80	100.60	93.18	78.68	58.78	41.83	32.76	25.97	18.680	10.670	5.837	2.205	1.381	
60		2	1	2	R	0	455.80	369.50	197.90	155.40	123.10	102.80	85.54	71.39	59.53	70.35	55.00	39.32	28.91	20.500	12.840	5.616	2.524	1.516	
61		2	1	1	T	0	242.40	363.40	273.70	185.20	149.10	112.90	100.90	79.11	65.67	62.93	50.86	41.36	29.47	18.980	13.200	6.181	2.399	1.650	
62		2	1	2	R	0	252.40	327.50	231.00	162.50	119.20	84.92	64.46	59.41	46.18	51.40	40.46	31.54	23.87	15.470	10.050	5.419	2.352	1.615	
63		2	1	1	T	0	323.00	486.20	317.70	201.20	156.70	105.90	81.32	67.36	49.56	41.24	34.12	27.36	28.34	16.520	11.090	4.558	2.470	1.113	
64		2	1	2	R	0	281.60	301.90	219.80	154.10	123.60	78.97	63.14	50.90	43.33	36.67	26.59	21.87	19.85	14.550	9.642	3.521	1.727	0.000	
65		2	1	1	T	0	88.79	192.40	141.90	110.20	98.33	84.61	83.14	86.48	117.50	104.80	87.45	69.57	43.45	31.970	24.240	15.020	6.978	4.735	
66		2	1	2	R	0	82.18	168.60	106.80	93.56	91.58	83.07	92.48	94.59	108.40	111.50	97.54	65.19	48.10	35.220	30.440	16.380	7.805	4.874	
67		2	2	1	R	0	234.10	386.80	218.00	144.90	127.80		81.87	62.82	53.32	59.12	37.06	25.70	17.64	14.500	8.106	3.167	1.556	0.000	
68		2	2	2	T	0	280.70	451.60	287.70	222.70	193.80	164.60	119.50	102.20	96.15	75.77	48.28	36.58	26.03	18.000	11.030	4.468	2.243	1.209	
69		2	2	1	R	0	188.80	295.70	167.20	138.30	106.50	78.03	72.00	69.29	59.51	47.79	37.40	27.15	21.02	16.030	10.730	5.356	2.626	1.733	
70		2	2	2	T	0	407.30	511.60	396.50	266.70	215.80	152.50	110.70	83.04	70.29	58.99	43.41	37.33	28.53	22.350	12.980	6.720	3.670	1.629	
71		2	2	1	R	0	334.50	406.80	215.90	187.80	147.20	134.40	123.20	103.20	90.10	87.26	60.60	49.50	36.18	31.120	14.260	8.525	2.938	2.011	
72		2	2	2	T	0	345.10	435.20	283.80	228.40	206.20	173.90	163.30	170.00	131.50	120.70	83.92	64.40	51.85	36.010	22.920	10.300	4.686	2.668	
73		2	1	1	T	0	251.80	433.10	309.70	214.40	174.40	118.60	106.40	87.60	82.83	69.72	45.09	36.60	27.57	20.980	15.330	8.701	3.716	3.401	
74		2	1	2	R	0	286.10	288.00	214.30	125.60	104.20	76.94	54.22	48.90	48.97	39.95	33.64	23.59	18.27	16.170	11.070	5.634	3.495	1.893	
75		2	1	1	T	0	361.20	556.70	256.20	227.60	166.70	136.30	103.40	86.72	91.53	75.82	58.18	49.54	38.79	29.050	18.880	10.630	6.042	4.011	
76		2	1	2	R	0	421.80	416.00	240.10	171.10	127.00	92.81	73.15	94.84	67.05	59.42	42.10	33.51	26.71	20.740	13.250	8.044	4.038	2.671	
77		2	2	1	R	0	431.20	625.20	399.20	315.30	252.70	196.60	194.50	184.90	134.40	99.66	73.36	59.27	46.05	32.430	20.660	12.830	5.374	3.975	
78		2	2	2	T	0	581.30	794.50	597.30	413.50	299.90	201.10	183.80	173.70	120.20	103.40	68.70	54.69	44.07	31.380	26.200	14.740	8.066	4.517	
79		2	1	1	T	0	287.30	490.10	311.80	203.50	173.80	148.20	127.90	119.70	92.32	71.26	60.50	45.06	29.84	19.990	12.940	6.323	2.987	1.741	
80		2	1	2	R	0	487.20	481.30	310.50	220.60	172.90	134.60	96.04	91.10	93.60	73.01	48.27	42.17	27.02	18.330	13.740	5.087	2.547	1.134	
81		2	2	1	R	0	163.30	183.00	118.80	115.40	120.30	126.60	128.50	113.90	84.35	64.26	41.90	33.51	22.91	15.430	10.610	5.480	2.293	1.540	
82		2	2	2	T	0	156.20	246.80	151.00	119.40	114.50	104.90	101.90	97.27	83.75	66.87	44.43	33.15	23.71	17.160	10.900	5.547	2.269	1.527	
83		2	2	1	R	0	947.10	818.20	426.40	315.70	271.00	204.30	165.90	147.00	121.40	104.60	67.62	53.92	37.11	27.370	17.060	9.074	2.899	2.036	
84		2	2	2	T	0	1033.00	828.20	459.20	365.50	318.90	229.40	180.70	147.30	139.40	126.10	69.98	59.67	40.18	29.860	19.830	8.591	4.244	2.433	
85		2	1	1	T	0	602.20	722.20	417.90	360.30	314.10	266.10	222.70	212.60	157.30	123.70	79.46	62.85	44.54	31.240	20.290	8.922	2.829	1.569	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE
86	(b) (6)	2	1	2	R	0	702.10	593.00	347.00	237.00	181.60	139.30	170.00	171.20	158.70	119.40	72.03	52.79	30.67	22.110	12.980	6.455	2.513	1.548	
87		3	2	1	R	0	277.80	297.20	194.60	153.50	166.60	167.60	192.20	193.20	156.10	123.50	88.25	56.11	35.49	27.660	15.430	4.751	1.839	0.000	
88		3	2	2	T	0	306.90	356.20	298.00	233.00	225.20	202.70	226.00	223.80	172.60	151.60	94.53	70.72	44.96	28.720	14.580	5.741	2.084	1.181	
89		3	2	1	R	0	286.10	418.40	274.70	198.10	155.20	115.30	85.24	66.17	53.35	42.28	30.06	24.48	19.92	15.690	9.632	5.213	2.135	1.411	
90		3	2	2	T	0	508.90	551.30	376.20	243.30	188.50	136.70	95.42	86.20	76.47	74.67	45.92	34.56	27.95	18.750	13.680	6.165		1.468	
91		3	1	1	T	0	163.70	292.10	229.20	150.60	121.80	105.50	85.91	71.41	58.21	46.44	32.47	25.52	21.30	16.470	9.149	4.190	1.935	1.271	
92		3	1	2	R	0	240.60	250.30	166.70	143.60	115.80	90.45	75.13	57.48	44.81	37.39	27.52	19.68	18.10	11.420	7.698	3.288	1.494	0.000	
93		3	2	1	R	0	133.40	285.00	203.20	143.50	111.00	115.40	155.50	131.60	114.50	107.30	85.98	63.11	54.59	43.500	27.610	18.750	10.110	7.227	
94		3	2	2	T	0	270.40	321.70	255.30	169.10	149.20	159.80	113.90	100.50	104.80	89.16	65.94	52.09	47.61	35.060	27.150	14.550	11.130	6.535	
95		3	2	1	R	0	355.10	497.20	263.50	184.50	144.10	102.10	94.13	73.82	56.80	49.68	33.39	29.32	21.35	15.560	10.280	5.127	2.318	1.645	
96		3	2	2	T	0	561.80	554.20	355.50	223.00	171.00	124.80	95.28	80.60	60.40	49.43	34.80	30.99	22.70	17.040	10.890	6.277	2.569	1.643	
97		3	1	1	T	0	535.90	546.50	331.30	235.80	172.60	120.00	82.70	69.70	53.53	46.38	34.39	29.09	20.11	16.380	10.200	6.647	3.399	2.232	
98		3	1	2	R	0	391.50	358.10	207.40	137.10	106.40	71.81	58.59	44.38	33.34	30.00	22.20	17.41	15.10	12.390	6.629	4.767	2.267	1.679	
99		3	1	1	T	0	609.60	549.00	325.90	231.90	174.30	134.00	107.10	96.49	82.27	69.56	49.10	40.46	28.48	17.280	12.870	5.727	1.817	0.000	
100		3	1	2	R	0	586.60	463.70	294.00	203.80	170.50	129.00	91.77	74.84	57.25	51.17	37.71	29.13	20.99	15.170	10.450	5.163	1.682	0.000	
101		3	2	1	R	0	353.30	440.70	248.60	158.20	113.40	79.94	69.21	70.55	48.05	40.23	29.90	25.42	19.78	14.040	10.400	6.676	3.662	2.383	
102		3	2	2	T	0	337.30	468.60	308.50	194.20	139.80	107.30	86.86	79.35	57.23	52.46	34.81	28.17	22.91	17.860	12.160	7.639	4.501	3.144	
103		3	2	1	R	0	208.10	343.10	221.20	152.00	123.30	104.90	86.78	86.42	73.10	59.86	42.90	32.81	23.77	15.650	9.392	5.021	2.007	1.010	
104		3	2	2	T	0	370.90	531.30	333.40	217.60	171.00	131.20	104.20	100.20	80.94	69.22	48.94	38.65	28.07	21.570	13.000	7.117	2.527	1.944	
105		3	2	1	R	0	188.40	259.20	190.00	135.00	95.97	76.89	64.16	56.25	54.83	51.59	36.12	28.70	20.75	16.560	11.120	6.178	2.942	1.483	
106		3	2	2	T	0	255.60	246.90	199.60	138.80	107.30	91.32	84.90	75.32	60.58	51.58	39.62	32.95	25.62	19.780	12.620	6.343	2.541	1.848	
107		3	1	1	T	0	299.90	514.90	312.60	222.40	133.60	129.90	109.10	110.20	103.10	89.82	62.37	51.06	38.20	27.500	17.910	9.977	3.947	2.351	
108		3	1	2	R	0	385.90	379.00	238.60	175.50	140.50	97.95	89.41	90.83	68.05	67.58	50.84	36.04	27.41	21.210	14.960	7.897	3.764	2.428	
109		3	2	1	R	0	256.80	570.80	342.40	226.90	177.90	142.90	118.50	125.50	119.90	100.90	72.64	58.58	38.50	27.490	17.420	10.000	4.330	2.947	
110		3	2	2	T	0	532.50	598.50	387.60	249.50	208.30	142.30	113.80	99.16	83.00	88.47	69.83	59.10	44.19	28.690	20.960	11.860	6.231	3.995	
111		3	2	1	R	0	363.10	474.20	296.50	221.20	173.80	164.40	148.40	137.80	121.30	99.56	77.81	65.76	53.95	38.610	25.520	14.790	7.415	5.085	
112		3	2	2	T	0	498.10	655.00	378.20	255.60	203.40	146.70	118.30	110.40	94.25	82.76	63.98	51.35	45.70	34.230	28.860	14.200	8.586	4.800	
113		3	1	1	T	0	404.20	525.10	336.50	240.50	172.20	140.20	115.50	98.77	107.20	66.80	52.87	41.50	27.69	20.390	14.830	6.046	3.016	1.905	
114		3	1	2	R	0	406.70	397.60	237.00	161.20	112.80	95.27	72.21	65.87	73.05	61.38	43.07	34.83	23.90	16.770	11.700	4.617	1.927	1.208	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	KE
115	(b) (6)	3	1	1	T	0	439.10	794.30	488.20	338.80	231.60	174.20	173.00	161.90	106.10	85.95	61.35	50.63	32.02	23.830	15.340	5.589	2.686	1.634	
116		3	1	2	R	0	547.30	590.40	359.10	250.70	194.10	134.10	127.70	130.60	121.20	92.12	55.69	36.45	25.71	17.500	12.170	5.378	1.984	1.116	
117		3	2	1	R	0	439.30	535.70	309.20	220.20	198.40	151.60	120.50	99.81	77.42	65.15	46.91	36.54	27.56	19.800	11.630	6.656	2.684	1.881	
118		3	2	2	T	0	757.90	781.80	485.90	349.20	252.80	218.60	169.60	153.20	112.10	88.76	68.06	49.89	37.08	27.840	17.220	8.431	3.829	2.376	
119		3	2	1	R	0	954.50	813.30	451.40	318.20	238.00	172.90	142.00	120.70	96.41	76.43	52.46	44.97	33.90	22.760	15.630	6.591	2.924	1.669	
120		3	2	2	T	0	786.90	773.80	495.50	354.90	278.20	211.10	157.00	130.20	122.80	105.00	75.86	55.84	42.85	30.810	19.340	8.919	3.562	2.308	
121		3	1	1	T	0	357.60	496.90	338.40	266.40	231.50	224.60	201.40	209.50	206.30	173.90	123.40	94.31	66.63	51.120	31.090	14.670	7.917	4.518	
122		3	1	2	R	0	471.10	455.10	382.30	272.30	235.40	202.70	174.50	176.10	182.40	162.20	110.60	90.24	60.30	44.200	24.980	14.580	6.227	4.350	
123		3	2	1	R	0	460.30	626.90	395.20	281.20	226.90	172.30	156.40	153.80	127.70	105.20	82.91	66.63	50.33	38.870	23.280	12.300	5.598	3.294	
124		3	2	2	T	0	566.60	648.40	435.20	316.60	256.80	225.40	179.00	173.70	131.90	112.80	92.45	69.16	52.82	40.400	26.620	14.290	5.476	3.456	

Obs	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19
1	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
2	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.55000	0.75000	1.00000	1.50000	2.05000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
3	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	50.1833
4	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
5	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
6	18	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
7	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0833	48.0000
8	18	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
9	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0167	48.0000
10	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
11	19	0	0.033333	0.10000	0.20000	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
12	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
13	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
14	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
15	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
16	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.50000	2.00000	3.00000	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000
17	19	0	0.033333	0.08333	0.16667	0.25000	0.33333	0.50000	0.75000	1.00000	1.53333	2.00000	3.03333	4	6.00000	8.00000	12.0000	24.0000	36.0000	48.0000

5.9.3.5 Fasting Study Output (SA)

Fasting STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	62	(b) (6)
trt	2	1 2
per	2	1 2
seq	2	1 2
GRP	3	1 2 3

Number of Observations Read	124
Number of Observations Used	124

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	65	13.19475155	0.20299618	11.86	<.0001
Error	58	0.99257574	0.01711337		
Corrected Total	123	14.18732729			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.930038	1.963053	0.130818	6.664013

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.00160684	0.00160684	0.09	0.7604
GRP	2	0.23825539	0.11912770	6.96	0.0020
seq	1	0.02239971	0.02239971	1.31	0.2573
seq*GRP	2	0.83586102	0.41793051	24.42	<.0001
sub(seq*GRP)	56	11.05730599	0.19745189	11.54	<.0001
per(GRP)	2	0.01638044	0.00819022	0.48	0.6221
trt	1	1.02294216	1.02294216	59.77	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per	1	0.01301088	0.01301088	0.76	0.3868

Source	DF	Type III SS	Mean Square	F Value	Pr > F
GRP	2	0.21689260	0.10844630	6.34	0.0032
seq	1	0.00730607	0.00730607	0.43	0.5161
seq*GRP	2	0.83586102	0.41793051	24.42	<.0001
sub(seq*GRP)	56	11.05730599	0.19745189	11.54	<.0001
per(GRP)	2	0.03885575	0.01942788	1.14	0.3284
trt	1	1.02294216	1.02294216	59.77	<.0001

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00730607	0.00730607	0.04	0.8482
GRP	2	0.21689260	0.10844630	0.55	0.5805

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.18396078	0.02379400	7.73	<.0001

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	65	13.14331515	0.20220485	12.51	<.0001
Error	58	0.93783099	0.01616950		
Corrected Total	123	14.08114614			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.933398	1.894373	0.127159	6.712478

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.00160448	0.00160448	0.10	0.7539
GRP	2	0.26544053	0.13272026	8.21	0.0007
seq	1	0.02066649	0.02066649	1.28	0.2629
seq*GRP	2	0.87444349	0.43722175	27.04	<.0001
sub(seq*GRP)	56	10.96000853	0.19571444	12.10	<.0001
per(GRP)	2	0.01733194	0.00866597	0.54	0.5880
trt	1	1.00381969	1.00381969	62.08	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per	1	0.01267157	0.01267157	0.78	0.3797
GRP	2	0.23384401	0.11692201	7.23	0.0016
seq	1	0.00592974	0.00592974	0.37	0.5472
seq*GRP	2	0.87444349	0.43722175	27.04	<.0001
sub(seq*GRP)	56	10.96000853	0.19571444	12.10	<.0001
per(GRP)	2	0.03587957	0.01793979	1.11	0.3366
trt	1	1.00381969	1.00381969	62.08	<.0001

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00592974	0.00592974	0.03	0.8624
GRP	2	0.23384401	0.11692201	0.60	0.5537

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.18223322	0.02312853	7.88	<.0001

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	65	17.42928409	0.26814283	7.96	<.0001
Error	58	1.95484251	0.03370418		
Corrected Total	123	19.38412660			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.899152	3.012942	0.183587	6.093280

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.14114256	0.14114256	4.19	0.0453
GRP	2	0.35911231	0.17955615	5.33	0.0075
seq	1	0.02994404	0.02994404	0.89	0.3498
seq*GRP	2	0.90711872	0.45355936	13.46	<.0001
sub(seq*GRP)	56	14.77851061	0.26390198	7.83	<.0001
per(GRP)	2	0.11418624	0.05709312	1.69	0.1928
trt	1	1.09926961	1.09926961	32.62	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per	1	0.07880154	0.07880154	2.34	0.1317
GRP	2	0.39297055	0.19648528	5.83	0.0049
seq	1	0.02092288	0.02092288	0.62	0.4340
seq*GRP	2	0.90711872	0.45355936	13.46	<.0001
sub(seq*GRP)	56	14.77851061	0.26390198	7.83	<.0001
per(GRP)	2	0.21934777	0.10967389	3.25	0.0458
trt	1	1.09926961	1.09926961	32.62	<.0001

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.02092288	0.02092288	0.08	0.7793
GRP	2	0.39297055	0.19648528	0.74	0.4796

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.19070049	0.03339194	5.71	<.0001

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	trt	AUCRATIO
1	(b) (6)	1	0.97
2		1	0.97
3		1	0.96
4		1	0.96
5		1	0.95
6		1	0.96
7		1	0.95
8		1	0.95
9		1	0.96
10		1	0.97
11		1	0.95
12		1	0.94
13		1	0.94
14		1	0.98
15		1	0.97
16		1	0.95
17		1	0.96
18		1	0.94

Obs	sub	trt	AUCRATIO
19	(b) (6)	1	0.95
20		1	0.96
21		1	0.97
22		1	0.96
23		1	0.96
24		1	0.93
25		1	0.96
26		1	0.97
27		1	0.97
28		1	0.96
29		1	0.95
30		1	0.96
31		1	0.96
32		1	0.97
33		1	0.92
34		1	0.97
35		1	0.96
36		1	0.96
37		1	0.91
38		1	0.92
39		1	0.94
40		1	0.96
41		1	0.96
42		1	0.97
43		1	0.98
44		1	0.98
45		1	0.97
46		1	0.96
47		1	0.88
48		1	0.96
49		1	0.93
50		1	0.97
51		1	0.89
52		1	0.96
53		1	0.95
54		1	0.96
55		1	0.93
56		1	0.93
57		1	0.96
58		1	0.97

Obs	sub	trt	AUCRATIO
59	(b) (6)	1	0.96
60	(b) (6)	1	0.97
61	(b) (6)	1	0.95
62	(b) (6)	1	0.96
63	(b) (6)	2	0.97
64	(b) (6)	2	0.97
65	(b) (6)	2	0.97
66	(b) (6)	2	0.95
67	(b) (6)	2	0.94
68	(b) (6)	2	0.96
69	(b) (6)	2	0.95
70	(b) (6)	2	0.96
71	(b) (6)	2	0.95
72	(b) (6)	2	0.97
73	(b) (6)	2	0.91
74	(b) (6)	2	0.92
75	(b) (6)	2	0.94
76	(b) (6)	2	0.95
77	(b) (6)	2	0.97
78	(b) (6)	2	0.95
79	(b) (6)	2	0.95
80	(b) (6)	2	0.94
81	(b) (6)	2	0.96
82	(b) (6)	2	0.95
83	(b) (6)	2	0.96
84	(b) (6)	2	0.96
85	(b) (6)	2	0.97
86	(b) (6)	2	0.92
87	(b) (6)	2	0.98
88	(b) (6)	2	0.97
89	(b) (6)	2	0.98
90	(b) (6)	2	0.96
91	(b) (6)	2	0.95
92	(b) (6)	2	0.96
93	(b) (6)	2	0.95
94	(b) (6)	2	0.95
95	(b) (6)	2	0.93
96	(b) (6)	2	0.96
97	(b) (6)	2	0.94
98	(b) (6)	2	0.96

Obs	sub	trt	AUCRATIO
99	(b) (6)	2	0.93
100	(b) (6)	2	0.93
101	(b) (6)	2	0.94
102	(b) (6)	2	0.98
103	(b) (6)	2	0.96
104	(b) (6)	2	0.97
105	(b) (6)	2	0.97
106	(b) (6)	2	0.98
107	(b) (6)	2	0.96
108	(b) (6)	2	0.95
109	(b) (6)	2	0.88
110	(b) (6)	2	0.95
111	(b) (6)	2	0.91
112	(b) (6)	2	0.96
113	(b) (6)	2	0.91
114	(b) (6)	2	0.97
115	(b) (6)	2	0.96
116	(b) (6)	2	0.94
117	(b) (6)	2	0.95
118	(b) (6)	2	0.92
119	(b) (6)	2	0.97
120	(b) (6)	2	0.98
121	(b) (6)	2	0.95
122	(b) (6)	2	0.97
123	(b) (6)	2	0.95
124	(b) (6)	2	0.95

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	2	1.47	1.48	3.36	0.40	0.92	1.09
(b) (6)	1	1.26	1.26	1.13	1.00	1.00	1.00
(b) (6)	2	0.78	0.79	0.81	2.50	1.16	0.86
(b) (6)	1	1.23	1.22	1.28	1.00	0.78	1.29
(b) (6)	2	1.62	1.60	1.70	1.00	1.05	0.95
(b) (6)	1	1.10	1.10	1.12	3.00	1.00	1.00
(b) (6)	1	1.34	1.33	0.97	1.00	1.05	0.95
(b) (6)	1	0.93	0.94	0.89	1.00	0.90	1.12
(b) (6)	1	1.08	1.07	0.90	2.50	1.09	0.91
(b) (6)	2	1.45	1.45	1.44	1.00	0.95	1.05

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	2	1.55	1.49	2.62	1.00	0.80	1.24
	2	1.15	1.12	1.52	1.00	1.12	0.89
	1	1.21	1.21	1.37	1.00	0.94	1.07
	2	1.33	1.30	1.12	1.00	0.93	1.08
	2	1.36	1.36	1.67	0.29	0.97	1.03
	2	1.35	1.35	1.21	1.00	0.95	1.05
	1	1.11	1.09	0.76	1.00	1.13	0.89
	1	1.12	1.12	0.98	1.00	1.02	0.98
	1	1.13	1.15	0.90	1.00	0.95	1.05
	1	1.24	1.23	0.98	1.00	1.08	0.93
	1	1.72	1.69	1.94	1.00	1.14	0.88
	2	0.91	0.92	0.98	2.50	0.94	1.06
	2	0.96	0.98	1.00	1.00	0.91	1.10
	2	1.33	1.31	1.54	1.00	1.04	0.96
	2	0.57	0.58	0.78	1.00	0.79	1.27
	2	1.14	1.15	1.30	1.00	0.91	1.10
	1	1.47	1.47	1.23	1.00	0.95	1.06
	1	1.39	1.39	1.14	2.50	1.00	1.00
	2	1.25	1.25	1.07	1.00	0.98	1.02
	1	0.92	0.92	0.66	2.50	0.99	1.01
	1	1.24	1.22	1.11	1.00	1.14	0.88
	1	1.32	1.29	1.61	1.00	0.80	1.26
	1	0.92	0.93	1.14	1.00	0.91	1.10
	2	1.45	1.43	1.17	1.00	0.79	1.27
	2	1.38	1.35	1.73	1.00	1.11	0.90
	2	1.36	1.35	1.07	1.00	1.04	0.96
	1	1.47	1.50	1.50	1.00	0.93	1.08
	1	1.38	1.39	1.32	2.50	0.95	1.05
	2	1.10	1.10	1.27	1.00	1.01	0.99
	1	1.08	1.09	1.01	2.50	0.83	1.21
	2	1.00	1.00	1.35	1.00	1.02	0.98
	2	1.10	1.11	1.09	1.00	0.93	1.07
	1	1.28	1.27	1.03	2.50	1.21	0.83
	2	1.17	1.17	1.20	1.20	0.75	1.34
	2	1.41	1.39	1.32	1.00	0.98	1.02
	1	1.27	1.26	1.17	1.00	0.78	1.28
	2	0.90	0.90	1.13	1.00	0.98	1.02
	2	1.12	1.11	1.13	0.40	1.04	0.96
	1	1.49	1.47	1.40	2.50	1.08	0.93
	1	1.22	1.21	1.04	1.00	1.04	0.96

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	2	1.18	1.21	1.06	1.00	0.91	1.09
	2	1.29	1.32	1.55	1.00	0.89	1.13
	2	1.11	1.12	0.99	0.40	0.98	1.02
	1	1.27	1.24	1.33	1.67	1.13	0.88
	2	1.08	1.10	1.05	1.00	0.91	1.10
	2	0.96	0.96	1.38	1.00	1.06	0.94
	1	1.29	1.31	1.29	2.50	0.89	1.12
	1	1.19	1.20	1.35	1.00	0.91	1.10
	2	1.41	1.40	1.46	1.00	1.06	0.95
	2	1.22	1.23	0.82	1.00	0.97	1.04
	1	1.11	1.10	1.05	2.50	1.05	0.95
	2	1.10	1.09	1.03	1.00	1.06	0.94

5.9.3.6 Firm Reviewer Ratio (SA)

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	(b) (6)	1	2	1	2	614.04	631.88	223.20	R	602.36	620.21	223.20	0.98098	0.98152	1
2		1	2	2	1	905.63	937.31	750.70	T	890.18	921.86	750.70	0.98294	0.98352	1
3		1	1	1	1	1184.15	1219.26	538.60	T	1160.15	1195.26	538.60	0.97973	0.98032	1
4		1	1	2	2	940.11	969.40	474.80	R	924.23	950.37	474.80	0.98312	0.98038	1
5		1	2	1	2	642.50	660.49	528.30	R	628.88	648.21	528.30	0.97881	0.98141	1
6		1	2	2	1	501.48	521.76	425.80	T	490.33	510.38	425.80	0.97777	0.97819	1
7		1	1	1	1	640.35	666.65	532.90	T	628.15	653.04	532.90	0.98095	0.97958	1
8		1	1	2	2	520.92	547.03	417.30	R	511.07	536.62	417.30	0.98109	0.98095	1
9		1	2	1	2	448.25	477.36	238.20	R	441.99	471.10	238.20	0.98602	0.98687	1
10		1	2	2	1	724.08	765.58	405.90	T	712.77	754.27	405.90	0.98438	0.98523	1
11		1	1	1	1	1023.11	1070.46	545.30	T	1000.27	1047.63	545.30	0.97768	0.97867	1
12		1	1	2	2	932.42	974.76	486.00	R	916.64	958.98	486.00	0.98308	0.98382	1
13		1	1	1	1	826.31	868.64	318.80	T	813.52	855.65	318.80	0.98452	0.98504	1
14		1	1	2	2	618.48	653.23	328.20	R	609.49	643.40	328.20	0.98546	0.98495	1
15		1	1	1	1	722.13	763.64	489.50	T	710.64	752.16	489.50	0.98410	0.98496	1
16		1	1	2	2	778.54	810.98	547.90	R	765.49	797.93	547.90	0.98324	0.98391	1
17		1	1	1	1	1011.81	1054.57	570.40	T	993.28	1035.02	570.40	0.98168	0.98146	1
18		1	1	2	2	939.68	985.94	633.80	R	922.42	966.45	633.80	0.98163	0.98023	1
19		1	2	1	2	801.04	823.75	493.70	R	786.27	808.99	493.70	0.98157	0.98208	1
20		1	2	2	1	1158.36	1198.54	711.70	T	1138.16	1179.19	711.70	0.98256	0.98385	1
21		1	2	1	2	235.91	259.62	75.92	R	232.42	256.14	75.92	0.98524	0.98659	1
22		1	2	2	1	366.02	386.01	198.60	T	360.18	381.35	198.60	0.98404	0.98791	1
23		1	2	1	2	537.55	585.89	321.90	R	528.06	576.40	321.90	0.98235	0.98380	1
24		1	2	2	1	618.98	655.08	489.70	T	608.32	644.43	489.70	0.98279	0.98373	1

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
25	(b) (6)	1	1	1	1	640.08	683.80	474.10	T	630.51	674.24	474.10	0.98506	0.98601	1
26		1	1	2	2	530.87	565.39	345.20	R	523.04	552.50	345.20	0.98525	0.97720	1
27		1	2	1	2	497.35	521.37	230.10	R	487.58	512.52	230.10	0.98037	0.98303	1
28		1	2	2	1	661.04	676.33	258.40	T	645.81	660.49	258.40	0.97696	0.97659	1
29		1	2	1	2	751.53	773.09	298.00	R	736.83	756.38	298.00	0.98045	0.97839	1
30		1	2	2	1	1018.84	1049.46	498.20	T	999.24	1027.88	498.20	0.98076	0.97944	1
31		1	2	1	2	696.53	730.75	423.90	R	684.51	718.59	423.90	0.98275	0.98336	1
32		1	2	2	1	940.33	989.91	514.80	T	925.26	974.84	514.80	0.98397	0.98478	1
33		1	1	1	1	1083.85	1126.69	416.90	T	1066.14	1108.98	416.90	0.98365	0.98427	1
34		1	1	2	2	980.41	1035.22	549.50	R	964.81	1019.62	549.50	0.98409	0.98493	1
35		1	1	1	1	488.32	520.50	363.30	T	481.21	513.38	363.30	0.98544	0.98634	1
36		1	1	2	2	435.35	463.97	372.20	R	428.96	457.58	372.20	0.98532	0.98623	1
37		1	1	1	1	1236.19	1305.01	321.50	T	1215.15	1282.02	321.50	0.98297	0.98238	1
38		1	1	2	2	1091.49	1139.69	357.20	R	1073.25	1120.89	357.20	0.98329	0.98351	1
39		1	1	1	1	890.81	926.92	539.60	T	875.85	911.02	539.60	0.98320	0.98285	1
40		1	1	2	2	718.22	752.36	548.60	R	706.44	740.58	548.60	0.98359	0.98434	1
41		1	1	1	1	1629.71	1674.46	918.80	T	1595.88	1643.77	918.80	0.97924	0.98167	1
42		1	1	2	2	949.40	990.57	474.40	R	932.85	970.90	474.40	0.98256	0.98014	1
43		1	2	1	2	897.26	932.94	532.30	R	880.06	914.13	532.30	0.98083	0.97984	1
44		1	2	2	1	819.99	856.51	519.70	T	806.32	841.06	519.70	0.98334	0.98196	1
45	2	2	1	2	1125.59	1158.80	811.00	R	1107.44	1140.65	811.00	0.98388	0.98434	1	
46	2	2	2	1	1085.03	1132.72	808.90	T	1069.05	1116.74	808.90	0.98527	0.98589	1	
47	2	2	1	2	628.61	679.62	460.80	R	619.27	662.56	460.80	0.98515	0.97490	1	
48	2	2	2	1	834.16	893.30	707.60	T	822.18	879.74	707.60	0.98564	0.98482	1	
49	2	2	1	2	1118.75	1136.90	520.60	R	1093.11	1108.56	520.60	0.97708	0.97507	1	

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
50	(b) (6)	2	2	2	1	638.22	663.98	408.50	T	627.39	650.69	408.50	0.98303	0.97998	1
51		2	2	1	2	536.09	552.08	295.90	R	525.03	539.97	295.90	0.97937	0.97805	1
52		2	2	2	1	613.64	634.54	386.10	T	601.90	621.93	386.10	0.98086	0.98012	1
53		2	1	1	1	1014.86	1041.95	496.20	T	992.26	1017.48	496.20	0.97773	0.97651	1
54		2	1	2	2	691.96	709.16	402.50	R	675.02	690.60	402.50	0.97552	0.97383	1
55		2	1	1	1	1083.21	1124.51	580.40	T	1062.04	1098.73	580.40	0.98045	0.97707	1
56		2	1	2	2	780.97	809.44	507.40	R	766.68	793.50	507.40	0.98169	0.98030	1
57		2	2	1	2	631.17	666.61	378.70	R	621.19	656.62	378.70	0.98419	0.98503	1
58		2	2	2	1	789.43	832.08	405.80	T	777.36	820.01	405.80	0.98471	0.98549	1
59		2	1	1	1	630.25	653.57	303.10	T	619.87	643.18	303.10	0.98353	0.98411	1
60		2	1	2	2	683.38	708.61	455.80	R	670.28	695.51	455.80	0.98084	0.98152	1
61		2	1	1	1	696.89	724.45	363.40	T	684.44	710.73	363.40	0.98213	0.98106	1
62		2	1	2	2	563.03	593.70	327.50	R	554.30	582.83	327.50	0.98449	0.98170	1
63		2	1	1	1	595.56	613.94	486.20	T	583.65	603.61	486.20	0.98000	0.98317	1
64		2	1	2	2	451.46	474.18	301.90	R	441.91	464.63	301.90	0.97885	0.97987	1
65		2	1	1	1	1118.94	1219.23	192.40	T	1102.97	1200.71	192.40	0.98573	0.98481	1
66		2	1	2	2	1216.89	1310.65	168.60	R	1197.23	1292.30	168.60	0.98384	0.98599	1
67		2	2	1	2	489.48	509.59	386.80	R	478.86	501.48	386.80	0.97829	0.98409	1
68		2	2	2	1	710.04	729.85	451.60	T	696.91	716.73	451.60	0.98151	0.98201	1
69		2	2	1	2	553.85	587.52	295.70	R	545.17	578.84	295.70	0.98432	0.98522	1
70		2	2	2	1	765.44	794.05	511.60	T	753.50	782.12	511.60	0.98441	0.98497	1
71		2	2	1	2	869.02	903.78	406.80	R	852.29	879.93	406.80	0.98075	0.97361	1
72		2	2	2	1	1180.38	1224.60	435.20	T	1158.87	1203.10	435.20	0.98178	0.98244	1
73		2	1	1	1	792.82	868.85	433.10	T	781.42	847.88	433.10	0.98562	0.97586	1
74	2	1	2	2	538.38	577.71	288.00	R	530.57	569.90	288.00	0.98549	0.98648	1	

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
75	(b) (6)	2	1	1	1	993.31	1085.50	556.70	T	978.50	1070.69	556.70	0.98509	0.98636	1
76		2	1	2	2	721.78	780.10	421.80	R	711.89	770.21	421.80	0.98629	0.98732	1
77		2	2	1	2	1215.46	1297.49	625.20	R	1198.61	1274.37	625.20	0.98614	0.98218	1
78		2	2	2	1	1332.93	1425.17	794.50	T	1314.85	1407.66	794.50	0.98643	0.98772	1
79		2	1	1	1	790.08	820.95	490.10	T	777.43	808.30	490.10	0.98399	0.98459	1
80		2	1	2	2	734.92	751.56	487.20	R	719.10	737.24	487.20	0.97849	0.98094	1
81		2	2	1	2	617.06	644.77	183.00	R	607.12	633.45	183.00	0.98388	0.98245	1
82		2	2	2	1	618.85	645.84	246.80	T	608.58	633.72	246.80	0.98340	0.98123	1
83		2	2	1	2	1065.24	1097.74	947.10	R	1045.37	1074.64	947.10	0.98135	0.97896	1
84		2	2	2	1	1176.00	1217.72	1033.00	T	1153.89	1195.60	1033.00	0.98119	0.98184	1
85		2	1	1	1	1210.19	1231.52	722.20	T	1185.48	1206.14	722.20	0.97958	0.97939	1
86		2	1	2	2	945.79	971.15	702.10	R	928.40	953.77	702.10	0.98162	0.98210	1
87		3	2	1	2	925.34	944.63	297.20	R	902.78	923.53	297.20	0.97562	0.97766	1
88		3	2	2	1	1085.28	1101.84	356.20	T	1062.93	1079.50	356.20	0.97941	0.97972	1
89		3	2	1	2	554.53	579.97	418.40	R	545.74	571.18	418.40	0.98414	0.98483	1
90		3	2	2	1	780.52	807.63	551.30	T	754.26	781.97	551.30	0.96635	0.96822	1
91		3	1	1	1	524.42	547.20	292.10	T	515.49	538.28	292.10	0.98298	0.98369	1
92		3	1	2	2	414.18	435.04	250.30	R	406.85	428.72	250.30	0.98230	0.98546	1
93		3	2	1	2	1348.20	1535.16	285.00	R	1333.66	1520.62	285.00	0.98921	0.99053	1
94		3	2	2	1	1214.50	1387.21	321.70	T	1200.25	1362.20	321.70	0.98827	0.98197	1
95	3	2	1	2	589.63	621.01	497.20	R	579.78	608.82	497.20	0.98328	0.98036	1	
96	3	2	2	1	658.19	688.21	561.80	T	648.01	676.27	561.80	0.98454	0.98265	1	
97	3	1	1	1	643.89	695.11	546.50	T	635.77	686.99	546.50	0.98739	0.98832	1	
98	3	1	2	2	430.81	472.24	391.50	R	425.24	466.68	391.50	0.98707	0.98821	1	
99	3	1	1	1	715.92	738.79	609.60	T	701.38	724.25	609.60	0.97970	0.98033	1	

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
100	(b) (6)	3	1	2	2	587.58	609.69	586.60	R	576.54	597.80	586.60	0.98122	0.98051	1
101	(b) (6)	3	2	1	2	578.05	635.00	440.70	R	571.06	628.01	440.70	0.98790	0.98899	1
102	(b) (6)	3	2	2	1	684.74	766.99	468.60	T	677.17	751.78	468.60	0.98895	0.98017	1
103	(b) (6)	3	2	1	2	588.38	604.31	343.10	R	578.54	594.47	343.10	0.98327	0.98371	1
104	(b) (6)	3	2	2	1	760.67	795.30	531.30	T	747.66	777.82	531.30	0.98290	0.97803	1
105	(b) (6)	3	2	1	2	561.12	587.34	259.20	R	552.44	577.38	259.20	0.98454	0.98305	1
106	(b) (6)	3	2	2	1	624.47	657.68	255.60	T	614.00	643.19	255.60	0.98323	0.97797	1
107	(b) (6)	3	1	1	1	948.87	989.07	514.90	T	932.62	971.00	514.90	0.98287	0.98173	1
108	(b) (6)	3	1	2	2	749.32	796.34	385.90	R	737.87	782.53	385.90	0.98472	0.98265	1
109	(b) (6)	3	2	1	2	1009.64	1066.96	570.80	R	994.18	1047.29	570.80	0.98468	0.98157	1
110	(b) (6)	3	2	2	1	1087.60	1172.95	598.50	T	1072.88	1158.24	598.50	0.98647	0.98745	1
111	(b) (6)	3	2	1	2	1271.26	1381.61	474.20	R	1254.72	1365.06	474.20	0.98698	0.98802	1
112	(b) (6)	3	2	2	1	1221.60	1319.48	655.00	T	1202.66	1300.54	655.00	0.98449	0.98564	1
113	(b) (6)	3	1	1	1	790.76	824.13	525.10	T	775.97	807.59	525.10	0.98129	0.97993	1
114	(b) (6)	3	1	2	2	610.90	629.76	406.70	R	598.07	616.03	406.70	0.97901	0.97821	1
115	(b) (6)	3	1	1	1	931.53	957.85	794.30	T	912.21	938.52	794.30	0.97926	0.97983	1
116	(b) (6)	3	1	2	2	782.57	798.97	590.40	R	767.42	783.37	590.40	0.98064	0.98047	1
117	(b) (6)	3	2	1	2	744.92	780.33	535.70	R	733.36	765.64	535.70	0.98449	0.98117	1
118	(b) (6)	3	2	2	1	1052.61	1094.97	781.80	T	1035.78	1078.14	781.80	0.98401	0.98463	1
119	(b) (6)	3	2	1	2	916.76	943.28	954.50	R	899.52	924.86	954.50	0.98119	0.98048	1
120	(b) (6)	3	2	2	1	1118.31	1156.27	786.90	T	1098.48	1133.89	786.90	0.98227	0.98064	1
121	(b) (6)	3	1	1	1	1635.72	1720.39	496.90	T	1608.90	1693.57	496.90	0.98360	0.98441	1
122	(b) (6)	3	1	2	2	1479.01	1564.66	471.10	R	1456.47	1542.12	471.10	0.98476	0.98560	1
123	(b) (6)	3	2	1	2	1242.03	1301.44	626.90	R	1222.27	1281.68	626.90	0.98409	0.98482	1
124	(b) (6)	3	2	2	1	1362.90	1421.44	648.40	T	1340.10	1395.95	648.40	0.98327	0.98206	1

5.9.4 Fasting Study MGR001-1014

5.9.4.1 Fasting Study Data (FP)

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18
1	(b) (6)	1	2	1	R	0		143.00	218.70	228.10	245.80	264.40	262.50	225.30	179.60	130.90	101.00	82.03	41.78	27.44	14.33	4.582	3.141
2		1	2	2	T	0	58.840	136.90	147.40	190.20	206.30	254.30	270.40	246.80	190.20	148.30	109.30	77.05	47.31	32.51	19.11	7.346	5.760
3		1	1	1	T	0	13.050	38.25	50.07	61.43	76.83	84.16	139.00	138.20	135.60	117.00	104.70	90.10	62.85	46.61	28.99	11.850	5.289
4		1	1	2	R	0	6.747	19.17	56.22	69.34	82.47	116.20	129.10	141.00	164.60	147.30	142.00	102.80	80.72	62.99	34.31	10.730	4.016
5		1	2	1	R	0	22.950	120.50	73.74	105.90	145.40	169.50	178.30	167.70	157.50	134.70	104.10	77.63	45.63	32.09	14.89	6.193	3.019
6		1	2	2	T	0	6.535	40.30	60.93	60.57	117.10	118.80	139.60	120.90	107.30	89.35	72.83	58.35	33.88	26.77	14.34	5.972	3.328
7		1	1	1	T	0	8.667	24.94	45.15	62.63	91.72	91.12	111.20	116.60	114.60	97.83	81.21	58.77	39.76	31.41	18.96	9.247	4.645
8		1	1	2	R	0	18.350	41.68	85.13	89.37	128.00	142.90	172.10	167.50	132.70	124.30	99.42	79.40	45.88	36.59	21.91	10.040	6.413
9		1	1	1	T	0	4.052	29.36	38.70	68.15	101.90	170.80	147.30	182.60	154.70	153.50	155.00	136.90	92.62	77.19	49.24	23.400	8.125
10		1	1	2	R	0	120.900	213.70	142.60	281.40	209.40	185.30	250.00	294.50	198.80	219.50	168.40	152.70	108.40	80.13	50.16	18.880	6.266
11		1	2	1	R	0	8.463	35.78	64.86	90.37	103.40	161.80	158.40	190.40	206.50	194.50	153.00	130.50	74.22	49.63	33.40	12.070	6.444
12		1	2	2	T	0	29.930	28.54	97.12	132.90	142.10	181.50	202.90	181.10	203.60	169.50	149.30	117.90	81.26	64.70	40.40	17.360	9.340
13		1	1	1	T	0	45.330	73.79	74.54	114.60	139.50	163.20	176.00	185.60	132.80	134.60	97.66	95.90	58.03	43.02	31.99	12.880	5.823
14		1	1	2	R	0	52.260	99.00	147.40	181.90	176.50	231.60	227.60	191.00	174.50	140.20	106.60	102.70	63.54	43.86	31.14	11.950	4.711
15		1	1	1	T	0	12.530	38.44	55.85	81.86	107.40	134.00	141.80	157.30	174.80	162.20	126.20	106.30	74.50	50.89	31.17	10.720	4.660
16		1	1	2	R	0	18.970	41.86	68.57	120.80	127.40	156.40	203.80	203.20	200.40	193.20	145.70	117.70	71.81	43.81	25.08	9.165	4.000
17		1	1	1	T	0	26.130	46.60	92.51	126.80	163.50	230.60	269.50	259.40	226.40	186.40	140.40	109.30	64.93	46.17	31.18	18.340	11.020
18		1	1	2	R	0	54.520	106.90	156.00	205.80	223.80	299.00	306.90	331.10	269.60	256.40	177.80	140.50	74.93	60.66	34.34	15.210	8.704
19		1	2	1	R	0	66.710	125.80	86.76	141.90	309.20	233.40	246.10	262.10	218.90	221.60	185.90	175.60	112.20	79.90	59.97	14.680	8.520
20		1	2	2	T	0	22.930	60.33	67.35	87.17	112.80	166.10	156.90	178.80	188.70	193.00	164.20	133.20	83.02	69.52	36.02	13.540	6.084
21		1	2	1	R	0	27.040	65.93	72.10	120.40	122.00	194.70	205.40	211.80	195.20	174.70	141.30	111.40	66.28	48.65	26.42	8.581	4.858
22		1	2	2	T	0	17.000	60.04	65.29	104.20	128.20	127.50	167.70	191.00	166.00	173.90	144.10	110.50	54.54	49.94	31.13	12.000	7.505
23		1	2	1	R	0	15.640	33.03	78.39	133.30	114.90	160.00	154.70	182.40	179.80	159.20	125.90	119.20	56.95	45.36	23.10	9.650	3.788
24		1	2	2	T	0	17.090	67.04	111.70	125.00	177.40	216.20	219.20	210.00	180.10	162.70	135.50	113.80	81.27	49.37	31.84	15.030	7.207
25		1	2	1	R	0	36.120	48.22	109.30	130.50	136.80	195.10	219.30	208.30	187.30	169.80	115.30	99.05	45.97	30.54	19.25	5.788	4.094
26		1	2	2	T	0	21.700	48.80	94.79	115.20	153.00	200.10	224.10	209.10	179.20	170.30	144.40	117.90	64.34	52.16	27.45	9.584	4.647

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18
27	(b) (6)	1	1	1	T	0	15.050	42.10	61.66	106.20	168.00	166.40	172.60	178.40	162.90	144.80	106.80	91.89	52.15	39.17	25.78	10.490	5.388
28		1	1	2	R	0	22.060	42.02	75.80	139.30	179.00	153.40	171.10	183.30	148.50	123.80	98.12	71.69	43.84	33.29	17.81	8.092	3.858
29		1	1	1	T	0	18.330	53.48	80.64	106.50	141.30	180.30	228.10	217.40	217.80	149.40	131.20	123.30	76.74	57.38	33.19	14.240	7.866
30		1	1	2	R	0	26.550	54.16	112.40	161.90	165.80	217.20	237.10	241.90	223.90	179.20	143.10	131.40	79.11	47.00	28.32	12.460	5.788
31		1	2	1	R	0	18.780	50.46	142.40	164.30	199.90	238.40	254.70	241.80	262.00	216.50	169.10	114.30	71.38	55.88	33.19	12.330	4.884
32		1	2	2	T	0	8.171	28.18	94.20	109.50	132.60	165.60	212.00	216.70	218.80	196.80	156.70	135.90	75.99	61.47	41.26	16.350	7.931
33		1	1	1	T	0	8.122	29.70	32.34	60.40	85.70	95.45	107.80	95.57	84.33	69.99	53.34	46.62	29.92	24.98	19.48	10.450	5.626
34		1	1	2	R	0	34.590	39.35	56.73	88.74	91.81	107.00	100.90	105.70	82.81	68.38	49.01	43.98	24.85	19.99	14.24	7.890	4.312
35		1	2	1	R	0	34.310	96.36	128.80	177.30	181.80	237.00	252.20	215.60	218.10	167.00	132.80	86.90	60.09	44.36	22.24	9.565	6.236
36		1	2	2	T	0	23.180	64.17	88.87	104.20	127.90	145.00	159.10	163.20	149.10	138.50	96.79	85.97	51.31	37.75	24.53	8.917	6.833
37		1	1	1	T	0	29.340	50.15	58.20	102.40	119.50	134.90	145.60	139.00	128.20	120.40	94.81	78.10	49.98	33.52	20.19	8.917	5.418
38		1	1	2	R	0	34.220	52.20	96.70	119.50	125.70	159.70	202.10	212.70	186.20	198.00	141.20	117.50	65.27	52.32	25.75	10.930	4.957
39		1	2	1	R	0	33.080	77.40	112.20	118.20	164.20	183.70	218.60	196.00	179.70	141.70	111.70	88.55	47.80	31.90	18.25	7.946	4.457
40		1	2	2	T	0	19.980	31.08	73.39	91.67	105.10	145.50	140.40	141.60	123.90	102.30	88.62	70.01	46.26	33.80	19.79	10.690	6.078
41		1	2	1	R	0	16.790	28.60	46.97	59.79	76.43	98.99	141.60	151.40	174.40	170.80	144.80	116.50	82.49	65.11	34.83	15.310	4.974
42		1	2	2	T	0	16.360	64.43	65.46	109.70	104.10	157.30	175.10	204.80	191.60	193.90	173.00	166.50	105.60	77.58	48.42	23.230	10.120
43		1	1	1	T	0	12.040	48.10	71.00	88.12	91.49	127.00	152.70	185.90	173.90	179.80	140.00	140.70	77.40	63.24	44.10	15.940	6.159
44		1	1	2	R	0	14.260	35.37	61.51	128.20	136.50	187.60	197.20	206.60	204.10	191.20	153.20	161.30	94.84	69.27	45.89	17.240	6.458
45		2	2	1	R	0	28.780	47.67	74.17	96.56	102.50	157.00	187.90	214.70	230.10	200.30	169.80	136.40	88.57	66.57	39.20	14.000	5.250
46		2	2	2	T	0	19.480	41.91	62.52	88.74	117.80	136.80	176.40	196.00	180.70	176.90	156.30	135.80	93.32	72.61	41.72	17.320	8.783
47		2	1	1	T	0	9.328	27.47	46.68	63.86	86.12	109.40	110.10	138.00	169.70	167.80	152.10	100.70	61.58	47.57	26.66	14.300	4.798
48		2	1	2	R	0	4.692	28.79	53.97	72.77	78.75	92.02	126.90	136.10	117.00	106.30	92.06	79.08	43.09	32.32	18.18	7.947	2.381
49		2	1	1	T	0	83.730	110.20	138.00	159.10	116.60	208.50	149.30	145.70	126.30	120.40	91.55	70.38	46.80	38.89	20.01	7.984	3.678
50		2	1	2	R	0	85.960	115.70	235.20	188.60	176.30	191.50	164.70	167.50	148.40	129.90	111.10	82.87	54.98	48.05	22.95	7.945	4.906
51		2	1	1	T	0	20.870	84.16	70.21	120.70	155.60	173.60	213.50	236.20	196.80	202.10	166.70	152.10	91.15	60.82	36.62	13.810	6.308
52		2	1	2	R	0	31.780	75.77	167.20	228.70	261.70	293.00	287.30	240.10	209.50	214.10	176.10	151.30	80.65	60.15	31.96	10.280	4.637
53		2	1	1	T	0	25.940	33.74	94.45	137.70	140.20	213.70	209.90	248.80	247.40	242.10	241.70	192.20	131.60	111.70	73.92	35.210	19.080
54		2	1	2	R	0	26.480	71.80	109.50	158.20	171.10	197.30	230.60	233.90	211.20	221.20	192.80	163.00	102.50	80.09	52.18	21.160	10.630
55		2	2	1	R	0	73.680	56.19	98.74	109.70	130.00	170.40	205.20	234.80	218.70	214.20	195.70	155.20	108.60	77.01	46.84	12.390	5.882

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18
56	(b) (6)	2	2	2	T	0	38.800	43.15	93.71	104.20	139.90	166.20	200.10	205.90	212.10	219.40	194.20	181.60	141.70	99.21	56.60	21.230	13.090
57		2	2	1	R	0	23.420	41.46	69.26	98.00	126.70	158.60	177.90	178.50	157.70	151.90	129.80	106.10	65.44	49.44	26.41	8.185	3.909
58		2	2	2	T	0	18.980	52.75	70.73	89.27	114.40	118.70	136.40	130.60	133.30	125.50	98.16	89.53	53.21	38.48	24.35	8.362	4.674
59		2	2	1	R	0	16.710	146.90	120.20	78.67	108.70	171.10	174.10	182.90	152.90	150.50	134.90	101.80	61.40	41.38	23.77	8.480	3.159
60		2	2	2	T	0	12.830	40.88	43.32	70.68	90.14	89.88	106.30	100.70	100.80	93.88	95.02	75.75	41.75	33.03	19.80	9.088	3.866
61		2	1	1	T	0	72.730	77.35	99.58	131.50	172.50	171.20	188.20	159.40	158.00	153.90	131.30	111.20	58.47	37.39	24.94	9.382	4.990
62		2	1	2	R	0		143.40	157.90	223.30	210.60	248.10	252.50	268.30	240.40	220.10	161.70	128.20	68.58	44.99	27.99	10.130	5.335
63		2	2	1	R	0	43.380	73.12	117.90	193.40	178.40	270.60	257.30	272.00	261.40	249.70	196.60	189.10	122.60	95.01	47.63	14.970	6.839
64		2	2	2	T	0	33.520	74.48	114.80	163.10	191.90	214.20	240.70	263.70	239.80	223.70	202.00	175.70	114.30	95.98	52.20	20.100	10.120
65		2	2	1	R	0	30.910	90.72	94.44	155.50	201.50	236.40	268.00	221.70	205.80	185.60	162.00	133.50	84.32	61.38	33.51	10.850	4.266
66		2	2	2	T	0	13.340	57.43	59.51	113.90	144.90	119.00	143.00	122.30	99.05	93.49	86.69	69.18	43.11	40.30	28.22	11.220	5.793
67		2	1	1	T	0	24.060	52.45	42.22	61.68	95.61	107.90	110.90	160.20	169.60	173.80	160.30	135.60	84.83	59.98	34.76	12.860	5.814
68		2	1	2	R	0	28.350	47.88	58.72	87.44	127.00	176.70	220.40	208.70	216.70	196.50	176.70	150.70	87.65	68.30	35.56	11.760	5.812
69		2	2	1	R	0	15.690	92.93	61.68	101.50	130.90	144.90	157.50	134.40	112.60	90.67	69.13	62.45	33.41	28.87	15.62	5.617	2.510
70		2	2	2	T	0	36.490	113.00	106.30	141.10	101.40	127.10	110.80	99.23	87.62	88.01	62.68	62.50	31.15	27.13	15.15	6.639	3.287
71		2	1	1	T	0	44.960	60.72	75.08	114.00	138.80	150.40	189.10	196.90	145.60	143.10	112.20	95.45	60.69	47.27	26.62	12.410	4.303
72		2	1	2	R	0	50.740	187.30	205.30	183.30	180.90	218.40	266.20	215.30	190.50	165.60	144.90	123.30	65.95	49.28	26.87	10.750	3.658
73		2	2	1	R	0	40.250	58.62	144.80	187.90	233.10	330.30	351.00	327.50	326.30	287.60	227.40	163.80	100.30	71.47	38.03	14.270	7.113
74		2	2	2	T	0	22.660	51.87	110.90	154.70	200.20	274.60	240.00	238.90	235.40	225.60	160.10	140.80	92.04	62.82	32.29	12.890	
75		2	1	1	T	0	28.770	105.30	166.40	227.00	262.00	309.20	319.00	303.20	265.80	275.60	203.70	167.20	99.01	81.68	39.06	17.700	9.243
76		2	1	2	R	0	25.670	95.41	172.70	229.00	247.50	320.40	281.20	304.40	253.80	262.10	204.50	168.80	99.77	69.55	33.04	12.740	7.290
77		2	1	1	T	0	48.320	82.21	91.07	129.20	124.80	204.00	204.00	186.90	190.20	162.10	142.40	116.60	58.41	44.00	25.56	11.360	5.760
78		2	1	2	R	0	35.040	68.75	94.91	153.40	149.40	189.90	196.70	184.20	165.70	164.30	120.10	96.54	47.68	34.36	23.15	8.967	5.473
79		2	2	1	R	0	103.300	153.50	245.20	300.60	368.50	430.00	416.40	391.70	325.70	312.60	270.80	193.20	91.99	66.21	34.77	15.070	8.633
80		2	2	2	T	0	70.180	100.10	165.30	226.30	252.30	276.70	326.40	254.40	229.10	191.20	150.50	120.00	66.67	46.84	29.44	13.370	6.925
81			1	1	T	0	10.090	15.09	33.38	37.46	49.89	66.79	73.70	95.58	83.65	85.00	75.38	58.87	40.74	29.58	18.28	8.482	3.859
82			1	2	R	0	14.270	30.33	45.96	60.57	71.12	84.32	101.20	98.45	99.58	82.98	70.60	62.74	30.30	29.76	15.41	5.603	3.003
83		2	2	1	R	0	49.750	130.80	94.54	150.20	235.90	225.20	217.30	213.60	183.80	189.20	146.80	113.00	62.53	44.44	24.72	10.650	4.938
84		2	2	2	T	0	37.180	109.90	82.58	114.90	131.60	159.50	160.00	161.60	134.60	122.90	100.30	77.86	43.42	35.64	18.73	8.161	3.876

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18
85	(b) (6)	3	2	1	R	0	26.920	61.68	92.09	117.70	146.30	194.70	183.50	202.60	195.20	186.60	152.60	130.20	83.03	54.57	31.85	10.430	3.728
86		3	2	2	T	0	14.950	63.16	100.30	155.20	161.70	180.50	170.10	208.50	205.20	212.50	179.60	156.90	85.57	68.48	41.16	14.570	6.405
87		3	1	1	T	0	19.740	41.61	76.53	101.00	140.90	170.20	176.70	210.40	197.90	170.50	131.90	122.10	73.97	57.01	31.54	13.360	7.364
88		3	1	2	R	0	47.400	102.50	90.44	136.90	146.10	199.60	224.60	189.50	161.70	130.40	136.00	89.45	67.92	47.67	23.86	10.030	5.055
89		3	1	1	T	0	16.820	49.23	50.29	79.44	91.20	120.20	162.50	137.50	120.60	132.40	128.60	103.90	72.62	55.54	30.43	11.810	5.637
90		3	1	2	R	0	29.120	46.76	84.36	101.90	158.20	196.50	265.70	221.90	209.80	207.80	197.20	154.80	108.10	80.33	39.49	12.510	5.105
91		3	2	1	R	0	9.237	29.18	51.50	70.28	73.62	86.34	94.71	91.99	99.01	103.20	93.29	72.85	52.33	28.28	22.48	11.480	6.014
92		3	2	2	T	0	9.337	19.56	45.37	54.36	70.57	82.78	84.12	88.98	100.50	84.23	72.14	64.98	42.97	33.45	23.07	11.830	6.133
93		3	1	1	T	0	44.650	73.40	121.00	158.90	173.60	212.40	254.70	292.50	258.50	235.90	185.30	169.30	92.46	70.30	39.17	17.780	10.330
94		3	1	2	R	0	51.180	109.80	156.40	208.40	243.90	250.40	283.20	275.20	263.00	242.50	176.80	146.40	81.58	62.39	32.43	11.320	7.184
95		3	1	1	T	0	13.050	38.32	67.12	88.21	119.50	161.80	225.90	215.30	221.00	208.00	200.50	197.30	99.58	84.02	48.56	19.600	8.737
96		3	1	2	R	0	25.210	62.57	89.93	186.50	280.20	278.40	300.10	274.30	267.20	243.00	211.60	194.50	97.58	88.50	48.02	18.360	9.405
97		3	2	1	R	0	32.390	85.69	115.60	147.50	173.90	254.70	284.10	250.30	205.50	179.60	141.50	108.90	60.41	45.16	22.90	8.283	5.781
98		3	2	2	T	0	42.790	80.61	93.43	120.40	154.00	193.00	191.70	216.00	169.60	154.50	122.50	99.61	59.51	41.62	24.73	13.710	5.961
99		3	1	1	T	0	42.690	87.15	101.90	118.10	148.60	192.90	208.20	198.20	177.70	152.50	103.50	90.94	49.26	32.88	17.60	7.794	3.877
100		3	1	2	R	0	90.910	194.50	130.40	273.40	250.00	238.00	210.80	207.40	166.80	167.50	133.90	116.60	57.57	44.77	25.35	9.451	4.369
101		3	2	1	R	0	7.388	111.20	86.99	119.20	293.60	229.60	250.40	251.20	207.20	193.60	167.20	83.88	54.63	31.58	10.360	4.624	
102		3	2	2	T	0	8.248	32.80	52.16	76.16	93.75	140.20	166.20	152.90	129.60	135.30	117.70	96.57	51.03	37.95	26.03	9.862	5.116
103		3	2	1	R	0	47.020	83.31	163.80	177.80	216.20	180.80	299.70	295.20	274.80	254.60	207.70	173.40	96.69	72.58	40.04	12.090	5.172
104		3	2	2	T	0	16.010	45.12	87.47	94.73	115.90	131.20	164.50	165.60	162.70	155.20	106.40	109.00	67.08	52.69	29.98	8.528	
105	3	2	1	R	0	34.970	85.47	93.17	122.00	173.10	188.10	190.10	162.80	128.40	154.80	126.30	97.73	67.30	54.62	28.14	11.660	6.730	
106	3	2	2	T	0	22.700	51.49	67.57	96.04	117.30	131.50	127.00	121.80	115.80	98.83	91.68	82.21	55.36	46.36	30.55	18.230	9.812	
107	3	2	1	R	0	10.210	49.35	58.24	81.96	124.10	176.50	196.20	240.40	232.00	227.00	208.30	148.00	77.29	57.73	31.56	9.699	4.168	
108	3	2	2	T	0	31.370	60.54	87.14	97.76	135.80	166.70	198.00	238.40	255.40	252.40	249.40	189.20	133.40	97.47	49.62	21.500	9.267	
109	3	1	1	T	0	18.380	28.27	46.35	65.27	60.20	86.90	119.00	117.70	88.10	72.01	53.91	49.39	28.64	23.84	12.52	4.682	2.655	
110	3	1	2	R	0	19.450	35.73	75.33	96.42	122.20	196.50	215.80	210.60	181.30	149.40	125.50	87.19	53.10	44.29	20.55	6.300	5.012	
111	3	1	1	T	0	18.450	39.80	54.09	73.86	84.62	104.00	119.40	131.10	124.40	115.30	86.47	72.87	41.07	36.44	20.66	7.039	5.060	
112	3	1	2	R	0	38.640	94.93	69.82	148.40	153.40	195.10	187.20	208.00	150.10	154.90	130.70	98.14	51.01	43.89	19.74	8.033	5.492	
113	3	2	1	R	0	22.820	51.37	85.35	140.80	154.70	168.40	195.80	176.80	166.20	139.20	117.40	97.14	51.12	37.98	20.65	7.172	2.704	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18
114	(b) (6)	3	2	2	T	0	17.800	50.24	64.31	107.70	124.90	140.50	152.40	138.90	135.10	132.50	108.80	90.57	49.54	40.72	20.69	8.424	3.564
115		3	1	1	T	0	54.290	103.10	113.20	125.60	189.70	198.00	234.10	252.20	217.90	184.10	142.50	122.90	80.52	61.49	36.07	20.020	10.870
116		3	1	2	R	0	41.610	68.39	110.10	175.50	196.40	220.70	224.40	232.80	231.50	214.10	176.80	133.10	78.49	59.06	30.95	16.820	7.635
117		3	2	1	R	0	23.380	54.32	116.00	167.70	161.90	237.80	228.60	247.30	234.40	197.60	165.70	117.80	73.27	49.21	37.01	16.260	8.181
118		3	2	2	T	0	22.930	36.55	74.37	105.20	134.60	137.10	184.90	181.10	172.30	145.60	128.60	92.04	63.78	47.56	31.63	16.920	5.506
119		3	2	1	R	0	17.210	73.70	67.63	135.10	165.80	105.90	168.90	147.30	162.00	155.70	120.60	100.50	64.86	52.66	26.52	10.570	6.825
120		3	2	2	T	0	12.480	31.72	55.30	122.30	132.10	141.80	136.00	135.10	138.20	109.40	108.80	101.50	56.79	42.85	24.69	9.401	4.385
121		3	2	1	R	0	14.760	58.54	79.21	121.20	139.40	134.50	184.80	206.90	201.20	186.20	168.10	143.90	91.90	60.15	32.63	10.720	3.801
122		3	2	2	T	0	11.620	33.53	54.98	104.60	120.20	160.20	172.90	181.00	190.40	201.70	183.90	160.60	96.72	73.98	43.60	17.730	5.430
123		3	1	1	T	0	33.560	97.06	174.20	213.90	289.70	240.90	345.30	344.50	243.30	289.40	242.50	244.80	109.00	79.92	46.40	25.380	15.390
124		3	1	2	R	0	33.680	67.50	110.20	192.90	169.00	221.90	234.70	288.60	199.70	210.90	176.00	137.00	64.35	58.03	34.72	17.940	8.682
125		3	1	1	T	0	24.330	104.70	106.10	165.80	233.50	255.10	250.70	237.90	217.20	188.50	156.00	131.50	78.75	57.53	27.83	9.807	4.306
126		3	1	2	R	0	30.720	79.98	119.70	184.00	224.60	277.60	339.20	292.50	245.00	206.40	155.50	127.00	67.79	51.57	25.23	8.024	4.272

Obs	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	trt
1	1.780	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.02	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
2	2.735	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
3	3.528	16	19	0	0.03	0.08	0.17	0.25	0.37	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.03	12.03	24.00	36.00	48.00	1
4	2.156	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.80	1.00	1.52	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
5	2.091	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.02	8.00	12.00	24.00	36.00	48.00	2
6	2.017	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
7	3.598	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.08	3.05	4.00	6.00	8.05	12.00	24.00	36.00	48.05	1
8	3.707	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.78	1.00	1.57	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.03	48.03	2
9	4.653	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
10	4.700	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
11	3.598	16	19	0	0.03	0.08	0.17	0.28	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.05	12.00	24.00	36.00	48.00	2
12	5.431	16	19	0	0.03	0.08	0.17	0.25	0.37	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
13	4.604	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.13	6.00	8.05	12.07	24.00	36.00	48.00	1
14	4.189	16	19	0	0.03	0.08	0.20	0.30	0.33	0.50	0.78	1.00	1.52	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2

Obs	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	trt
15	2.886	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
16	2.421	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
17	8.865	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
18	7.152	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
19	4.441	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.02	12.00	24.00	36.03	48.28	2
20	3.574	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
21	3.414	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.03	6.00	8.00	12.00	24.00	36.00	48.00	2
22	4.821	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
23	2.187	16	19	0	0.03	0.08	0.20	0.28	0.33	0.55	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.03	12.00	24.00	36.00	48.00	2
24	3.778	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.57	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
25	2.104	16	19	0	0.03	0.08	0.20	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
26	2.835	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
27	3.251	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
28	2.535	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
29	6.083	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
30	3.123	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.03	8.00	12.00	24.00	36.00	48.00	2
31	3.357	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.03	6.00	8.00	12.00	24.00	36.00	48.00	2
32	4.495	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.57	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
33	5.237	16	19	0	0.03	0.08	0.17	0.28	0.33	0.50	0.75	1.00	1.50	2.00	3.03	4.05	6.00	8.00	12.33	24.00	36.00	48.00	1
34	3.584	16	19	0	0.07	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.05	2
35	4.516	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
36	3.608	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
37	2.963	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
38	5.012	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.02	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
39	3.730	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
40	4.873	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
41	3.942	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.02	4.03	6.00	8.00	12.00	24.00	36.00	48.00	2
42	6.332	16	19	0	0.03	0.08	0.17	0.28	0.33	0.58	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
43	4.563	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1

Obs	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	trt
44	3.889	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
45	3.533	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.02	2
46	5.064	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
47	3.727	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.10	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
48	2.420	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.57	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
49	2.349	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
50	2.942	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
51	4.293	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
52	2.009	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
53	11.060	16	19	0	0.03	0.08	0.17	0.25	0.37	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
54	5.645	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
55	3.503	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
56	8.280	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
57	3.520	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
58	3.757	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
59	2.488	16	19	0	0.03	0.13	0.22	0.25	0.33	0.50	0.75	1.00	1.50	2.07	3.00	4.00	6.00	8.00	12.00	24.00	37.23	48.00	2
60	2.645	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.20	6.32	8.07	12.00	24.00	36.00	48.00	1
61	3.775	16	19	0	0.03	0.08	0.17	0.25	0.40	0.50	0.75	1.00	1.50	2.00	3.03	4.00	6.00	8.00	12.00	24.00	36.13	48.00	1
62	3.606	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
63	4.721	16	19	0	0.03	0.08	0.17	0.25	0.33	0.53	0.75	1.00	1.50	2.00	3.08	4.05	6.00	8.00	12.00	24.00	36.00	48.00	2
64	7.528	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
65	2.838	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
66	3.497	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
67	4.132	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
68	3.451	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
69	1.266	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
70	1.702	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
71	2.489	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.05	8.00	12.00	24.00	36.00	48.00	1
72	2.752	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2

Obs	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	trt
73	5.745	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
74	5.156	15	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.80	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
75	5.056	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
76	4.553	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
77	3.469	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.53	2.00	3.00	4.03	6.08	8.00	12.00	24.10	36.00	48.00	1
78	3.900	16	19	0	0.03	0.10	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
79	5.407	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
80	4.664	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.52	2.00	3.00	4.00	6.03	8.00	12.00	24.00	36.00	48.00	1
81	2.530	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
82	1.575	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
83	4.405	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.02	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
84	3.196	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
85	2.061	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
86	4.340	16	19	0	0.03	0.08	0.17	0.28	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.02	36.02	48.00	1
87	4.495	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
88	3.860	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
89	3.600	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
90	3.155	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
91	4.137	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
92	4.677	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
93	8.239	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
94	5.134	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
95	6.904	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
96	5.166	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
97	4.377	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.05	8.00	12.00	24.00	36.00	48.00	2
98	5.432	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.93	2.00	3.00	4.05	6.00	8.00	12.00	24.00	36.00	48.00	1
99	3.743	16	19	0	0.03	0.10	0.18	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.42	1
100	2.965	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.83	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
101		15	18	0	0.03	0.10	0.22	0.25	0.33	0.53	0.75	1.05	1.50	2.03	3.00	4.10	6.00	8.03	12.00	24.00	36.00	48.00	2

Obs	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	trt
102	3.357	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.80	1.00	1.78	2.00	3.23	4.00	6.00	8.00	12.03	24.00	36.20	48.00	1
103	3.504	16	19	0	0.03	0.08	0.20	0.25	0.33	0.53	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
104		14	17	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.60	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
105	3.734	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
106	4.848	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
107	2.621	16	19	0	0.03	0.08	0.17	0.25	0.37	0.55	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
108	5.755	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
109	2.451	16	19	0	0.03	0.08	0.18	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.02	24.00	36.00	48.00	1
110	2.778	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.83	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
111	2.710	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
112	3.891	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
113	2.131	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	34.98	48.00	2
114	2.188	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
115	7.265	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
116	6.693	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
117	3.508	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
118	4.808	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
119	4.858	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
120	2.625	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
121	1.746	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
122	3.573	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
123	9.350	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
124	5.755	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
125	5.307	16	19	0	0.03	0.08	0.17	0.25	0.37	0.50	0.75	1.00	1.58	2.00	3.12	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
126	2.919	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.80	1.02	1.50	2.00	3.00	4.00	6.00	8.00	12.02	24.00	36.00	48.00	2

5.9.4.2 Fasting Study Output (FP)

Fasting STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	62	(b) (6)
trt	2	1 2
per	2	1 2
seq	2	1 2
GRP	3	1 2 3

Number of Observations Read	126
Number of Observations Used	124

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	65	9.04940383	0.13922160	6.26	<.0001
Error	58	1.29056228	0.02225107		
Corrected Total	123	10.33996611			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.875187	2.043868	0.149168	7.298316

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.00307775	0.00307775	0.14	0.7113
GRP	2	0.26321156	0.13160578	5.91	0.0046
seq	1	0.01875357	0.01875357	0.84	0.3624
seq*GRP	2	0.04553132	0.02276566	1.02	0.3659
sub(seq*GRP)	56	8.55463890	0.15276141	6.87	<.0001
per(GRP)	2	0.10206663	0.05103332	2.29	0.1100
trt	1	0.06212410	0.06212410	2.79	0.1001

Source	DF	Type III SS	Mean Square	F Value	Pr > F

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per	1	0.00442602	0.00442602	0.20	0.6573
GRP	2	0.26855237	0.13427618	6.03	0.0042
seq	1	0.01995329	0.01995329	0.90	0.3476
seq*GRP	2	0.04553132	0.02276566	1.02	0.3659
sub(seq*GRP)	56	8.55463890	0.15276141	6.87	<.0001
per(GRP)	2	0.09911655	0.04955827	2.23	0.1170
trt	1	0.06212410	0.06212410	2.79	0.1001

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01995329	0.01995329	0.13	0.7192
GRP	2	0.26855237	0.13427618	0.88	0.4209

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.04480233	0.02681304	-1.67	0.1001

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	65	8.71650515	0.13410008	5.88	<.0001
Error	58	1.32308373	0.02281179		
Corrected Total	123	10.03958889			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.868213	2.055727	0.151036	7.347072

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.00322052	0.00322052	0.14	0.7085
GRP	2	0.22656497	0.11328248	4.97	0.0102
seq	1	0.03319174	0.03319174	1.46	0.2326
seq*GRP	2	0.04465810	0.02232905	0.98	0.3819
sub(seq*GRP)	56	8.28866661	0.14801190	6.49	<.0001
per(GRP)	2	0.08940118	0.04470059	1.96	0.1501
trt	1	0.03080203	0.03080203	1.35	0.2500

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per	1	0.00476295	0.00476295	0.21	0.6494
GRP	2	0.23225994	0.11612997	5.09	0.0092
seq	1	0.03389556	0.03389556	1.49	0.2278
seq*GRP	2	0.04465810	0.02232905	0.98	0.3819
sub(seq*GRP)	56	8.28866661	0.14801190	6.49	<.0001
per(GRP)	2	0.08740638	0.04370319	1.92	0.1564
trt	1	0.03080203	0.03080203	1.35	0.2500

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.03389556	0.03389556	0.23	0.6341
GRP	2	0.23225994	0.11612997	0.78	0.4613

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.03154716	0.02714877	-1.16	0.2500

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	65	8.90864305	0.13705605	6.10	<.0001
Error	58	1.30245496	0.02245612		
Corrected Total	123	10.21109801			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.872447	2.809592	0.149854	5.333644

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.01510694	0.01510694	0.67	0.4155
GRP	2	0.22107464	0.11053732	4.92	0.0106
seq	1	0.06326956	0.06326956	2.82	0.0986
seq*GRP	2	0.53432189	0.26716095	11.90	<.0001
sub(seq*GRP)	56	6.87231714	0.12271995	5.46	<.0001
per(GRP)	2	0.08197603	0.04098802	1.83	0.1703

Source	DF	Type I SS	Mean Square	F Value	Pr > F
trt	1	1.12057685	1.12057685	49.90	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per	1	0.01096710	0.01096710	0.49	0.4874
GRP	2	0.23068908	0.11534454	5.14	0.0088
seq	1	0.07026042	0.07026042	3.13	0.0822
seq*GRP	2	0.53432189	0.26716095	11.90	<.0001
sub(seq*GRP)	56	6.87231714	0.12271995	5.46	<.0001
per(GRP)	2	0.07044110	0.03522055	1.57	0.2171
trt	1	1.12057685	1.12057685	49.90	<.0001

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.07026042	0.07026042	0.57	0.4524
GRP	2	0.23068908	0.11534454	0.94	0.3967

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.19027923	0.02693630	-7.06	<.0001

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	trt	AUCRATIO
1	(b) (6)	1	0.96
2		1	0.95
3		1	0.96
4		1	0.92
5		1	0.97
6		1	0.95
7		1	0.94
8		1	0.97
9		1	0.87
10		1	0.97
11		1	0.94
12		1	0.96
13		1	0.97
14		1	0.96
15		1	0.93
16		1	0.96

Obs	sub	trt	AUCRATIO
17	(b) (6)	1	0.86
18		1	0.94
19		1	0.95
20		1	0.90
21		1	0.95
22		1	0.96
23		1	0.96
24		1	0.96
25		1	0.96
26		1	0.96
27		1	0.93
28		1	0.94
29		1	0.94
30		1	0.95
31		1	0.95
32		1	0.94
33		1	0.95
34		1	0.96
35		1	0.97
36		1	0.97
37		1	0.95
38		1	0.96
39		1	0.96
40		1	0.95
41		1	0.95
42		1	0.94
43		1	0.96
44		1	0.95
45		1	0.96
46		1	0.91
47		1	0.92
48		1	0.95
49		1	0.92
50		1	0.93
51		1	0.95
52		1	0.97
53		1	0.93
54		1	0.96
55		1	0.93
56		1	0.95

Obs	sub	trt	AUCRATIO
57	(b) (6)	1	0.97
58		1	0.92
59		1	0.94
60		1	0.97
61		1	0.97
62		1	0.93
63		1	0.94
64		2	0.97
65		2	0.98
66		2	0.96
67		2	0.94
68		2	0.97
69		2	0.96
70		2	0.95
71		2	0.97
72		2	0.92
73		2	0.97
74		2	0.96
75		2	0.98
76		2	0.97
77		2	0.96
78		2	0.97
79		2	0.97
80		2	0.89
81		2	0.93
82		2	0.93
83		2	0.93
84		2	0.96
85		2	0.97
86		2	0.97
87		2	0.96
88		2	0.96
89		2	0.99
90		2	0.96
91		2	0.98
92		2	0.95
93		2	0.97
94		2	0.96
95		2	0.97
96		2	0.98

Obs	sub	trt	AUCRATIO
97	(b) (6)	2	0.97
98	(b) (6)	2	0.98
99	(b) (6)	2	0.97
100	(b) (6)	2	0.95
101	(b) (6)	2	0.96
102	(b) (6)	2	0.94
103	(b) (6)	2	0.96
104	(b) (6)	2	0.97
105	(b) (6)	2	0.94
106	(b) (6)	2	0.98
107	(b) (6)	2	0.95
108	(b) (6)	2	0.98
109	(b) (6)	2	0.92
110	(b) (6)	2	0.95
111	(b) (6)	2	0.97
112	(b) (6)	2	0.94
113	(b) (6)	2	0.97
114	(b) (6)	2	0.97
115	(b) (6)	2	0.98
116	(b) (6)	2	0.95
117	(b) (6)	2	0.98
118	(b) (6)	2	0.96
119	(b) (6)	2	0.93
120	(b) (6)	2	0.97
121	(b) (6)	2	0.92
122	(b) (6)	2	0.97
123	(b) (6)	2	0.93
124	(b) (6)	2	0.99
125	(b) (6)	2	0.94
126	(b) (6)	2	0.97

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

sub	seq	RAUCT12	RAUC12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	2	1.14	1.15	1.02	1.50	0.92	1.09
(b) (6)	1	0.87	0.89	0.84	0.49	0.77	1.30
(b) (6)	2	0.79	0.80	0.78	1.00	0.98	1.02
(b) (6)	1	0.81	0.82	0.68	1.28	0.98	1.02
(b) (6)	1	0.90	0.91	0.62	1.00	0.99	1.01
(b) (6)	2	1.13	1.15	0.99	1.00	0.91	1.10

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	1	0.95	0.96	0.80	2.00	0.95	1.05
	1	0.99	1.00	0.86	2.00	1.02	0.98
	1	0.88	0.92	0.81	0.75	0.81	1.23
	2	0.75	0.76	0.62	6.06	0.93	1.07
	2	1.04	1.06	0.90	1.00	0.90	1.11
	2	1.24	1.25	1.20	0.75	0.89	1.12
	2	1.24	1.24	1.02	1.00	1.08	0.93
	1	1.20	1.20	0.97	1.00	1.04	0.96
	1	1.03	1.08	0.94	0.75	0.77	1.30
	2	1.07	1.08	0.84	1.05	0.95	1.06
	1	1.18	1.21	1.01	1.50	0.97	1.03
	2	0.86	0.85	0.65	1.33	1.15	0.87
	1	0.72	0.71	0.68	0.75	1.10	0.91
	2	0.92	0.95	0.67	0.67	0.89	1.12
	2	1.34	1.36	1.17	0.67	0.91	1.10
	1	0.90	0.91	0.90	1.00	0.92	1.08
	2	1.04	1.06	0.85	0.67	0.85	1.17
	1	1.46	1.46	1.25	1.50	0.96	1.04
	1	0.86	0.86	0.89	2.94	1.08	0.92
	1	1.02	1.05	0.81	2.00	0.79	1.26
	1	1.34	1.37	1.06	1.00	0.86	1.17
	2	1.23	1.28	0.93	2.00	0.73	1.36
	2	0.86	0.87	0.76	0.75	0.91	1.10
	2	0.76	0.78	0.58	0.75	0.89	1.12
	1	0.80	0.82	0.70	0.75	0.93	1.08
	2	1.03	1.06	0.97	1.00	0.84	1.19
	2	0.66	0.68	0.54	0.44	0.83	1.20
	1	0.91	0.92	0.79	2.67	0.93	1.07
	2	0.96	0.97	0.90	0.33	0.87	1.15
	1	0.88	0.88	0.74	1.33	1.03	0.97
	2	0.84	0.83	0.78	0.67	1.10	0.91
	1	1.09	1.09	1.00	1.50	1.04	0.96
	1	1.14	1.11	1.04	1.00	1.14	0.87
	2	0.70	0.71	0.76	1.50	1.01	0.99
	1	1.09	1.11	0.94	1.33	0.90	1.11
	2	0.72	0.72	0.69	3.03	1.02	0.98
	2	1.20	1.22	1.05	2.00	0.82	1.22
	1	1.18	1.18	0.94	1.33	1.05	0.95
	1	0.71	0.73	0.61	1.00	0.84	1.19
	2	0.96	0.98	0.97	0.75	0.95	1.05

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	1	1.13	1.17	1.03	1.33	0.87	1.15
	1	0.94	0.96	0.75	1.00	0.91	1.10
	2	0.98	0.99	0.76	1.33	1.01	0.99
	1	0.81	0.84	0.76	3.00	0.73	1.37
	2	0.71	0.72	0.57	1.51	0.65	1.54
	2	0.63	0.64	0.55	1.33	1.68	0.60
	2	0.95	0.97	0.69	0.67	0.93	1.08
	2	1.44	1.46	1.06	1.50	0.88	1.14
	1	0.55	0.57	0.55	0.90	0.88	1.14
	1	0.79	0.77	0.63	1.00	1.22	0.82
	2	0.96	0.96	0.78	1.00	0.97	1.03
	1	1.03	1.04	1.08	1.00	1.01	0.99
	2	0.83	0.85	0.75	0.75	0.87	1.14
	2	0.86	0.83	0.84	0.67	1.35	0.74
	2	1.18	1.19	0.97	2.00	0.88	1.13
	1	1.45	1.47	1.20	0.75	0.87	1.15
	1	1.02	1.06	0.75	0.63	0.82	1.23

5.9.4.3 Firm Reviewer Ratio (FP)

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	(b) (6)	1	2	1	2	1081.74	1113.93	264.40	R	1059.06	1091.26	264.40	0.97904	0.97964	1
2		1	2	2	1	1228.93	1282.95	270.40	T	1206.52	1253.96	270.40	0.98176	0.97740	1
3		1	1	1	1	1246.48	1305.86	139.00	T	1219.80	1274.16	139.00	0.97859	0.97572	1
4		1	1	2	2	1434.87	1462.73	164.60	R	1391.87	1415.85	164.60	0.97004	0.96794	1
5		1	2	1	2	1015.84	1053.82	178.30	R	996.22	1034.20	178.30	0.98069	0.98138	1
6		1	2	2	1	800.44	837.85	139.60	T	785.15	822.56	139.60	0.98089	0.98175	1
7		1	1	1	1	929.86	1006.06	116.60	T	914.95	991.15	116.60	0.98396	0.98518	1
8		1	1	2	2	1145.86	1222.92	172.10	R	1126.45	1203.51	172.10	0.98306	0.98413	1
9		1	1	1	1	1934.64	2003.27	182.60	T	1889.90	1954.27	182.60	0.97687	0.97554	1
10		1	1	2	2	2142.35	2211.08	294.50	R	2086.66	2140.89	294.50	0.97401	0.96825	1
11		1	2	1	2	1580.09	1639.14	206.50	R	1543.37	1598.38	206.50	0.97676	0.97514	1
12		1	2	2	1	1783.51	1881.66	203.60	T	1749.44	1847.59	203.60	0.98090	0.98189	1
13		1	1	1	1	1354.03	1437.50	185.60	T	1324.62	1398.77	185.60	0.97827	0.97306	1
14		1	1	2	2	1420.37	1492.71	231.60	R	1388.51	1451.15	231.60	0.97757	0.97216	1
15		1	1	1	1	1398.10	1441.54	174.80	T	1363.17	1403.12	174.80	0.97502	0.97335	1
16		1	1	2	2	1410.65	1447.69	203.80	R	1378.72	1415.76	203.80	0.97736	0.97794	1
17		1	1	1	1	1736.50	1984.91	269.50	T	1716.43	1934.31	269.50	0.98844	0.97451	1
18		1	1	2	2	1983.13	2146.14	331.10	R	1947.83	2073.42	331.10	0.98220	0.96612	1
19		1	2	1	2	2254.02	2318.34	309.20	R	2176.57	2234.43	309.20	0.96564	0.96381	1
20		1	2	2	1	1695.89	1751.36	193.00	T	1654.45	1709.92	193.00	0.97556	0.97634	1
21		1	2	1	2	1418.14	1479.22	211.80	R	1385.29	1433.39	211.80	0.97684	0.96902	1
22		1	2	2	1	1469.32	1564.71	191.00	T	1437.15	1518.26	191.00	0.97810	0.97031	1
23		1	2	1	2	1295.92	1328.70	182.40	R	1264.29	1297.07	182.40	0.97559	0.97619	1
24		1	2	2	1	1600.81	1664.40	219.20	T	1572.38	1635.96	219.20	0.98224	0.98292	1

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
25	(b) (6)	1	2	1	2	1167.97	1204.10	219.30	R	1138.63	1171.03	219.30	0.97488	0.97254	1
26		1	2	2	1	1448.26	1493.41	224.10	T	1413.27	1458.42	224.10	0.97584	0.97657	1
27		1	1	1	1	1256.06	1312.78	178.40	T	1230.53	1287.25	178.40	0.97968	0.98056	1
28		1	1	2	2	1048.91	1095.07	183.30	R	1030.01	1076.18	183.30	0.98199	0.98275	1
29		1	1	1	1	1643.94	1772.37	228.10	T	1613.56	1741.98	228.10	0.98152	0.98286	1
30		1	1	2	2	1594.99	1645.77	241.90	R	1563.84	1614.62	241.90	0.98047	0.98107	1
31		1	2	1	2	1696.95	1748.60	262.00	R	1658.22	1703.16	262.00	0.97718	0.97401	1
32		1	2	2	1	1807.74	1880.89	218.80	T	1766.97	1833.34	218.80	0.97745	0.97472	1
33		1	1	1	1	838.95	975.81	107.80	T	828.01	947.69	107.80	0.98696	0.97118	1
34		1	1	2	2	713.47	804.28	107.00	R	703.88	780.68	107.00	0.98656	0.97066	1
35		1	2	1	2	1394.98	1498.99	252.20	R	1371.99	1475.99	252.20	0.98352	0.98466	1
36		1	2	2	1	1195.65	1267.61	163.20	T	1170.52	1230.00	163.20	0.97899	0.97033	1
37		1	1	1	1	1067.81	1124.66	145.60	T	1049.23	1106.07	145.60	0.98260	0.98348	1
38		1	1	2	2	1476.06	1581.56	212.70	R	1444.94	.	212.70	0.97892	.	1
39		1	2	1	2	1162.15	1245.95	218.60	R	1142.26	.	218.60	0.98288	.	1
40		1	2	2	1	1063.44	1186.06	145.50	T	1049.44	1172.06	145.50	0.98683	0.98819	1
41		1	2	1	2	1576.30	1638.05	174.40	R	1539.05	1589.14	174.40	0.97636	0.97014	1
42		1	2	2	1	2116.17	2225.76	204.80	T	2074.43	2184.01	204.80	0.98027	0.98125	1
43		1	1	1	1	1725.66	1796.26	185.90	T	1677.94	1742.31	185.90	0.97234	0.96997	1
44		1	1	2	2	1914.68	1970.33	206.60	R	1864.19	1917.12	206.60	0.97363	0.97299	1
45	2	2	1	2	1774.20	1825.93	230.10	R	1729.09	1774.18	230.10	0.97457	0.97166	1	
46	2	2	2	1	1842.05	1928.80	196.00	T	1803.39	1890.13	196.00	0.97901	0.97995	1	
47	2	1	1	1	1372.28	1436.22	169.70	T	1344.65	1399.52	169.70	0.97986	0.97445	1	
48	2	1	2	2	941.53	981.55	136.10	R	919.26	952.71	136.10	0.97635	0.97061	1	
49	2	1	1	1	1060.80	1099.94	208.50	T	1038.35	1077.49	208.50	0.97884	0.97959	1	

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
50	(b) (6)	2	1	2	2	1229.46	1282.59	235.20	R	1201.88	1255.01	235.20	0.97757	0.97850	1
51		2	1	1	1	1789.92	1861.33	236.20	T	1749.16	1813.67	236.20	0.97722	0.97439	1
52		2	1	2	2	1752.05	1778.55	293.00	R	1705.80	1735.34	293.00	0.97360	0.97570	1
53		2	1	1	1	2971.88	3182.15	248.80	T	2918.76	3129.04	248.80	0.98213	0.98331	1
54		2	1	2	2	2223.09	2315.13	233.90	R	2174.73	2266.76	233.90	0.97824	0.97911	1
55		2	2	1	2	1977.17	2026.48	234.80	R	1916.09	1958.47	234.80	0.96911	0.96644	1
56		2	2	2	1	2433.05	2592.03	219.40	T	2380.37	2539.35	219.40	0.97835	0.97968	1
57		2	2	1	2	1316.58	1378.83	178.50	R	1282.93	1322.66	178.50	0.97445	0.95926	1
58		2	2	2	1	1128.77	1201.62	136.40	T	1102.94	1161.46	136.40	0.97711	0.96657	1
59		2	2	1	2	1261.15	1299.77	182.90	R	1230.74	1265.59	182.90	0.97589	0.97370	1
60		2	2	2	1	961.88	1007.93	106.30	T	942.23	988.27	106.30	0.97956	0.98050	1
61		2	1	1	1	1307.53	1379.52	188.20	T	1279.90	1344.67	188.20	0.97887	0.97474	1
62		2	1	2	2	1628.18	1691.92	268.30	R	1593.75	1650.89	268.30	0.97885	0.97575	1
63		2	2	1	2	2280.42	2353.82	272.00	R	2218.48	2270.06	272.00	0.97284	0.96442	1
64		2	2	2	1	2352.57	2491.64	263.70	T	2300.44	2396.07	263.70	0.97784	0.96165	1
65		2	2	1	2	1676.65	1717.49	268.00	R	1633.39	1667.96	268.00	0.97419	0.97116	1
66		2	2	2	1	1111.56	1172.15	144.90	T	1087.05	1143.26	144.90	0.97795	0.97535	1
67		2	1	1	1	1590.98	1660.01	173.80	T	1553.06	1610.23	173.80	0.97617	0.97002	1
68		2	1	2	2	1757.54	1811.31	220.40	R	1712.17	1765.94	220.40	0.97419	0.97495	1
69		2	2	1	2	827.68	845.89	157.50	R	807.51	827.90	157.50	0.97563	0.97874	1
70		2	2	2	1	794.43	822.56	141.10	T	777.08	805.21	141.10	0.97816	0.97891	1
71		2	1	1	1	1319.94	1356.51	196.90	T	1291.13	1327.70	196.90	0.97817	0.97876	1
72		2	1	2	2	1496.43	1538.16	266.20	R	1461.83	1497.34	266.20	0.97688	0.97346	1
73		2	2	1	2	2204.38	2312.67	351.00	R	2159.29	2243.02	351.00	0.97954	0.96988	1
74	2	2	2	1	1842.46	1930.84	274.60	T	1796.68	1901.62	274.60	0.97515	0.98487	1	

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
75	(b) (6)	2	1	1	1	2235.25	2324.69	319.00	T	2191.03	2280.48	319.00	0.98022	0.98098	1
76		2	1	2	2	2044.74	2128.74	320.40	R	2002.26	2086.26	320.40	0.97922	0.98004	1
77		2	1	1	1	1424.35	1486.69	204.00	T	1396.30	1458.65	204.00	0.98031	0.98114	1
78		2	1	2	2	1254.06	1334.24	196.70	R	1228.98	1300.56	196.70	0.98000	0.97476	1
79		2	2	1	2	2382.67	2488.33	430.00	R	2337.55	2443.21	430.00	0.98106	0.98187	1
80		2	2	2	1	1679.70	1770.18	326.40	T	1650.79	1741.28	326.40	0.98279	0.98367	1
81		.	1	1	1	830.82	875.99	95.58	T	815.19	860.37	95.58	0.98119	0.98216	1
82		.	1	2	2	762.88	788.19	101.20	R	743.20	768.51	101.20	0.97420	0.97503	1
83		2	2	1	2	1462.50	1551.44	235.90	R	1434.75	1503.65	235.90	0.98103	0.96920	1
84		2	2	2	1	1059.72	1123.12	161.60	T	1039.45	1089.44	161.60	0.98087	0.97001	1
85		3	2	1	2	1555.94	1582.70	202.60	R	1514.29	1539.28	202.60	0.97323	0.97256	1
86		3	2	2	1	1864.84	1933.63	212.50	T	1817.10	1876.59	212.50	0.97440	0.97050	1
87		3	1	1	1	1583.54	1667.29	210.40	T	1552.33	1636.08	210.40	0.98029	0.98128	1
88		3	1	2	2	1337.84	1413.16	224.60	R	1312.44	1387.76	224.60	0.98101	0.98203	1
89		3	1	1	1	1373.89	1434.37	162.50	T	1342.79	1403.27	162.50	0.97736	0.97831	1
90		3	1	2	2	1924.01	1968.67	265.70	R	1871.33	1903.72	265.70	0.97262	0.96701	1
91		3	2	1	2	1031.48	1118.20	103.20	R	1015.40	1099.31	103.20	0.98441	0.98310	1
92		3	2	2	1	988.05	1091.13	100.50	T	972.96	1067.12	100.50	0.98473	0.97799	1
93		3	1	1	1	2110.95	2300.34	292.50	T	2073.58	2262.98	292.50	0.98230	0.98376	1
94		3	1	2	2	1869.17	1972.12	283.20	R	1828.86	1906.73	283.20	0.97843	0.96684	1
95	3	1	1	1	2186.21	2310.61	225.90	T	2133.16	2237.32	225.90	0.97573	0.96828	1	
96	3	1	2	2	2327.52	2411.78	300.10	R	2270.93	2355.19	300.10	0.97569	0.97654	1	
97	3	2	1	2	1447.46	1546.11	284.10	R	1418.91	.	284.10	0.98028	.	1	
98	3	2	2	1	1411.38	1532.54	216.00	T	1389.26	1494.83	216.00	0.98432	0.97539	1	
99	3	1	1	1	1155.83	1241.05	208.20	T	1134.74	.	208.20	0.98175	.	1	

Obs	sub (b) (6)	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
100		3	1	2	2	1422.20	1471.55	273.40	R	1389.72	1431.09	273.40	0.97716	0.97250	1
101		3	2	1	2	1717.27	1770.37	293.60	R	1673.08	1730.84	293.60	0.97427	0.97767	1
102		3	2	2	1	1213.73	1272.99	166.20	T	1186.70	1241.51	166.20	0.97773	0.97527	1
103		3	2	1	2	2039.57	2091.11	299.70	R	1983.99	2027.32	299.70	0.97275	0.96949	1
104		3	2	2	1	1292.24	1329.64	165.60	T	1299.83	1329.22	165.60	1.00588	0.99968	1
105		3	2	1	2	1414.63	1482.43	190.10	R	1385.98	1453.78	190.10	0.97975	0.98067	1
106		3	2	2	1	1344.45	1439.17	131.50	T	1324.98	1419.70	131.50	0.98552	0.98647	1
107		3	2	1	2	1682.38	1720.23	240.40	R	1636.19	1668.22	240.40	0.97254	0.96976	1
108		3	2	2	1	2421.71	2516.25	255.40	T	2369.42	2463.96	255.40	0.97841	0.97922	1
109		3	1	1	1	669.31	723.16	119.00	T	655.16	.	119.00	0.97887	.	1
110		3	1	2	2	1221.16	1274.65	215.80	R	1192.05	.	215.80	0.97616	.	1
111		3	1	1	1	988.10	1038.72	131.10	T	964.59	1006.40	131.10	0.97621	0.96888	1
112		3	1	2	2	1257.33	1346.23	208.00	R	1231.88	1320.78	208.00	0.97975	0.98109	1
113		3	2	1	2	1153.70	1186.50	195.80	R	1125.69	1152.83	195.80	0.97573	0.97162	1
114		3	2	2	1	1108.94	1143.49	152.40	T	1083.69	1118.24	152.40	0.97723	0.97792	1
115		3	1	1	1	1869.67	2030.58	252.20	T	1843.36	2004.27	252.20	0.98593	0.98705	1
116		3	1	2	2	1812.30	1961.48	232.80	R	1783.03	1932.21	232.80	0.98385	0.98508	1
117		3	2	1	2	1760.47	1814.75	247.30	R	1725.80	1779.61	247.30	0.98031	0.98064	1
118		3	2	2	1	1461.22	1546.39	184.90	T	1433.35	1509.11	184.90	0.98093	0.97589	1
119		3	2	1	2	1369.70	1475.14	168.90	R	1342.81	1448.24	168.90	0.98036	0.98177	1
120		3	2	2	1	1181.19	1223.26	141.80	T	1153.36	1195.43	141.80	0.97644	0.97725	1
121		3	2	1	2	1624.79	1646.13	206.90	R	1580.05	1601.39	206.90	0.97247	0.97282	1
122		3	2	2	1	1910.43	1959.78	201.70	T	1860.34	1904.78	201.70	0.97378	0.97193	1
123		3	1	1	1	2665.07	2876.53	345.30	T	2616.34	2827.80	345.30	0.98171	0.98306	1
124		3	1	2	2	1839.56	1952.45	288.60	R	1804.83	1917.72	288.60	0.98112	0.98221	1

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
125	(b) (6)	3	1	1	1	1625.99	1735.90	255.10	T	1588.99	.	255.10	0.97724	.	1
126		3	1	2	2	1594.08	1643.39	339.20	R	1556.39	1594.99	339.20	0.97636	0.97055	1

5.9.4.4 Fasting Study Data (SA)

Obs	sub (b) (6)	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18
1		1	1	1	T	0	210.80	243.1	178.5	118.80	101.90	92.47	90.03	86.96	89.95	70.98	48.27	35.53	22.08	15.420	10.270	4.555	2.153
2		1	1	2	R	0	213.40	295.7	192.8	153.20	107.50	83.58	62.76	59.84	63.94	53.94	46.23	30.40	19.57	14.950	11.700	4.879	2.187
3		1	2	1	R	0	106.00	212.2	157.7	130.70	132.00	120.10	101.40	94.22	83.26	58.84	41.08	28.31	21.34	14.910	9.631	5.209	1.814
4		1	2	2	T	0	58.99	133.6	109.9	91.37	92.18	85.91	78.59	79.03	65.52	50.87	33.21	22.18	15.98	12.220	8.149	3.264	1.602
5		1	1	1	T	0	154.40	177.8	138.9	107.70	94.79	81.62	81.92	75.15	66.57	58.07	41.88	31.37	23.87	15.750	11.830	5.596	3.036
6		1	1	2	R	0	268.50	280.3	201.3	144.30	125.30	101.90	82.24	71.47	77.06	68.28	56.83	43.04	28.21	20.050	14.480	6.703	2.993
7		1	1	1	T	0	209.00	336.1	196.1	130.40	119.30	92.85	64.36	65.22	53.17	46.01	35.17	28.16	21.32	18.110	10.690	7.693	3.458
8		1	1	2	R	0	349.70	414.0	220.8	156.90	107.00	78.04	57.60	49.60	38.71	37.21	28.95	23.08	15.57	14.360	10.990	6.918	3.456
9		1	2	1	R	0	202.90	347.9	266.9	165.50	143.80	115.80	102.40	96.67	82.80	79.86	68.52	52.93	41.17	33.020	21.440	13.180	6.472
10		1	2	2	T	0	260.30	358.6	285.3	209.80	164.60	133.80	103.50	93.25	100.50	85.98	75.99	60.13	50.47	43.800	25.190	14.640	7.758
11		1	1	1	T	0	354.00	418.6	269.1	208.00	180.00	139.90	109.10	100.60	122.20	124.80	104.20	86.25	72.88	53.860	39.680	16.970	6.301
12		1	1	2	R	0	506.40	564.9	325.1	244.10	233.00	237.90	226.40	209.60	200.50	182.30	139.20	103.10	78.84	63.140	45.870	22.320	10.940
13		1	1	1	T	0	160.30	255.4	187.1	123.50	104.00	87.89	76.11	65.18	52.85	39.67	27.50	20.16	13.73	10.630	7.320	4.275	1.754
14		1	1	2	R	0	289.60	338.3	231.3	179.60	148.80	140.50	110.20	95.60	72.11	58.67	37.94	26.52	18.04	13.830	8.612	5.021	2.204
15		1	1	1	T	0	181.20	261.8	263.4	221.20	227.80	229.20	273.70	280.20	242.10	226.90	171.90	140.30	88.81	54.820	38.960	21.110	9.220
16		1	1	2	R	0	432.20	497.4	316.2	255.30	202.00	180.70	152.20	172.50	221.80	249.00	172.30	122.00	81.01	63.860	34.530	18.930	6.541
17		1	2	1	R	0	480.20	504.5	282.1	199.90	185.90	150.60	122.60	133.70	120.60	97.13	72.23	55.03	39.59	31.650	24.190	9.647	4.823
18		1	2	2	T	0	246.70	308.8	226.6	157.30	127.60	117.10	116.90	137.30	118.20	101.50	68.07	45.18	32.15	26.860	17.620	8.146	3.442
19		1	2	1	R	0	413.60	483.7	303.1	198.00	187.40	143.40	128.80	111.80	88.33	80.85	57.49	44.34	34.70	25.320	16.960	8.281	2.861
20		1	2	2	T	0	318.20	449.0	264.3	198.40	172.60	129.90	114.10	105.20	92.79	84.44	62.05	44.33	31.57	27.060	17.340	8.195	3.360
21		1	2	1	R	0	176.10	222.8	150.8	123.10	111.20	87.72	73.17	69.74	53.79	46.83	31.48	25.52	17.98	11.580	7.628	4.971	2.061
22		1	2	2	T	0	155.00	265.7	164.7	133.40	109.80	84.67	68.54	60.87	49.70	43.47	32.17	23.53	17.48	13.340	7.664	5.292	1.913
23		1	2	1	R	0	208.50	218.6	136.0	127.80	103.80	110.80	94.03	83.25	63.79	63.50	42.21	29.26	19.85	16.530	8.701	4.512	1.953
24		1	2	2	T	0	203.60	233.9	172.8	137.40	112.30	111.20	92.90	83.26	70.33	60.48	39.15	29.48	19.08	15.810	9.596	4.613	1.608
25		1	1	1	T	0	139.30	231.0	215.5	174.70	182.80	178.10	158.90	128.00	123.70	122.30	67.54	53.09	32.29	20.340	13.750	5.561	1.619
26		1	1	2	R	0	154.20	237.7	162.2	180.70	141.20	126.30	134.90	159.40	170.70	126.60	72.63	50.33	27.22	22.070	12.440	4.734	1.703
27		1	1	1	T	0	341.50	460.1	265.4	181.50	162.20	113.90	81.81	70.91	51.30	49.00	39.19	34.88	30.07	23.650	13.330	6.973	2.713

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18
28	(b) (6)	1	1	2	R	0	457.90	449.2	270.3	183.10	137.30	99.94	76.69	55.83	72.22	64.94	47.27	39.15	31.20	19.820	14.600	7.662	3.108
29		1	2	1	R	0	297.50	389.1	292.8	196.20	151.00	112.70	94.75	82.06	73.50	60.25	41.39	29.61	18.77	13.430	10.240	5.061	2.602
30		1	2	2	T	0	182.40	355.3	298.2	177.10	144.10	120.70	104.60	95.14	77.41	58.99	39.08	28.72	20.25	15.150	9.694	5.324	2.375
31		1	1	1	T	0	99.52	187.7	158.2	171.30	165.80	146.70	158.20	139.70	126.80	102.70	73.37	48.02	36.93	26.900	16.220	8.855	3.394
32		1	1	2	R	0	208.80	204.1	155.6	152.70	144.80	147.90	158.80	182.40	141.80	112.00	76.24	60.39	44.09	30.840	19.910	9.839	4.024
33		1	2	1	R	0	241.60	396.7	284.9	231.00	192.80	170.20	163.80	148.50	161.80	138.90	105.90	75.62	48.07	30.800	20.250	9.411	4.090
34		1	2	2	T	0	205.00	308.6	210.8	174.70	151.30	130.50	125.10	120.40	123.80	103.80	74.45	48.90	38.41	24.240	17.320	6.640	3.171
35		1	1	1	T	0	155.60	253.6	188.5	144.40	123.80	100.10	84.71	77.07	73.07	69.38	49.66	33.93	23.17	15.860	11.680	5.565	2.524
36		1	1	2	R	0	380.60	428.6	274.9	184.20	139.30	104.40	79.63	67.57	71.50	65.57	40.07	33.13	21.36	18.010	11.730	5.907	2.283
37		1	2	1	R	0	187.00	240.8	178.3	122.30	123.10	101.30	101.40	101.40	101.20	82.96	59.91	40.75	26.81	18.040	13.710	6.335	2.783
38		1	2	2	T	0	98.44	150.5	136.8	108.80	100.40	107.30	113.00	114.60	124.00	96.85	65.14	49.93	30.80	22.880	14.100	7.048	2.990
39		1	2	1	R	0	278.30	397.6	301.0	191.10	142.50	96.86	67.49	53.60	43.88	35.07	26.70	20.23	16.92	13.770	7.684	4.424	1.832
40		1	2	2	T	0	287.80	516.6	332.0	212.80	165.40	99.77	86.57	63.02	45.63	41.86	33.53	25.83	22.35	17.700	11.030	5.207	2.247
41		1	1	1	T	0	197.90	456.8	295.9	212.00	153.60	117.10	89.57	78.62	58.21	57.69	41.26	34.61	22.02	18.560	12.850	6.370	2.867
42		1	1	2	R	0	465.10	579.8	360.4	257.00	191.00	138.40	100.90	92.12	74.05	56.88	42.13	36.99	28.52	25.320	17.610	8.053	3.463
43		2	2	1	R	0	413.30	435.4	265.7	188.60	155.60	150.30	124.20	99.47	77.90	68.17	46.89	38.96	29.68	22.120	18.100	8.113	3.099
44		2	2	2	T	0	319.60	372.2	275.9	189.80	146.10	99.34	91.04	104.50	71.70	66.39	45.32	36.11	26.37	19.890	15.500	7.277	3.135
45		2	1	1	T	0	175.70	281.4	201.9	155.70	120.60	97.58	78.67	68.18	60.00	49.27	36.05	25.00	15.69	14.290	8.846	5.156	2.023
46		2	1	2	R	0	68.38	175.6	156.6	114.70	87.54	64.04	52.36	45.86	35.02	30.84	23.78	17.62	12.68	10.220	6.151	3.369	1.452
47		2	1	1	T	0	202.60	285.2	216.3	139.90	115.70	78.15	66.69	84.61	73.52	57.55	39.82	27.58	19.41	15.460	9.706	3.260	1.304
48		2	1	2	R	0	312.10	357.7	261.2	167.70	142.00	104.70	82.95	76.42	110.10	91.35	43.97	31.11	18.22	14.790	9.582	3.965	1.528
49		2	1	1	T	0	284.00	362.8	222.4	156.90	126.90	96.02	85.30	74.84	59.59	55.05	41.61	34.08	25.36	18.110	11.290	6.018	3.200
50		2	1	2	R	0	312.40	351.0	270.9	192.00	143.10	100.50	79.90	74.35	59.78	53.89	42.94	36.55	26.59	18.350	12.430	6.115	3.439
51		2	1	1	T	0	552.60	554.5	400.4	260.80	193.30	145.80	121.50	101.80	107.20	92.93	66.71	53.38	35.55	26.030	18.890	7.539	3.028
52		2	1	2	R	0	518.30	487.0	267.3	218.60	155.80	112.80	83.45	72.74	56.05	64.27	46.22	38.11	24.55	19.980	13.540	6.776	2.468
53		2	2	1	R	0	723.90	556.9	335.0	207.30	165.80	125.10	85.14	67.71	48.40	44.95	31.42	25.35	19.67	15.230	10.800	5.389	2.613
54		2	2	2	T	0	624.70	582.3	336.6	265.40	217.40	131.40	79.30	67.80	57.12	49.31	34.71	26.23	22.76	16.220	11.640	6.321	2.684
55		2	2	1	R	0	438.10	438.9	229.9	175.20	147.60	123.10	112.70	95.12	62.66	54.41	38.66	30.51	21.23	15.810	12.130	4.514	1.868
56		2	2	2	T	0	356.30	383.3	216.6	178.00	156.20	122.10	102.50	84.01	59.42	54.44	37.49	28.99	19.56	14.130	8.716	3.674	1.661

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18
57	(b) (6)	2	2	1	R	0	318.30	259.6	189.0	163.80	137.00	104.70	112.10	97.86	109.20	92.03	70.74	54.02	37.28	32.500	24.740	12.430	5.423
58		2	2	2	T	0	192.50	196.9	155.2	106.60	90.42	101.60	90.51	94.40	81.82	79.94	64.91	49.61	37.54	27.580	18.880	11.930	5.980
59		2	2	1	R	0	803.40	715.5	407.6	308.10	227.90	195.90	163.60	159.90	129.30	117.00	84.02	72.66	50.88	35.920	25.080	10.080	4.412
60		2	2	2	T	0	778.60	743.8	471.3	332.10	257.00	197.70	183.80	191.20	154.10	136.00	109.90	81.85	53.97	40.060	24.260	9.398	4.070
61		2	2	1	R	0	357.30	526.4	329.0	257.00	238.70	208.50	191.90	164.00	109.50	85.12	57.98	43.71	33.66	25.230	17.290	7.128	3.435
62		2	2	2	T	0	137.70	217.9	166.0	141.60	126.60	113.10	127.80	142.90	118.90	95.93	64.66	42.17	29.61	23.180	15.450	6.574	3.310
63		2	1	1	T	0	432.20	462.0	313.9	233.10	174.10	122.10	116.20	100.00	81.25	67.38	51.69	38.46	30.81	23.180	13.370	8.037	3.502
64		2	1	2	R	0	557.20	536.5	387.2	240.40	179.60	131.30	102.30	84.62	78.01	66.58	49.38	42.28	29.11	24.070	14.990	8.175	3.980
65		2	2	1	R	0	126.50	203.5	138.9	123.70	109.30	98.20	92.45	97.05	98.63	80.57	48.12	35.19	20.02	18.630	12.380	4.757	1.982
66		2	2	2	T	0	111.00	192.8	125.1	99.77	87.04	75.31	79.45	73.64	62.85	57.35	37.00	25.69	15.61	11.550	7.919	3.610	1.910
67		2	1	1	T	0	230.40	253.0	171.7	128.50	104.90	78.93	67.78	61.13	48.05	37.09	24.58	18.44	11.97	9.387	7.113	4.181	1.922
68		2	1	2	R	0	307.30	387.1	253.2	169.80	132.70	95.01	82.88	67.02	51.36	37.73	27.30	21.59	15.12	11.970	7.133	4.527	2.197
69		2	2	1	R	0	491.40	506.6	346.9	229.00	167.40	127.00	105.80	101.20	123.70	110.60	88.16	77.90	57.27	42.630	29.020	18.040	9.499
70		2	2	2	T	0	336.70	340.5	271.7	164.40	146.00	120.20	98.32	104.30	118.00	105.50	81.96	65.52	57.39	43.590	28.430	16.630	
71		2	1	1	T	0	410.90	498.2	289.7	179.80	134.20	89.12	70.95	57.23	38.23	36.21	23.51	21.62	16.49	14.190	8.187	5.906	2.654
72		2	1	2	R	0	425.60	381.8	252.8	155.90	116.50	81.38	56.67	48.64	35.57	31.06	24.22	19.52	16.68	15.220	7.501	4.785	2.629
73		2	1	1	T	0	341.10	343.1	211.1	155.60	110.30	97.32	81.86	75.10	100.20	84.11	53.11	40.46	28.89	20.090	13.640	7.261	2.645
74		2	1	2	R	0	271.60	276.6	208.1	128.40	116.00	94.29	90.56	80.73	74.19	79.08	47.37	32.37	23.24	17.420	11.110	7.364	2.841
75		2	2	1	R	0	916.70	802.9	421.8	303.90	273.90	194.30	137.20	112.80	101.80	99.28	71.02	53.98	37.52	28.800	19.810	8.163	3.476
76		2	2	2	T	0	543.50	449.3	290.8	251.90	193.50	194.50	151.20	123.50	104.00	91.70	57.08	40.46	33.83	20.340	13.520	5.527	2.618
77			1	1	T	0	107.70	163.8	135.5	111.10	91.44	82.74	78.79	82.39	79.34	72.75	92.76	64.12	54.87	36.620	27.160	12.450	6.206
78			1	2	R	0	100.30	197.2	165.9	119.20	103.10	94.11	92.61	87.80	94.82	75.67	70.20	60.66	45.92	32.600	22.110	12.080	4.782
79		2	2	1	R	0	512.60	535.8	290.3	196.80	170.50	131.40	84.88	67.44	58.54	58.79	48.44	39.73	28.21	19.210	13.580	6.430	2.488
80		2	2	2	T	0	328.90	354.1	228.3	166.00	118.90	97.66	85.93	87.40	64.89	67.06	55.18	39.50	28.69	19.570	13.390	5.203	2.325
81		3	2	1	R	0	329.90	389.9	233.5	147.10	116.70	88.40	76.44	67.75	57.94	47.07	29.95	22.15	17.30	12.960	7.953	4.562	1.906
82	3	2	2	T	0	231.60	353.0	256.2	160.70	133.70	103.70	81.20	66.96	51.92	41.39	27.25	21.30	14.08	13.780	8.528	4.110	1.786	
83	3	1	1	T	0	292.10	400.3	275.5	181.60	150.80	97.62	72.98	63.72	49.69	41.46	28.51	25.73	20.49	14.870	9.850	4.203	2.020	
84	3	1	2	R	0	313.70	403.1	251.5	157.50	121.30	85.29	61.84	47.98	40.51	35.13	27.88	21.82	19.09	13.530	8.594	4.018	2.174	
85	3	1	1	T	0	112.30	226.6	153.8	112.00	98.62	75.56	66.80	59.29	45.89	41.39	31.06	20.48	16.01	12.420	8.290	4.747	2.511	

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18
86	(b) (6)	3	1	2	R	0	407.40	346.8	229.5	147.10	120.70	82.71	62.86	48.44	39.71	33.95	27.96	19.04	16.58	13.420	8.550	5.255	2.524
87	(b) (6)	3	2	1	R	0	237.90	298.3	205.5	156.20	147.10	120.80	117.90	90.16	66.31	56.89	39.49	31.41	22.67	17.510	11.150	5.760	2.134
88	(b) (6)	3	2	2	T	0	186.00	214.3	152.4	103.30	96.06	75.62	73.16	61.69	54.00	41.14	33.21	23.70	19.66	13.500	9.256	4.671	2.131
89	(b) (6)	3	1	1	T	0	412.40	600.0	372.9	258.40	206.00	146.80	118.50	106.20	96.12	83.38	51.53	40.76	28.93	20.940	11.900	5.964	2.200
90	(b) (6)	3	1	2	R	0	498.10	508.1	366.6	244.80	202.70	138.30	115.10	96.21	77.70	60.46	39.99	31.48	21.31	16.940	10.630	4.366	1.719
91	(b) (6)	3	1	1	T	0	212.70	447.0	321.1	205.40	167.80	123.10	101.70	87.81	74.38	63.79	42.25	33.53	24.00	19.070	12.740	7.455	3.091
92	(b) (6)	3	1	2	R	0	465.50	525.6	366.0	239.90	177.60	136.80	94.03	88.05	79.48	61.99	47.41	37.22	28.28	23.630	13.350	7.638	3.376
93	(b) (6)	3	2	1	R	0	282.60	410.3	265.9	192.20	151.30	115.10	117.30	160.70	123.70	83.58	53.78	39.81	31.48	21.670	12.840	5.850	2.335
94	(b) (6)	3	2	2	T	0	316.10	360.5	247.7	169.70	153.30	128.80	124.50	159.80	105.90	99.40	57.16	43.68	29.34	21.000	13.080	5.864	2.460
95	(b) (6)	3	1	1	T	0	233.40	398.6	278.2	236.40	189.80	146.10	148.20	166.90	144.90	134.70	98.14	77.09	57.56	41.490	21.190	8.868	3.330
96	(b) (6)	3	1	2	R	0	551.90	631.5	406.1	292.60	243.70	188.10	179.60	142.60	105.70	105.00	93.67	72.04	73.25	50.930	27.450	10.750	3.806
97	(b) (6)	3	2	1	R	0	133.80	384.2	241.1	157.60	129.50	90.92	81.43	78.98	80.21	59.80	49.23	32.81	25.080	16.410	7.770	3.476	
98	(b) (6)	3	2	2	T	0	64.75	134.4	127.3	96.70	80.09	87.22	116.30	105.90	81.37	78.87	55.42	42.69	30.36	22.120	13.410	7.541	3.106
99	(b) (6)	3	2	1	R	0	800.60	673.9	372.6	273.20	204.30	112.60	91.93	79.38	79.56	59.96	37.98	35.94	28.30	22.480	15.960	7.518	2.607
100	(b) (6)	3	2	2	T	0	379.00	426.9	279.9	152.40	131.00	95.55	70.65	60.18	43.66	52.74	37.64	31.99	24.71	18.510	10.160	4.586	
101	(b) (6)	3	2	1	R	0	392.20	463.7	353.0	315.20	311.30	253.50	214.20	163.40	110.90	88.59	57.68	43.03	26.19	19.720	10.770	5.953	2.235
102	(b) (6)	3	2	2	T	0	244.80	375.9	293.5	253.80	250.20	292.10	269.20	212.10	157.10	110.80	62.87	37.75	27.99	21.030	10.060	4.826	1.920
103	(b) (6)	3	2	1	R	0	304.60	469.0	297.3	247.60	181.00	128.10	85.22	93.90	93.16	56.58	39.41	28.17	21.18	15.070	9.641	4.612	1.749
104	(b) (6)	3	2	2	T	0	718.50	662.7	404.7	245.80	230.80	174.70	131.90	124.50	87.70	70.93	45.03	34.83	27.36	21.900	11.360	6.578	2.412
105	(b) (6)	3	1	1	T	0	73.11	118.9	113.7	116.30	111.20	121.20	110.90	119.90	100.90	89.76	61.59	58.68	39.00	29.340	15.290	7.252	2.865
106	(b) (6)	3	1	2	R	0	226.70	285.2	221.0	158.10	162.30	148.10	114.60	103.20	100.00	82.69	66.02	51.68	39.58	30.390	15.530	8.143	2.858
107	(b) (6)	3	1	1	T	0	188.70	245.3	170.9	124.80	112.00	97.31	98.20	109.60	82.67	67.08	45.76	38.08	27.48	21.170	14.160	6.569	2.742
108	(b) (6)	3	1	2	R	0	325.10	351.1	231.2	167.70	136.50	104.10	77.92	65.73	73.71	69.23	56.14	40.21	33.70	24.810	15.790	7.581	3.521
109	(b) (6)	3	2	1	R	0	190.90	253.1	173.7	135.40	113.40	96.11	95.34	76.92	69.23	59.32	40.44	33.88	22.78	17.510	11.520	7.003	3.358
110	(b) (6)	3	2	2	T	0	193.70	266.9	174.5	128.80	110.90	99.02	79.99	71.94	66.94	59.63	45.09	33.86	24.59	18.800	11.380	6.947	3.068
111	(b) (6)	3	1	1	T	0	327.10	570.3	414.9	273.80	230.70	184.80	220.70	194.10	147.70	118.60	86.48	64.19	47.37	34.920	22.540	11.500	5.061
112	(b) (6)	3	1	2	R	0	465.30	512.1	396.0	252.00	228.20	209.80	170.70	147.70	111.60	100.40	74.48	53.14	35.30	28.320	18.310	12.240	4.585
113	(b) (6)	3	2	1	R	0	250.60	433.3	313.2	201.70	157.00	139.70	122.20	109.00	93.37	73.49	48.55	34.00	25.45	18.470	12.990	7.132	3.088
114	(b) (6)	3	2	2	T	0	178.00	328.3	245.1	163.70	143.90	111.20	112.80	97.63	76.71	59.90	39.64	28.95	20.77	14.350	10.440	5.829	2.634

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18
115	(b) (6)	3	2	1	R	0	231.10	311.7	189.8	161.90	134.50	114.60	99.43	89.08	80.86	75.47	56.26	42.78	30.27	21.980	13.100	6.916	2.603
116		3	2	2	T	0	102.80	132.4	135.6	134.30	129.60	154.10	137.60	139.60	120.90	108.20	87.31	61.97	40.05	29.270	16.020	8.216	2.780
117		3	2	1	R	0	494.70	586.5	308.5	214.60	167.10	123.20	120.60	115.60	107.70	83.46	63.63	48.19	29.76	21.650	12.190	6.739	2.611
118		3	2	2	T	0	569.40	584.4	368.0	263.40	195.90	161.90	149.60	143.50	107.90	98.01	71.22	50.16	35.97	24.780	16.050	7.611	2.947
119		3	1	1	T	0	631.90	829.0	494.3	360.70	259.70	172.20	140.30	100.20	84.18	67.05	57.39	52.68	38.23	24.040	18.200	12.650	3.886
120		3	1	2	R	0	483.80	591.2	345.0	259.40	181.00	143.70	109.40	90.43	82.17	81.77	64.77	46.60	37.47	26.950	15.570	11.530	3.718
121		3	1	1	T	0	223.90	400.7	266.2	190.40	170.20	129.70	129.90	134.20	107.50	73.04	56.10	47.35	29.30	26.460	14.180	6.226	2.718
122		3	1	2	R	0	302.80	468.0	327.1	242.00	190.50	161.10	153.40	136.00	108.50	89.22	65.35	51.15	38.20	28.660	15.200	7.225	2.818

Obs	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	trt
1	1.244	16	19	0	0.03	0.08	0.17	0.25	0.37	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.03	12.03	24.00	36.00	48.00	1
2	1.332	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.80	1.00	1.52	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
3	1.021	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.02	8.00	12.00	24.00	36.00	48.00	2
4	0.000	15	18	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
5	1.417	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.08	3.05	4.00	6.00	8.05	12.00	24.00	36.00	48.05	1
6	1.626	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.78	1.00	1.57	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.03	48.03	2
7	2.748	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
8	2.814	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
9	4.889	16	19	0	0.03	0.08	0.17	0.28	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.05	12.00	24.00	36.00	48.00	2
10	5.085	16	19	0	0.03	0.08	0.17	0.25	0.37	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
11	3.825	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.13	6.00	8.05	12.07	24.00	36.00	48.00	1
12	5.178	16	19	0	0.03	0.08	0.20	0.30	0.33	0.50	0.78	1.00	1.52	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
13	1.349	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
14	1.439	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
15	5.907	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
16	4.865	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
17	2.673	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.02	12.00	24.00	36.03	48.28	2
18	1.974	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
19	1.682	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.03	6.00	8.00	12.00	24.00	36.00	48.00	2

Obs	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	trt
20	1.941	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
21	1.463	16	19	0	0.03	0.08	0.20	0.28	0.33	0.55	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.03	12.00	24.00	36.00	48.00	2
22	1.447	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.57	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
23	0.000	15	18	0	0.03	0.08	0.20	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
24	1.131	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
25	0.000	15	18	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
26	0.000	15	18	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
27	1.933	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
28	1.694	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.03	8.00	12.00	24.00	36.00	48.00	2
29	1.631	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.03	6.00	8.00	12.00	24.00	36.00	48.00	2
30	1.755	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.57	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
31	2.431	16	19	0	0.03	0.08	0.17	0.28	0.33	0.50	0.75	1.00	1.50	2.00	3.03	4.05	6.00	8.00	12.33	24.00	36.00	48.00	1
32	2.991	16	19	0	0.07	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.05	2
33	2.083	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
34	1.853	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
35	1.259	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
36	1.422	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.02	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
37	1.809	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
38	2.147	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
39	1.443	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.02	4.03	6.00	8.00	12.00	24.00	36.00	48.00	2
40	1.580	16	19	0	0.03	0.08	0.17	0.28	0.33	0.58	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
41	1.697	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
42	2.057	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
43	1.952	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.02	2
44	2.177	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
45	1.605	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.10	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
46	1.070	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.57	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
47	0.000	15	18	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
48	0.000	15	18	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2

Obs	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	trt
49	2.286	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
50	2.050	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
51	1.561	16	19	0	0.03	0.08	0.17	0.25	0.37	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
52	1.636	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
53	1.356	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
54	1.400	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
55	1.215	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
56	1.013	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
57	3.769	16	19	0	0.03	0.13	0.22	0.25	0.33	0.50	0.75	1.00	1.50	2.07	3.00	4.00	6.00	8.00	12.00	24.00	37.23	48.00	2
58	3.987	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.20	6.32	8.07	12.00	24.00	36.00	48.00	1
59	2.433	16	19	0	0.03	0.08	0.17	0.25	0.33	0.53	0.75	1.00	1.50	2.00	3.08	4.05	6.00	8.00	12.00	24.00	36.00	48.00	2
60	2.186	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
61	1.962	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
62	1.450	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
63	1.962	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
64	2.398	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
65	1.266	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
66	0.000	15	18	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
67	1.281	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.05	8.00	12.00	24.00	36.00	48.00	1
68	1.893	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
69	6.052	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
70	6.174	15	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.80	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
71	2.339	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
72	1.741	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
73	1.853	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.53	2.00	3.00	4.03	6.08	8.00	12.00	24.10	36.00	48.00	1
74	2.368	16	19	0	0.03	0.10	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
75	2.277	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
76	1.612	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.52	2.00	3.00	4.00	6.03	8.00	12.00	24.00	36.00	48.00	1
77	3.429	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1

Obs	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	trt
78	3.173	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
79	1.511	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.02	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
80	1.442	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
81	1.296	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
82	1.150	16	19	0	0.03	0.08	0.17	0.28	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.02	36.02	48.00	1
83	0.000	15	18	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
84	0.000	15	18	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
85	1.567	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
86	1.689	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
87	1.249	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
88	1.234	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
89	1.422	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
90	1.257	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
91	2.119	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
92	2.054	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
93	1.399	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.05	8.00	12.00	24.00	36.00	48.00	2
94	1.874	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.93	2.00	3.00	4.05	6.00	8.00	12.00	24.00	36.00	48.00	1
95	1.976	16	19	0	0.03	0.10	0.18	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.42	1
96	2.318	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.83	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
97	.	15	18	0	0.03	0.10	0.22	0.25	0.33	0.53	0.75	1.05	1.50	2.03	3.00	4.10	6.00	8.03	12.00	24.00	36.00	48.00	2
98	1.776	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.80	1.00	1.78	2.00	3.23	4.00	6.00	8.00	12.03	24.00	36.20	48.00	1
99	1.328	16	19	0	0.03	0.08	0.20	0.25	0.33	0.53	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
100	.	14	17	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.60	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
101	1.498	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
102	0.000	15	18	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
103	1.277	16	19	0	0.03	0.08	0.17	0.25	0.37	0.55	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
104	1.605	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
105	1.405	16	19	0	0.03	0.08	0.18	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.02	24.00	36.00	48.00	1
106	1.827	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.83	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2

Obs	c19	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	trt
107	1.619	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
108	2.428	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
109	1.654	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	34.98	48.00	2
110	1.946	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
111	3.623	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
112	3.531	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
113	1.541	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
114	1.626	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
115	1.590	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
116	1.571	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
117	2.496	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
118	2.203	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
119	2.942	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
120	3.147	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00	36.00	48.00	2
121	1.352	16	19	0	0.03	0.08	0.17	0.25	0.37	0.50	0.75	1.00	1.58	2.00	3.12	4.00	6.00	8.00	12.00	24.00	36.00	48.00	1
122	1.633	16	19	0	0.03	0.08	0.17	0.25	0.33	0.50	0.80	1.02	1.50	2.00	3.00	4.00	6.00	8.00	12.02	24.00	36.00	48.00	2

5.9.4.5 Fasting Study Output (SA)

Fasting STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	60	(b) (6)
trt	2	1 2
per	2	1 2
seq	2	1 2
GRP	3	1 2 3

Number of Observations Read	122
Number of Observations Used	120

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	63	12.81718021	0.20344730	16.13	<.0001
Error	56	0.70628848	0.01261229		
Corrected Total	119	13.52346869			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.947773	1.699674	0.112304	6.607414

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.00917289	0.00917289	0.73	0.3974
GRP	2	0.06648965	0.03324483	2.64	0.0805
seq	1	0.00227087	0.00227087	0.18	0.6730
seq*GRP	2	1.31078950	0.65539475	51.96	<.0001
sub(seq*GRP)	54	11.33388752	0.20988681	16.64	<.0001
per(GRP)	2	0.06791762	0.03395881	2.69	0.0765
trt	1	0.02665217	0.02665217	2.11	0.1516

Source	DF	Type III SS	Mean Square	F Value	Pr > F

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per	1	0.01145264	0.01145264	0.91	0.3447
GRP	2	0.10821773	0.05410886	4.29	0.0185
seq	1	0.01624889	0.01624889	1.29	0.2612
seq*GRP	2	1.31078950	0.65539475	51.96	<.0001
sub(seq*GRP)	54	11.33388752	0.20988681	16.64	<.0001
per(GRP)	2	0.06250821	0.03125410	2.48	0.0931
trt	1	0.02665217	0.02665217	2.11	0.1516

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01624889	0.01624889	0.08	0.7819
GRP	2	0.10821773	0.05410886	0.26	0.7737

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.02988530	0.02055836	-1.45	0.1516

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	63	12.63309232	0.20052527	16.79	<.0001
Error	56	0.66889794	0.01194461		
Corrected Total	119	13.30199026			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.949714	1.642346	0.109291	6.654590

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.00630970	0.00630970	0.53	0.4704
GRP	2	0.05778620	0.02889310	2.42	0.0983
seq	1	0.00030947	0.00030947	0.03	0.8727
seq*GRP	2	1.24635878	0.62317939	52.17	<.0001
sub(seq*GRP)	54	11.23336188	0.20802522	17.42	<.0001
per(GRP)	2	0.06053396	0.03026698	2.53	0.0884
trt	1	0.02843233	0.02843233	2.38	0.1285

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per	1	0.00804169	0.00804169	0.67	0.4154
GRP	2	0.09163472	0.04581736	3.84	0.0275
seq	1	0.00912714	0.00912714	0.76	0.3858
seq*GRP	2	1.24635878	0.62317939	52.17	<.0001
sub(seq*GRP)	54	11.23336188	0.20802522	17.42	<.0001
per(GRP)	2	0.05532676	0.02766338	2.32	0.1080
trt	1	0.02843233	0.02843233	2.38	0.1285

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00912714	0.00912714	0.04	0.8349
GRP	2	0.09163472	0.04581736	0.22	0.8030

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.03086722	0.02000678	-1.54	0.1285

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	63	18.14420249	0.28800321	6.21	<.0001
Error	56	2.59580403	0.04635364		
Corrected Total	119	20.74000652			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.874841	3.653549	0.215299	5.892872

Source	DF	Type I SS	Mean Square	F Value	Pr > F
per	1	0.06097751	0.06097751	1.32	0.2563
GRP	2	1.28549812	0.64274906	13.87	<.0001
seq	1	0.01606398	0.01606398	0.35	0.5584
seq*GRP	2	0.41674407	0.20837204	4.50	0.0155
sub(seq*GRP)	54	14.87505148	0.27546392	5.94	<.0001
per(GRP)	2	0.33074331	0.16537165	3.57	0.0348

Source	DF	Type I SS	Mean Square	F Value	Pr > F
trt	1	1.15912401	1.15912401	25.01	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per	1	0.05885708	0.05885708	1.27	0.2646
GRP	2	1.26674886	0.63337443	13.66	<.0001
seq	1	0.00679377	0.00679377	0.15	0.7033
seq*GRP	2	0.41674407	0.20837204	4.50	0.0155
sub(seq*GRP)	54	14.87505148	0.27546392	5.94	<.0001
per(GRP)	2	0.25521770	0.12760885	2.75	0.0724
trt	1	1.15912401	1.15912401	25.01	<.0001

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00679377	0.00679377	0.02	0.8758
GRP	2	1.26674886	0.63337443	2.30	0.1101

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.19708624	0.03941244	-5.00	<.0001

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	trt	AUCRATIO
1	(b) (6)	1	0.97
2		1	0.95
3		1	0.96
4		1	0.90
5		1	0.91
6		1	0.96
7		1	0.94
8		1	0.95
9		1	0.97
10		1	0.97
11		1	0.94
12		1	0.97
13		1	0.98
14		1	0.95
15		1	0.94
16		1	0.96

Obs	sub	trt	AUCRATIO
17	(b) (6)	1	0.97
18		1	0.97
19		1	0.95
20		1	0.95
21		1	0.96
22		1	0.95
23		1	0.94
24		1	0.97
25		1	0.93
26		1	0.98
27		1	0.97
28		1	0.97
29		1	0.91
30		1	0.98
31		1	0.97
32		1	0.96
33		1	0.94
34		1	0.94
35		1	0.91
36		1	0.90
37		1	0.96
38		1	0.97
39		1	0.95
40		1	0.97
41		1	0.96
42		1	0.95
43		1	0.93
44		1	0.96
45		1	0.97
46		1	0.95
47		1	0.96
48		1	0.98
49		1	0.96
50		1	0.96
51		1	0.97
52		1	0.97
53		1	0.98
54		1	0.96
55		1	0.94
56		1	0.95

Obs	sub	trt	AUCRATIO
57	(b) (6)	1	0.95
58		1	0.98
59		1	0.96
60		1	0.95
61		1	0.98
62		2	0.96
63		2	0.97
64		2	0.96
65		2	0.89
66		2	0.90
67		2	0.96
68		2	0.95
69		2	0.96
70		2	0.96
71		2	0.97
72		2	0.94
73		2	0.95
74		2	0.98
75		2	0.96
76		2	0.95
77		2	0.95
78		2	0.97
79		2	0.96
80		2	0.96
81		2	0.94
82		2	0.96
83		2	0.96
84		2	0.94
85		2	0.97
86		2	0.94
87		2	0.96
88		2	0.96
89		2	0.97
90		2	0.94
91		2	0.97
92		2	0.97
93		2	0.95
94		2	0.97
95		2	0.91
96		2	0.91

Obs	sub	trt	AUCRATIO
97	(b) (6)	2	0.92
98	(b) (6)	2	0.93
99	(b) (6)	2	0.97
100	(b) (6)	2	0.95
101	(b) (6)	2	0.97
102	(b) (6)	2	0.95
103	(b) (6)	2	0.93
104	(b) (6)	2	0.93
105	(b) (6)	2	0.97
106	(b) (6)	2	0.97
107	(b) (6)	2	0.95
108	(b) (6)	2	0.97
109	(b) (6)	2	0.98
110	(b) (6)	2	0.94
111	(b) (6)	2	0.98
112	(b) (6)	2	0.97
113	(b) (6)	2	0.97
114	(b) (6)	2	0.97
115	(b) (6)	2	0.94
116	(b) (6)	2	0.95
117	(b) (6)	2	0.94
118	(b) (6)	2	0.97
119	(b) (6)	2	0.97
120	(b) (6)	2	0.94
121	(b) (6)	2	0.94
122	(b) (6)	2	0.97

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	1	1.06	1.06	0.82	1.00	0.97	1.03
(b) (6)	2	0.75	0.77	0.63	1.00	1.11	0.90
(b) (6)	1	0.82	0.82	0.63	1.00	0.95	1.06
(b) (6)	1	1.10	1.08	0.81	1.00	1.02	0.98
(b) (6)	2	1.15	1.14	1.03	1.00	1.06	0.95
(b) (6)	1	0.76	0.75	0.74	1.00	1.11	0.90
(b) (6)	1	0.75	0.76	0.75	1.00	0.96	1.04
(b) (6)	1	1.08	1.09	0.56	12.5	0.93	1.07
(b) (6)	2	0.83	0.82	0.61	1.00	1.03	0.98

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	2	1.00	1.00	0.93	1.00	0.93	1.07
	2	0.99	0.99	1.19	1.00	1.03	0.97
	2	1.04	1.02	1.07	1.00	0.87	1.15
	1	1.01	1.01	0.97	1.00	1.00	1.00
	1	0.94	0.95	1.00	2.67	0.91	1.09
	2	1.01	1.01	0.91	1.00	0.96	1.04
	1	0.88	0.88	0.90	1.14	1.02	0.98
	2	0.76	0.77	0.78	1.00	0.97	1.03
	1	0.97	0.96	0.59	1.00	1.03	0.97
	2	1.10	1.11	0.63	1.00	0.94	1.06
	2	1.24	1.23	1.30	1.00	1.13	0.88
	1	0.81	0.81	0.79	1.00	0.94	1.06
	2	0.90	0.92	0.85	1.00	0.88	1.13
	1	1.47	1.47	1.60	1.00	0.99	1.01
	1	0.86	0.86	0.80	1.00	1.10	0.91
	1	0.96	0.97	1.03	1.00	0.91	1.10
	1	1.35	1.33	1.07	2.67	1.14	0.88
	2	1.08	1.08	0.86	1.00	1.04	0.96
	2	0.89	0.89	0.87	1.00	0.93	1.07
	2	0.88	0.90	0.62	2.67	0.83	1.20
	2	1.07	1.07	0.97	1.00	1.03	0.97
	2	0.86	0.85	0.41	1.00	1.07	0.93
	1	0.96	0.95	0.83	2.67	1.06	0.94
	2	0.71	0.73	0.95	1.00	0.99	1.01
	1	0.86	0.83	0.65	1.00	1.26	0.79
	2	0.96	0.96	0.67	1.00	1.02	0.98
	1	1.11	1.14	1.17	2.67	0.92	1.09
	1	1.11	1.08	1.24	0.80	1.25	0.80
	2	0.79	0.79	0.59	1.00	0.97	1.03
	1	1.10	1.10	0.83	1.00	1.02	0.98
	2	0.95	0.95	0.66	1.00	0.99	1.01
	2	0.97	0.97	0.91	1.00	1.08	0.92
	1	1.11	1.09	0.99	1.00	1.11	0.90
	1	0.94	0.94	0.56	2.67	1.01	0.99
	2	0.78	0.79	0.72	1.00	0.90	1.11
	1	1.19	1.19	1.18	1.00	1.00	1.00
	1	0.91	0.92	0.85	1.00	0.97	1.03
	2	1.03	1.04	0.88	1.00	0.88	1.13
	1	0.89	0.89	0.63	1.25	0.95	1.06
	2	0.91	0.90	0.35	0.80	0.84	1.18

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	2	0.70	0.71	0.53	2.67	1.27	0.79
	2	1.01	1.01	0.81	1.00	1.39	0.72
	2	1.29	1.29	1.53	0.38	0.98	1.02
	1	0.95	0.94	0.42	6.25	1.08	0.92
	1	0.90	0.88	0.70	1.00	1.16	0.87
	2	1.01	1.02	1.05	1.00	0.93	1.08
	1	1.15	1.14	1.11	1.00	1.07	0.94
	2	0.82	0.84	0.76	1.00	0.88	1.13
	2	1.27	1.26	0.49	6.25	1.10	0.91
	2	1.16	1.13	1.00	1.00	1.21	0.83
	1	1.10	1.08	1.40	1.00	1.12	0.89
	1	0.89	0.88	0.86	1.00	1.03	0.97

5.9.4.6 Firm Reviewer Ratio (SA)

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	(b) (6)	1	1	1	1	598.58	619.64	243.1	T	587.96	609.02	243.1	0.98226	0.98286	1
2		1	1	2	2	562.28	584.11	295.7	R	551.10	572.46	295.7	0.98012	0.98006	1
3		1	2	1	2	569.66	585.39	212.2	R	559.93	575.13	212.2	0.98292	0.98248	1
4		1	2	2	1	427.19	449.45	133.6	T	419.23	442.86	133.6	0.98135	0.98534	1
5		1	1	1	1	586.25	610.65	177.8	T	576.62	600.57	177.8	0.98357	0.98349	1
6		1	1	2	2	713.80	740.31	280.3	R	700.88	726.67	280.3	0.98190	0.98157	1
7		1	1	1	1	605.24	672.88	336.1	T	597.46	653.76	336.1	0.98715	0.97158	1
8		1	1	2	2	551.40	622.02	414.0	R	544.34	610.10	414.0	0.98720	0.98083	1
9		1	2	1	2	1042.17	1156.17	347.9	R	1029.23	1143.24	347.9	0.98759	0.98881	1
10		1	2	2	1	1201.65	1313.91	358.6	T	1185.46	1297.72	358.6	0.98653	0.98768	1
11		1	1	1	1	1519.27	1576.49	418.6	T	1484.16	1537.02	418.6	0.97689	0.97497	1
12		1	1	2	2	2004.13	2089.75	564.9	R	1967.99	2053.61	564.9	0.98197	0.98270	1
13		1	1	1	1	437.27	464.41	255.4	T	431.07	455.31	255.4	0.98583	0.98040	1
14		1	1	2	2	580.38	608.27	338.3	R	572.16	600.06	338.3	0.98585	0.98650	1
15		1	1	1	1	2042.50	2151.76	280.2	T	2009.91	2114.94	280.2	0.98404	0.98288	1
16		1	1	2	2	1882.97	1967.07	497.4	R	1845.38	1917.13	497.4	0.98004	0.97461	1
17		1	2	1	2	1076.70	1120.97	504.5	R	1054.42	1096.11	504.5	0.97930	0.97782	1
18		1	2	2	1	892.39	924.28	308.8	T	875.55	907.44	308.8	0.98113	0.98178	1
19		1	2	1	2	873.65	898.90	483.7	R	856.82	881.26	483.7	0.98073	0.98038	1
20		1	2	2	1	870.94	902.16	449.0	T	854.57	883.41	449.0	0.98120	0.97922	1
21		1	2	1	2	481.93	512.02	222.8	R	475.31	503.59	222.8	0.98626	0.98352	1
22		1	2	2	1	477.90	506.75	265.7	T	470.72	495.37	265.7	0.98498	0.97755	1
23		1	2	1	2	528.14	555.52	218.6	R	519.07	550.44	218.6	0.98282	0.99085	1
24		1	2	2	1	549.73	567.90	233.9	T	539.48	555.80	233.9	0.98136	0.97870	1

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
25	(b) (6)	1	1	1	1	814.81	833.07	231.0	T	796.01	814.28	231.0	0.97693	0.97744	1
26		1	1	2	2	804.34	823.55	237.7	R	785.44	806.00	237.7	0.97650	0.97868	1
27		1	1	1	1	693.65	728.09	460.1	T	680.99	708.86	460.1	0.98174	0.97360	1
28		1	1	2	2	734.81	762.41	457.9	R	721.55	748.85	457.9	0.98196	0.98222	1
29		1	2	1	2	606.30	637.98	389.1	R	597.33	627.91	389.1	0.98521	0.98421	1
30		1	2	2	1	609.66	645.15	355.3	T	601.00	633.49	355.3	0.98580	0.98193	1
31		1	1	1	1	924.05	967.55	187.7	T	909.16	949.32	187.7	0.98388	0.98116	1
32		1	1	2	2	1047.44	1102.06	208.8	R	1029.38	1079.87	208.8	0.98275	0.97986	1
33		1	2	1	2	1166.06	1198.71	396.7	R	1145.03	1177.68	396.7	0.98196	0.98245	1
34		1	2	2	1	888.94	918.81	308.6	T	871.08	899.53	308.6	0.97990	0.97902	1
35		1	1	1	1	619.23	639.45	253.6	T	608.47	628.69	253.6	0.98262	0.98317	1
36		1	1	2	2	640.32	663.76	428.6	R	628.39	650.07	428.6	0.98136	0.97938	1
37		1	2	1	2	720.86	752.32	240.8	R	708.24	738.79	240.8	0.98249	0.98202	1
38		1	2	2	1	792.16	831.78	150.5	T	778.50	814.68	150.5	0.98275	0.97944	1
39		1	2	1	2	480.90	510.25	397.6	R	473.70	497.07	397.6	0.98504	0.97418	1
40		1	2	2	1	596.92	625.35	516.6	T	586.01	610.06	516.6	0.98171	0.97555	1
41		1	1	1	1	666.76	696.40	456.8	T	655.16	684.80	456.8	0.98260	0.98334	1
42		1	1	2	2	824.81	858.69	579.8	R	809.06	841.07	579.8	0.98091	0.97949	1
43		2	2	1	2	816.28	846.94	435.4	R	799.89	829.68	435.4	0.97992	0.97961	1
44		2	2	2	1	738.09	776.90	372.2	T	724.77	762.56	372.2	0.98195	0.98155	1
45	2	1	1	1	519.66	551.46	281.4	T	511.75	539.99	281.4	0.98477	0.97920	1	
46	2	1	2	2	353.07	374.16	175.6	R	347.86	365.89	175.6	0.98525	0.97790	1	
47	2	1	1	1	507.83	522.70	285.2	T	495.77	511.36	285.2	0.97626	0.97830	1	
48	2	1	2	2	590.68	609.93	357.7	R	576.79	596.77	357.7	0.97648	0.97842	1	
49	2	1	1	1	637.14	687.73	362.8	T	628.39	678.97	362.8	0.98625	0.98727	1	

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
50	(b) (6)	2	1	2	2	664.99	706.11	351.0	R	655.30	696.42	351.0	0.98542	0.98627	1
51		2	1	1	1	948.01	970.33	554.5	T	927.89	949.75	554.5	0.97878	0.97879	1
52		2	1	2	2	704.05	730.76	518.3	R	690.34	715.20	518.3	0.98053	0.97870	1
53		2	2	1	2	609.62	633.03	723.9	R	599.29	622.71	723.9	0.98306	0.98369	1
54		2	2	2	1	658.97	682.27	624.7	T	647.74	670.68	624.7	0.98296	0.98302	1
55		2	2	1	2	617.32	636.05	438.9	R	603.67	621.15	438.9	0.97790	0.97659	1
56		2	2	2	1	548.88	565.65	383.3	T	538.77	555.54	383.3	0.98158	0.98213	1
57		2	2	1	2	1058.43	1128.73	318.3	R	1039.82	1107.06	318.3	0.98242	0.98080	1
58		2	2	2	1	928.68	1018.01	196.9	T	917.49	1006.82	196.9	0.98795	0.98901	1
59		2	2	1	2	1259.64	1296.95	803.4	R	1233.63	1269.45	803.4	0.97935	0.97880	1
60		2	2	2	1	1349.79	1382.35	778.6	T	1321.87	1354.42	778.6	0.97931	0.97980	1
61		2	2	1	2	944.76	977.19	526.4	R	927.16	957.85	526.4	0.98138	0.98021	1
62		2	2	2	1	810.29	832.65	217.9	T	794.57	816.92	217.9	0.98059	0.98111	1
63		2	1	1	1	797.81	833.55	462.0	T	786.10	821.84	462.0	0.98532	0.98595	1
64		2	1	2	2	831.66	877.93	557.2	R	819.35	865.63	557.2	0.98520	0.98598	1
65		2	2	1	2	628.88	648.57	203.5	R	614.58	632.86	203.5	0.97726	0.97578	1
66		2	2	2	1	444.70	474.83	192.8	T	437.30	469.53	192.8	0.98336	0.98884	1
67		2	1	1	1	415.59	441.56	253.0	T	409.93	435.24	253.0	0.98637	0.98568	1
68		2	1	2	2	485.81	534.11	387.1	R	479.85	518.12	387.1	0.98772	0.97006	1
69		2	2	1	2	1406.10	1541.99	506.6	R	1388.47	1524.36	506.6	0.98746	0.98856	1
70		2	2	2	1	1345.91	1481.62	340.5	T	1314.66	1460.76	340.5	0.97678	0.98592	1
71		2	1	1	1	525.02	586.59	498.2	T	517.80	562.34	498.2	0.98624	0.95864	1
72		2	1	2	2	474.79	516.74	425.6	R	468.41	510.35	425.6	0.98655	0.98765	1
73		2	1	1	1	736.64	768.39	343.1	T	723.08	753.44	343.1	0.98160	0.98054	1
74	2	1	2	2	662.65	713.49	276.6	R	652.74	696.35	276.6	0.98503	0.97598	1	

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
75	(b) (6)	2	2	1	2	1055.28	1092.48	916.7	R	1033.83	1067.48	916.7	0.97968	0.97712	1
76		2	2	2	1	830.62	857.76	543.5	T	815.56	840.89	543.5	0.98186	0.98032	1
77		.	1	1	1	1080.08	1139.67	163.8	T	1058.93	1116.70	163.8	0.98042	0.97984	1
78		.	1	2	2	983.44	1039.84	197.2	R	966.76	1020.58	197.2	0.98304	0.98148	1
79		2	2	1	2	714.12	738.17	535.8	R	700.37	723.69	535.8	0.98075	0.98037	1
80		2	2	2	1	679.63	702.72	354.1	T	665.70	687.48	354.1	0.97951	0.97831	1
81		3	2	1	2	499.72	524.34	389.9	R	492.02	514.72	389.9	0.98460	0.98166	1
82		3	2	2	1	486.02	506.18	353.0	T	477.48	495.91	353.0	0.98243	0.97971	1
83		3	1	1	1	509.13	537.90	400.3	T	499.83	530.42	400.3	0.98172	0.98609	1
84		3	1	2	2	457.26	491.50	403.1	R	449.92	484.16	403.1	0.98394	0.98506	1
85		3	1	1	1	457.38	490.75	226.6	T	451.45	484.83	226.6	0.98704	0.98792	1
86		3	1	2	2	485.32	521.52	407.4	R	478.94	515.14	407.4	0.98685	0.98776	1
87		3	2	1	2	619.12	638.95	298.3	R	608.29	627.21	298.3	0.98251	0.98163	1
88		3	2	2	1	482.48	504.16	214.3	T	474.87	496.55	214.3	0.98422	0.98490	1
89		3	1	1	1	782.54	805.69	600.0	T	768.44	791.59	600.0	0.98198	0.98250	1
90		3	1	2	2	655.92	676.48	508.1	R	643.59	661.67	508.1	0.98120	0.97811	1
91		3	1	1	1	712.68	753.28	447.0	T	702.04	738.73	447.0	0.98507	0.98068	1
92		3	1	2	2	781.38	819.71	525.6	R	769.47	807.79	525.6	0.98475	0.98547	1
93		3	2	1	2	786.46	808.64	410.3	R	771.28	793.46	410.3	0.98070	0.98123	1
94		3	2	2	1	811.08	844.66	360.5	T	794.90	825.44	360.5	0.98005	0.97724	1
95	3	1	1	1	1189.91	1219.53	398.6	T	1164.75	1194.38	398.6	0.97886	0.97937	1	
96	3	1	2	2	1339.55	1372.46	631.5	R	1307.36	1334.03	631.5	0.97597	0.97200	1	
97	3	2	1	2	796.15	846.81	384.2	R	781.69	835.44	384.2	0.98183	0.98657	1	
98	3	2	2	1	728.02	758.69	134.4	T	715.60	746.27	134.4	0.98295	0.98364	1	
99	3	2	1	2	800.18	818.89	800.6	R	782.43	800.64	800.6	0.97782	0.97771	1	

Obs	sub	GRP	seq	per	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
100	(b) (6)	3	2	2	1	560.10	585.47	426.9	T	560.50	576.23	426.9	1.00072	0.98422	1
101		3	2	1	2	859.40	885.46	463.7	R	845.84	871.90	463.7	0.98421	0.98468	1
102		3	2	2	1	870.94	895.01	375.9	T	855.72	883.54	375.9	0.98252	0.98719	1
103		3	2	1	2	620.29	642.08	469.0	R	609.23	629.51	469.0	0.98216	0.98043	1
104		3	2	2	1	797.52	825.54	718.5	T	783.83	811.85	718.5	0.98283	0.98341	1
105		3	1	1	1	828.04	848.87	121.2	T	811.11	831.94	121.2	0.97954	0.98005	1
106		3	1	2	2	874.10	903.46	285.2	R	857.95	887.31	285.2	0.98152	0.98212	1
107		3	1	1	1	697.04	723.36	245.3	T	683.98	709.05	245.3	0.98126	0.98021	1
108		3	1	2	2	774.88	820.52	351.1	R	761.82	807.46	351.1	0.98315	0.98409	1
109		3	2	1	2	630.13	660.16	253.1	R	621.14	648.72	253.1	0.98572	0.98267	1
110		3	2	2	1	635.75	673.93	266.9	T	626.75	664.94	266.9	0.98585	0.98666	1
111		3	1	1	1	1251.64	1320.60	570.3	T	1231.93	1295.49	570.3	0.98425	0.98099	1
112		3	1	2	2	1089.34	1160.92	512.1	R	1073.67	1137.61	512.1	0.98561	0.97992	1
113		3	2	1	2	746.97	772.54	433.3	R	735.25	760.37	433.3	0.98431	0.98424	1
114		3	2	2	1	615.95	646.57	328.3	T	607.08	636.77	328.3	0.98560	0.98484	1
115		3	2	1	2	731.80	757.92	311.7	R	719.09	743.50	311.7	0.98263	0.98096	1
116		3	2	2	1	930.27	953.69	154.1	T	912.53	935.95	154.1	0.98093	0.98140	1
117		3	2	1	2	826.02	878.51	586.5	R	812.32	853.96	586.5	0.98342	0.97205	1
118		3	2	2	1	954.25	992.52	584.4	T	937.67	973.25	584.4	0.98263	0.98058	1
119		3	1	1	1	1034.50	1087.61	829.0	T	1016.56	1066.20	829.0	0.98265	0.98031	1
120		3	1	2	2	944.17	1007.87	591.2	R	928.63	979.78	591.2	0.98354	0.97214	1
121		3	1	1	1	813.89	834.48	400.7	T	797.57	818.16	400.7	0.97995	0.98044	1
122	3	1	2	2	917.85	943.51	468.0	R	901.27	926.92	468.0	0.98193	0.98242	1	

5.10 Additional Attachments

5.10.1 Attachments for the Clinical Endpoint Study (MGR001-3001)

Table 86. Clinical Site and Principal Investigator Information

Site Number	Principal Investigator and Location	Address ²⁴¹	Enrolled (n)	Included in Firm's Safety population (n)	Included in Firm's MITT population (n)	Included in Firm's PP population (n)
3001001	Idalia A. Acosta, Miami, FL 33015	5941 NW 173 Dr, Ste 1 Miami, FL 33015	12	12	12	12
3001002	Niran J. Amar, Waco, TX 76712	333 Londonderry Dr, Ste 110 Waco, TX 76712	6	6	6	6
3001003	James W. Baker, Portland, OR 97223	9495 SW Locust St Portland, OR 97223	5	5	5	5
3001004	G Daniel Brooks, Bellevue, NE 68123-4303	3503 Samson Way, Ste 108 Bellevue, NE 68123-4303	13	13	13	13
3001006	Warner W. Carr, Mission Viejo, CA 92691	27800 Medical Center Rd, #240/#244 Mission Viejo, CA 92691	13	13	13	13
3001007	Jonathan Corren, Los Angeles, CA 90025	10780 Santa Monica Blvd Ste 280 Los Angeles, CA 90025	7	7	7	7
3001008	David Cypcar, Asheville, NC 28801	14 McDowell St Asheville, NC 28801	3	3	3	3
3001009	Joseph D. Diaz, San Antonio, TX 78229	2414 Babcock Rd, Ste 108-109 San Antonio, TX 78229	5	5	5	5
3001010	Manuel A. Franco, Miami, FL 33133	2720 SW 37 Ave Miami, FL 33133	40	40	40	40
3001011	Sherwin A. Gillman, Orange, CA 92868	725 West La Veta Ave, Ste 100 Orange, CA 92868	7	7	7	7
3001012	John T. Given, Canton, OH 44718	Allergy, Respiratory & Sleep Center 4048 Dressier Rd NW, Ste 100 Canton, OH 44718	2	2	2	2
3001013	Stanley Goldstein, Rockville Centre, NY 11570	242 Merrick Rd, Ste 401 Rockville Centre, NY 11570	1	1	1	1

²⁴¹ GS Review: ANDA 208891, New/ANDA, 12/29/2015 (Module 5.3.5.1\List Description Investigator Site\List and Description of Investigators and Sites, p. 1-23 of 224).

Site Number	Principal Investigator and Location	Address ²⁴¹	Enrolled (n)	Included in Firm's Safety population (n)	Included in Firm's MITT population (n)	Included in Firm's PP population (n)
3001014	Richard G. Gower, Spokane, WA 99202	324 S Sherman St Spokane, WA 99202	6	6	6	6
3001015	Leon S. Greos, Centennial, CO 80112	14000 E. Arapahoe Rd, Ste 260 Centennial, CO 80112	12	12	12	11
3001016	Amina Z. Haggag, Anaheim, CA 92801	Anaheim Clinical Trials, LLC 1085 N. Harbor Blvd Anaheim, CA 92801	32	32	31	31
3001017	Frank C. Hampel Jr., New Braunfels, TX 78130	705-A Landa St New Braunfels, TX 78130	12	12	12	12
3001018	Edward Francis Kent Jr., South Burlington, VT 05403	Timber Lane Allergy & Asthma Research, LLC 54 Timber Lane South Burlington, VT 05403	19	19	19	19
3001019	Phillip E. Korenblat, St. Louis, MO 63141	1040 N Mason Rd, Ste 112 St. Louis, MO 63141	32	32	32	31
3001020	Craig Fred LaForce, Raleigh, NC 27607	North Carolina Clinical Research 2615 Lake Dr, Ste 301 Raleigh, NC 27607	21	21	21	21
3001022	Edward E. Lisberg, River Forest, IL 60305	7420 Central Ave, Ste 2020 River Forest, IL 60305	14	14	14	13
3001023	Stephen Maddock, Lenexa, KS 66219	Analab Clinical Research Inc 15335 W 95th St Lenexa, KS 66219	54	54	54	53
3001024	Lyndon E. Mansfield, El Paso, TX 79903	2121 Wyoming Ave El Paso, TX 79903	10	10	10	10
3001025	Jonathan Matz, Baltimore, MD 21236	Chesapeake Clinical Research, Inc 7939 Honeygo Blvd, Ste 219 Baltimore, MD 21236	20	20	20	20
3001026	Curtis J. Mello, North Dartmouth, MA 02747	370 Faunce Corner Rd 2nd Fl North Dartmouth, MA 02747	5	5	5	5

Site Number	Principal Investigator and Location	Address ²⁴¹	Enrolled (n)	Included in Firm's Safety population (n)	Included in Firm's MITT population (n)	Included in Firm's PP population (n)
3001027	S. David Miller, North Dartmouth, MA 02747	Northeast Medical Research Associates, Inc. 49 State Rd Watuppa Bldg, Ste 202 North Dartmouth, MA 02747	22	22	21	21
3001028	Anthony Montanaro, Portland, OR 97202	6327 SE Milwaukie Ave, 2nd Floor Portland, OR 97202	14	14	14	14
3001029	Nancy K. Ostrom, San Diego, CA 92123	5776 Ruffin Rd San Diego, CA 92123	13	13	13	13
3001031	Amit I. Patel, Riverside, CA 92506	Integrated Research Group, Inc. 4646 Brockton Ave, Ste 202-3 Riverside, CA 92506	2	2	2	2
3001032	David S. Pearlman, Denver, CO 80230	125 Rampart Way, Ste 150 Denver, CO 80230	14	14	14	14
3001033	Andrew J. Pedinoff, Skillman, NJ 08558	Montgomery Professional Center 24 Vreeland Dr Skillman, NJ 08558	21	21	21	21
3001034	Warren William Pleskow, Encinitas, CA 92024	317 N El Camino Real, Ste 506 Encinitas, CA 92024	19	19	18	18
3001035	Larry S. Posner, Napa, CA 94558	1100 Pear Tree Lane Napa, CA 94558	2	2	2	2
3001036	Gordon D. Raphael, Bethesda, MD 20814	4915 Auburn Ave, Ste 202 Bethesda, MD 20814	28	28	28	28
3001037	Paul H. Ratner, San Antonio, TX 78229	7711 Louis Pasteur Dr, Ste 406 San Antonio, TX 78229	12	12	12	12
3001038	Syed M. Rehman, Toledo, OH 43617	7247 W. Central Ave, Ste A Toledo, OH 43617	10	10	10	10
3001039	Michael E. Ruff, Dallas, TX 75231	5499 Glen Lakes Dr, Ste 200 Dallas, TX 75231	19	19	19	19
3001040	Russell A. Settipane, East Providence, RI 02914	450 Veterans Memorial Pkwy #15 East Providence, RI 02914	1	1	1	1

Site Number	Principal Investigator and Location	Address ²⁴¹	Enrolled (n)	Included in Firm's Safety population (n)	Included in Firm's MITT population (n)	Included in Firm's PP population (n)
3001041	Ellen R. Sher, Ocean, NJ 07712	802 West Park Ave, Ste 213 Ocean, NJ 07712	8	8	8	8
3001042	Lawrence D. Sher, Rolling Hills Estates, CA 90274	550 Deep Valley Dr, Ste 317 Rolling Hills Estates, CA 90274	7	7	7	7
3001045	Stephen A. Tilles, Seattle, WA 98115	9725 Third Ave NE, Ste 500 Seattle, WA 98115	10	9	9	9
3001046	Mark L. Vandewalker, Columbia, MO 65203	601 W Nifong Bldg 2-A Columbia, MO 65203	16	16	16	16
3001047	David P. Chen, Bozeman, MT 59718	950 Stoneridge Dr, Ste 1 Bozeman, MT 59718	6	6	6	6
*3001048	Patrick H. Win, Shiloh, IL 62269	325 Tamarack Lane Shiloh, IL 62269	0	0	0	0
3001049	John A. Winder, Sylvania, OH 43560	5800 Monroe St, Ste A-9 Sylvania, OH 43560	4	4	4	4
3001050	James D. Wolfe, San Jose, CA 95117	4050 Moorpark Ave, Ste 6 San Jose, CA 95117	21	21	21	21
3001051	Robert N. Wolfe, Los Angeles, CA 90048	Southern California Institute For Respiratory Diseases, Inc. 8635 West 3rd St, Ste 965-W Los Angeles, CA 90048	21	21	21	21
3001053	Thomas R. Murphy, N. Charleston, SC 29420	7555 Northside Dr N. Charleston, SC 29420	11	11	11	11
3001054	David I. Bernstein, Cincinnati, OH 45231	Bernstein Clinical Research Center, LLC 8444 Winton Rd Cincinnati, OH 45231	6	6	6	6
3001055	Charles M. Fogarty, Spartanburg, SC 29303	485 Simuel Rd Spartanburg, SC 29303	5	5	5	5
3001056	Philip C. Halverson, Minneapolis, MN 55402	825 Nicollet Mall, Ste 1135 Minneapolis, MN 55402	6	6	6	6
3001057	Sanchayita "Ita" Tripathy, Rolla, MO 65401	509 East 10th St Rolla, MO 65401	12	12	12	12

Site Number	Principal Investigator and Location	Address ²⁴¹	Enrolled (n)	Included in Firm's Safety population (n)	Included in Firm's MITT population (n)	Included in Firm's PP population (n)
3001058	John F. Zwetchkenbaum, Warwick, RI 02886	470 Toll Gate Rd, Ste 203 Warwick, RI 02886	20	20	20	20
3001059	Dario D. Altamirano, Hialeah, FL 33012	900 W 49th St, Ste 430 Hialeah, FL 33012	7	7	7	6
3001060	Philip A. Emrie, Wheat Ridge, CO 80033	8550 W 38th Ave, Ste 202 Wheat Ridge, CO 80033	9	9	9	9
3001061	Timothy Harrison Elder, Gainesville, FL 32607	4343 W Newberry Rd, Ste 17 Gainesville, FL 32607	6	6	6	6
3001062	Gregory J. Feldman, Spartanburg, SC 29303	141 Harold Fleming Court Spartanburg, SC 29303	9	9	9	8
3001063	Jason H. Friesen, Eugene, OR 97401	Allergy and Asthma Research Group 1488 Oak St Eugene, OR 97401	20	20	20	20
3001064	Gregory M. Gottschlich, Cincinnati, OH 45242	9395 Kenwood Rd, Ste 101 Cincinnati, OH 45242	6	6	6	6
3001065	James Lawrence Pearle, Fullerton, CA 92835	301 W Bastanchury Rd, Ste 220 Fullerton, CA 92835	11	11	11	11
*3001066	Ronald H. Saff, Tallahassee, FL 32308	Allergy & Asthma Diagnostic Treatment Center 2300 Centerville Rd Tallahassee, FL 32308	0	0	0	0
3001067	Teresa S. Sligh, North Hollywood, CA 91606	6400 Laurel Canyon Blvd, Ste 300A North Hollywood, CA 91606	38	38	37	36
3001068	Kurt W. Jensen, Tacoma, WA 98405	Pulmonary Consultants, PLLC 1708 S. Yakima Ave, Ste 300 Tacoma, WA 98405	1	1	1	1
3001069	Edward M. Kerwin, Medford, OR 97504	Clinical Research Institute of Southern Oregon, PC 3860 Crater Lake Ave, Ste B Medford, OR 97504	22	22	22	22

Site Number	Principal Investigator and Location	Address ²⁴¹	Enrolled (n)	Included in Firm's Safety population (n)	Included in Firm's MITT population (n)	Included in Firm's PP population (n)
3001071	Daniel F. Soteres, Colorado Springs, CO 80907	2709 North Tejon St Colorado Springs, CO 80907	14	14	14	14
3001074	William R. Lumry, Dallas, TX 75231	10100 N Central Expressway, Ste 125 Dallas, TX 75231	14	14	14	14
3001075	Mikhail Palatnik, Gold River, CA 95670	2485 Sunrise Blvd Gold River, CA 95670	14	14	14	13
3001076	Paul Y. Qaqundah, Huntington Beach, CA 92647	17822 Beach Blvd, Ste 278 Huntington Beach, CA 92647	23	23	23	23
3001077	Weily Soong, Birmingham, AL 35209	504 Brookwood Blvd, Ste 250 Birmingham, AL 35209	4	4	4	4
3001078	Selwyn Spangenthal, Charlotte, NC 28207	1918 Randolph Rd, Ste 440 Charlotte, NC 28207	14	14	14	13
*3001079	William W. Storms, Colorado Springs, CO 80907	1625 Medical Center Point, Ste 190 Colorado Springs, CO 80907	0	0	0	0
3001080	Martha V. White, Wheaton, MD 20902	11002 Veirs Mill Rd, Ste 414 Wheaton, MD 20902	13	13	13	13
3001081	Isaac R. Melamed, Centennial, CO 80112	6801 S. Yosemite St Centennial, CO 80112	5	5	5	4
3001082	Vosudesh K. Pai, Lawrenceville, GA 30046	555 Old Norcross Rd, Ste 250 Lawrenceville, GA 30046	7	7	7	7
3001083	Paul A. Shapero, Bangor, ME 04401	700 Mt. Hope Ave, Ste 430 Bangor, ME 04401	3	3	3	3
3001084	Daniel Sousa, Fall River, MA 02720	373 New Boston Rd Fall River, MA 02720	6	6	6	6
3001085	Sheldon Spector, Los Angeles, CA 90025	11645 Wilshire Blvd, Ste 1155 Los Angeles, CA 90025	12	12	12	12
3001086	Gary C. Steven, Greenfield, WI 53228	8585 W Forest Home Ave, Ste 200 Greenfield, WI 53228	5	5	5	5

Site Number	Principal Investigator and Location	Address ²⁴¹	Enrolled (n)	Included in Firm's Safety population (n)	Included in Firm's MITT population (n)	Included in Firm's PP population (n)
3001087	Manuel A. Fernandez-Gonzalez, Miami, FL 33135	590 SW 27th Ave Miami, FL 33135	4	4	4	4
3001088	Agustin J. Latorre, Miami, FL 33155	6850 Coral Way, Ste 409 Miami, FL 33155	1	1	1	1
3001089	Robert S. Call, Henrico, VA 23233	9920 Independence Park Dr, Ste 101 Henrico, VA 23233	5	5	5	5
3001090	Marcy Jo Goisse, Smithfield, PA 15478	100 Ridge View Dr, Ste 3 Smithfield, PA 15478	21	21	21	21
3001091	Anoshie Ratnayake, Costa Mesa, CA 92626	3545 Howard Way Costa Mesa, CA 92626	1	1	1	1
3001092	Marvin Kalafer, Jenkintown, PA 19046	815 Greenwood Ave, Ste 12 Jenkintown, PA 19046	7	7	7	7
3001093	Santiago Reyes, Oklahoma City, OK 73112	3366 NW Expressway, Bldg D, Ste 330 Oklahoma City, OK 73112	3	3	3	3
3001095	Karl V. Sitz, Little Rock, AR 72205	18 Corporate Hill, Ste 110 Little Rock, AR 72205	5	5	5	4
3001096	Stephen G. Basheda, Pittsburgh, PA 15243	1050 Bower Hill Rd, Ste 307 Pittsburgh, PA 15243	4	4	4	4
3001097	Ifikhar Hussain, Tulsa, OK 74136	7307 S. Yale Ave, Ste 200 Tulsa, OK 74136	6	6	6	6
3001100	Manav Singla, White Marsh, MD 21162	Asthma Allergy & Sinus Center 5430 Campbell Blvd, Ste 103 White Marsh, MD 21162	2	2	2	1
3001102	Daniel Rodriguez, New Port Richey, FL 34653	Advanced Research Institute, Inc. 7114 Congress St New Port Richey, FL 34653	6	6	6	6

Site Number	Principal Investigator and Location	Address ²⁴¹	Enrolled (n)	Included in Firm's Safety population (n)	Included in Firm's MITT population (n)	Included in Firm's PP population (n)
3001104	Edward Joseph Campbell, Provo, UT 84604	2230 North at University Pkwy Cottontree Square, Bldg 6A Provo, UT 84604	6	6	6	6
3001107	Stephen Ryan, Tacoma, WA 98405	316 Martin Luther King Jr. Way, Ste 401 Tacoma, WA 98405	6	6	6	6
3001108	Tonny Tanus, Bakersfield, CA 93301	2116 17th St Bakersfield, CA 93301	18	18	18	14
3001109	Carl Thornblade, Missoula, MT 59808	2683 Palmer St, Ste B Missoula, MT 59808	1	1	1	1
3001111	Miguel E. Trevino, Clearwater, FL 33756	1573 South Fort Harrison Ave Clearwater, FL 33756	6	6	6	6
3001112	Steven F. Weinstein, Huntington Beach, CA 92647	Allergy and Asthma Specialists Medical Group 17742 Beach Blvd, Ste 310 Huntington Beach, CA 92647	16	16	15	15
3001114	David Fuentes, Boerne, TX 78006	1420 River Rd, Ste 100 Boerne, TX 78006	5	5	5	5
3001115	Susan L. Andrew, Dickinson, TX 77539	914 FM 517 Road West Dickinson, TX 77539	5	5	5	5
*3001116	William L. Ebbeling, Fresno, CA 93720	1646 E. Herndon Ave, Ste 106 Fresno, CA 93720	0	0	0	0
3001119	Bruce A. DeCotiis, Brick, NJ 08724	1673 Hwy 88 West Brick, NJ 08724	14	14	14	14
3001120	Ernesto Diaz, Coral Gables, FL 33134	5200 SW 8th St, Ste 119-120 Coral Gables, FL 33134	36	36	36	36
3001122	Lawrence P. Landwehr, Warrensburg, MO 64093	407A East Russell Ave, Ste 3 Warrensburg, MO 64093	6	6	6	5

* The firm stated that these sites screened subjects but did not enroll any subjects. [Error! Bookmark not defined.](#)

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* The firm stated that this is a misrandomized subject (please see Section 5.4.5 for details).

5.10.3 ECD Issued to the Firm on 8/10/2016

On 8/10/2016, an ECD with following comments were issued by DMEPA through DBI to the firm. The DMEPA's consult response to DBI's consult request includes evaluation of the firm's response dated 8/11/2016.

Deficiency Related to Device Orientation Study (MGR000-1004)

You state that 10 participants inhaled from the inhaler in the horizontal position at some point throughout the 3 tasks [Module 3.2.P.7, Section 3.2.P.7.2.6.1 Device Orientation Study (MGR000-1004)]. Please submit the breakdown of which task each participant executed the error. In addition, please include specifically which participants were Advair users and which were Advair/DPI naïve users.

5.10.4 ECD Issued to the Firm on 9/9/2016

On 9/9/2016, DBI issued an ECD with following comments to the firm. The current review includes evaluation of the firm's response dated 9/22/2016.

Deficiencies Related to Information Common to All In Vitro Studies (057755-02-04, MGF-PRO-2015-080, 057755-02-07, MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093)

1. Please provide MGR-METH-546070 (v. 7.0) [test method for the emitted dose study], and MGR-METH-546069 (v. 6.0) [test method of the aerodynamic particle size distribution (APSD) study].
2. You provided your single actuation content (SAC) and APSD study results in pdf format. Please provide it in SAS .xpt format.

In addition, it is noticed that you have repeats using a new device for multiple units in Studies 057755-02-04, MGF-PRO-2015-080 and 057755-02-07. Please provide the study results with their original value in one SAS .xpt file, and with their repeat values in a separate SAS .xpt file.

3. Please provide 20% serial chromatograms for each of your SAC and APSD study.
4. For each of your SAC and APSD study, you did not provide 100% raw numerical data (analyst's printouts) for all analytical runs (accepted and rejected) conducted during the UPLC sample analysis of these studies. The raw numerical data should include the data of peak area/height for the drug, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all samples, calibration standard samples, and quality control samples.

Deficiency Related to In Vitro Equivalence Studies 057755-02-04 and 057755-02-07

5. According to your study reports of the aforementioned studies, it is noted that you repeated several samples in your SAC and APSD study (e.g. 12/29/2015 submission, Module 3.2.P.2. Pharmaceutical Development\In Vitro Bio Equivalence Report – 100/50mcg – MGR-REP-2015-096, p. 5 of 181, (b) (4) device ID 115, Mylan unit 1R; 12/29/2015 submission, Module 3.2.P.2. Pharmaceutical Development\In Vitro Bio Equivalence Report – 500/50mcg – MGR-REP-2015-097, p. 6 of 181, (b) (4) device ID 111, Mylan unit 34R). For each of these repeat samples, please explain why their original assay was rejected, and please provide supporting documents (e.g. investigational report) for these sample rejections.

Deficiencies Related to In Vitro Equivalence Study MGF-PRO-2015-080 Only

6. According to your study report, the original samples of the following repeat samples were rejected due to poor chromatography. Please provide the rejected chromatograms of their

original samples as well as rejected and/or accepted chromatograms of these repeat samples.

Study	Flow Rate (L/min)	Lifestage	Analyte	Product (T/R)	Lot	Repeat Unit
APSD	60	Beginning	Fluticasone propionate (FP)	R	5ZP9304	198R
APSD	60	Beginning	Salmeterol	R	5ZP9304	198R
APSD	90 (original testing)	Beginning	FP	T	631-007	248R
APSD	90 (original testing)	Beginning	Salmeterol	T	631-007	248R

- In your study report, you stated that after completion of the initial testing for the study, “it was discovered that the flow meter used for the APSD testing at 90 L/min failed its calibration and was subsequently reading incorrect flow values. Therefore the APSD testing was repeated for the 90 L/min flow rate (MGR-PRO-2015-080 v3.0).” Please provide supporting documentation of the flow meter failure, the incorrect flow values measured, and corrective actions taken.

Deficiencies Related to All Pivotal Fasting Studies (MGR001-1006, MGR001-1007, MGR001-1005 and MGR001-1014)

- Please provide documentation demonstrating if the quality control samples (QCs) and calibration curve standards (CCs) were processed along with the subject samples in the same processing batch prior to analysis on LC-MS/MS.
- It is noticed that for samples identified for reassay, many of their original concentrations were listed as “not reportable”, “ALQ” or “BLQ”. Please provide their original concentration numbers (e.g. 12.34 pg/mL instead of “not reportable”) for each of the samples identified for reassay.

Deficiencies Related to Fasting Study MGR001-1006 Only

- For the 2 samples (Subject (b) (6), Period 2, 3 hrs; and Subject (b) (6) Period 1, 24 hrs) that were reassayed for FP and salmeterol due to poor chromatography, you provided their rejected chromatograms. Please also provide the accepted chromatograms of these reassay samples.
- In your bioanalytical report, you stated that the reassay of sample Subject (b) (6), Period 1, 0.08 hr for FP and salmeterol failed due to “documented sample processing error – insufficient volume in Aliquot 1, Aliquot 2 was utilized for re-assay in Run 78”. According to your numerical raw data, the response for internal standard (IS) was

acceptable (within 40%-180% of mean IS of its run as per SOP MGWBIO-SOP-BIO-GEN-0020). Therefore, please explain this discrepancy (you stated that there was insufficient volume, but IS response of this sample was acceptable) and explain how and when insufficient volume in Aliquot 1 was identified.

12. For Subject (b) (6) reinjection (Run ID 63) that had a run status as “N/A”, you stated that the run was “*not imported into (b) (4) due to analyst error (incorrect plate was injected)*”. You did not provide numerical raw data for this run. Please provide this information, and please also clarify which plate was incorrectly injected, and how it was identified.

Deficiencies Related to Fasting Study MGR001-1007 Only

13. For Subject (b) (6), Period 2, 3 hrs that were reassayed for FP due to “documented sample processing error – broken vial”, this sample still meets acceptance criteria for IS. Please explain this discrepancy (you stated that vial was broken, but IS response of this sample was acceptable) and explain how and when broken vial was identified.
14. You stated that the salmeterol run for Subject (b) (6) (Run #23) was rejected due to poor chromatography for salmeterol. Please provide the rejected chromatograms of this run and the accepted chromatograms of its repeat run.

Deficiencies Related to Fasting Study MGR001-1005 Only

15. Three (3) samples (Subject (b) (6), Period 2, 0.03 hr, 0.08 hr and 8 hrs) were reassayed for FP and salmeterol due to “documented sample processing error – insufficient sample volume”. According to the numerical raw data, the response for IS of these samples was acceptable (within 40%-180% of mean IS of its run). Therefore, please explain this discrepancy (you stated that there was insufficient volume, but IS response of these samples was acceptable) and explain how and when insufficient volume was identified.
16. For sample Subject (b) (6), Period 1, 0.08 hr that was reassayed for FP and salmeterol due to poor chromatography, please provide the rejected and accepted chromatograms of this sample.
17. You stated that the FP and salmeterol runs for Subjects (b) (6) (Run #s 23 and 34) were rejected due to “*sample processing/analyst error-plate was lost during assay procedure*”. Please provide numerical raw data of the original runs, as well as investigational report of this plate lost and corrective actions taken.

Deficiencies Related to Fasting Study MGR001-1014 Only

18. In your bioanalytical report, you stated that in Run #27, the carry-over check blank slightly exceeded 20% of the LLOQ peak response ratio for FP (23.6%). This carryover check blank sample was then re-injected to determine whether the initial result was due to autosampler carryover or to a small amount of FP present in the sample. You stated that the re-injection confirmed the presence of the FP peak, “*indicating that there had been no*

significant carryover in the run” (12/29/2015 submission, Module 5.3.1.4. mgr001-1014 – Bioanalytical Study Tagging File\Legacy Clinical Study Report\MGR001-1014 Bioanalytical Report, p. 9-10 of 13). Please explain how this conclusion was made, given that FP peak was present.

19. You stated that the FP and salmeterol run for Subject (b) (6) and Subject (b) (6) (Period 1) (Run # 50) was rejected because “*plate was lost during assay procedure (leaking (b) (4) tip)*”. You did not provide numerical raw data for this run. Therefore, please provide so, and please also provide investigational report of this plate lost and corrective actions taken.
20. You stated that the FP reassay run (Run # 48) was rejected because it did not meet batch acceptance criteria for FP QCs. However, among the 14 QCs included in this run, only 2 (1 mid QC “FZ CX 1” and 1 high QC “FZ D1”) were not within 15% of the theoretical value for FP. Therefore, please explain why this run was rejected.

Deficiencies Related to the Flow Profiling Study (MGR000-1003)

21. You provided your inhaled flow rate study datasets (e.g. “flow profile”, “adverse event”, “medication”, and “analysis sets and CIP violators”) in pdf format. Please also provide them in SAS .xpt format.

5.10.5 DBI’s Email Response to the Firm’s Clarification Email for ECD Issued on 9/9/2016

On 9/15/2016, the firm sent an email seeking clarification regarding one of the comments for this ECD. On the same day (9/15/2016), DBI responded to the firm’s clarification email.

From: Schley, Mignon
To: "Amy L Martin"
Bcc: Schley, Mignon
Subject: RE: Question pertaining to Mylan ANDA 208891 - ECD Dated 9/9/16
Date: Thursday, September 15, 2016 12:18:00 PM

Hi Amy,

This email is in response to your email inquiry on September 15, 2016.

Please see below for the response.

1. What you proposed to provide for the 20% serial chromatograms for each SAC and APSD study in the in vitro study under flow rate of 30 L/min, 60 L/min and 90 L/min is acceptable. However, please keep all the chromatograms available for further inquiry, in case we may need it in the future review process.
2. As a reminder, please note that Deficiencies #1-4 in the ECD letter are also applicable to your in vitro pressure differential (4 kPa) studies (MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093). In other words, study results (in SAS .xpt format), 20% serial chromatograms and 100% raw data should also be provided for these studies.

3. As a reminder, please note that for those original samples that were rejected due to poor chromatography (ECD Deficiency #6, as well as ECD Deficiency #5 if there were any samples rejected due to poor chromatograms), please provide the rejected chromatograms of their original samples as well as rejected and/or accepted chromatograms of their repeat samples.

Mignon Schley, PharmD
Bioequivalence Project Manager
Division of Bioequivalence 1
OB / OGD / CDER / FDA
/ (240) 402-6913
6 mignon.schley@fda.hhs.gov

-----Original Message-----

From: Amy L Martin [<mailto:AmyLynn.Martin@mylan.com>]
Sent: Thursday, September 15, 2016 10:34 AM
To: Schley, Mignon
Subject: RE: Question pertaining to Mylan ANDA 208891 - ECD Dated 9/9/16

Many thanks for your assistance.

-----Original Message-----

From: Schley, Mignon [<mailto:Mignon.Schley@fda.hhs.gov>]
Sent: Thursday, September 15, 2016 10:33 AM
To: Amy L Martin <AmyLynn.Martin@mylan.com>
Subject: RE: Question pertaining to Mylan ANDA 208891 - ECD Dated 9/9/16

Good Morning Amy,

I have forward your inquiry to the review team.

I will update you once I have received their response.

Thank you

Mignon Schley, PharmD
Bioequivalence Project Manager
Division of Bioequivalence 1
OB / OGD / CDER / FDA
/ (240) 402-6913
6 mignon.schley@fda.hhs.gov

-----Original Message-----

From: Amy L Martin [<mailto:AmyLynn.Martin@mylan.com>]
Sent: Thursday, September 15, 2016 10:24 AM
To: Schley, Mignon
Subject: Question pertaining to Mylan ANDA 208891 - ECD Dated 9/9/16

Dear Dr. Schley,

Good morning. I am writing to seek clarification regarding Comment #3 of the attached Bioequivalence ECD for ANDA 208891, wherein FDA requested that Mylan provide 20% serial chromatograms for each SAC and APSD study. In order to provide a representative serial sample at all three strengths and all three flow rates (which is at least 20% of the chromatograms) we wish to provide the following and would like to know if this proposal will complete the Agency's request?

1. 100/50mcg at 30 L/min,
2. 250/50mcg at 60 L/min
3. 500/50 mcg at 90 L/min

Feel free to contact me via telephone or email if additional details are needed. Thanks so much for your time.

All my best,

Amy
Amy Martin
Director of Regulatory Affairs
Mylan Pharmaceuticals Inc.
(304) 554-6008

-----Original Message-----

From: DoNotReply@fda.hhs.gov [mailto:DoNotReply@fda.hhs.gov]
Sent: Monday, September 12, 2016 1:17 PM
To: Joseph J. Sobecki <Joseph.Sobecki@mylan.com>
Cc: Mignon.Schley@fda.hhs.gov
Subject: [EASILY CORRECTABLE DEFICIENCY] Original ANDA 208891

September 09, 2016

ANDA 208891
EASILY CORRECTABLE DEFICIENCY
Original ANDA

MYLAN PHARMACEUTICALS INC.
781 CHESTNUT RIDGE ROAD
P.O. BOX 4310
MORGANTOWN, WV 26504-4310
UNITED STATES

Attention: Joseph J. Sobecki

Dear Joseph J. Sobecki:

Please refer to your Abbreviated New Drug Application (ANDA) submitted on December 29, 2015, under section 505(j) of the Federal Food, Drug, and Cosmetic Act for fluticasone propionate and salmeterol xinafoate inhalation powder, 0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ 0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation.

Please see the attached file for deficiency comments.

Provide a complete response to these deficiencies by September 22, 2016. We will not process or review a partial response. Send your submission through the Electronic Submission Gateway <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm>. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**EASILY CORRECTABLE DEFICIENCY
BIOEQUIVALENCE
REFERENCE #10126483**

If FDA does not receive a complete response by September 22, 2016, the review will be closed and the listed deficiencies will be incorporated in a subsequent COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions - Amendments and Easily Correctable Deficiencies Under GDUFA, available on FDA's website.

If you have any questions, contact Mignon Schley, Office of Bioequivalence Project Manager, at 240-402-6913 or mignon.schley@fda.hhs.gov.

Sincerely,

Mignon Schley, Pharm.D.
OFFICE OF GENERIC DRUGS
OFFICE OF BIOEQUIVALENCE
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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5.10.6 ECD Issued to the Firm on 9/22/2016

On 9/22/2016, an ECD with following comments were issued by DMEPA through DBI to the firm. This ECD was. The DMEPA's consult response to DBI's consult request includes evaluation of the firm's response dated 9/28/2016.

Deficiency Related to Device Orientation Study (MGR000-1004)

If the device is continually used in the wrong orientation (i.e., horizontal position), could such use lead to powder build-up or other device related issues? How would continual use of the device in the wrong orientation affect the delivery of subsequent doses?

5.10.7 ECD Issued to the Firm on 12/29/2016

On 12/29/2016, DBI issued an ECD with following comments to the firm. The current review includes evaluation of the firm's response dated 1/17/2017.

On December 16, 2009, Ropes & Gray LLP, on behalf of GlaxoSmithKline, submitted a citizen petition to FDA (Docket No. FDA-2009-P-0597) regarding applications that reference generic copies of oral inhalation products containing fluticasone propionate and/or salmeterol xinafoate.

(b) (4)

The issues raised by these petitions are currently under review by the Agency, and FDA has not made a final decision on these issues. The deficiency comments included in this communication reflect only our current thinking, and this communication does not represent a final decision by the Agency on the issues raised in the pending citizen petitions referenced above.

Deficiency Related to Information Common to All In Vitro Studies (057755-02-04, MGF-PRO-2015-080, 057755-02-07, MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093)

1. You did not provide detailed information about your study (e.g., street address, fax#, phone #, and principal investigator’s email address). Please provide the study information using the following table for each of your in vitro SAC and APSD studies (057755-02-04, MGF-PRO-2015-080, 057755-02-07, MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093).

Study No.	
Study site (name, street address, phone #, fax #)	
Principal Investigator (name, email)	
Study dates	
SOP No.	
SOP Effective Date	
SOP Title	
Testing Method Description	
Testing Equipment Used (e.g., name, model, etc)	
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc..)	
Analytical Method Description	
Analytical Equipment Used (e.g., name, model, etc)	

Deficiency Related to Method Validation Studies for SAC and APSD Studies

2. For the solution stability study in your method validation MDR-RGMETH-0032, please specify the storage condition (e.g. storage temperature) of your stock standard solutions, working standard solutions, and sample solutions used in this study. Please also specify how long and under what storage condition your study sample solutions, stock standard solutions and working standard solutions were stored in each of your in vitro SAC and APSD studies (057755-02-04, MGF-PRO-2015-080, 057755-02-07, MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093).

Deficiency Related to All Pivotal Fasting Studies (MGR001-1006, MGR001-1007, MGR001-1005 and MGR001-1014)

3. Please provide SOP for incurred sample reanalysis that was effective at the time of the fasting studies in current application.

Deficiency Related to Fasting Study MGR001-1006 Only

4. According to your product information summary table [12/29/2015 submission, Module 2.7.1\Summary of Biopharmaceutic Studies and Associated Analytical Methods (Biosummary Tables 1-6 and 9-17), p. 34 of 47], emitted dose of fluticasone propionate (FP) as % target for test product batch #631-002 is 104%. However, this value is 105.4% according to its Certificate of Analysis (COA) [12/29/2015 submission, Module 3.2.P.5.4\Lot 631-002 – Mylan Certificate of Analysis, p. 2 of 3]. Please explain this discrepancy.

Deficiency Related to Fasting Study MGR001-1007 Only

5. According to the your product information summary table [12/29/2015 submission, Module 2.7.1\Summary of Biopharmaceutic Studies and Associated Analytical Methods (Biosummary Tables 1-6 and 9-17), p. 35 of 47], emitted dose as % target for test product batch #631-006 is 100% for FP and 103% for salmeterol. However, this value is 101.0% and 100.0% according to its COA (12/29/2015 submission, Module 3.2.P.5.4\Lot 631-006 – Mylan Certificate of Analysis, p. 2 of 3). Please explain this discrepancy.

Deficiency Related to Fasting Study MGR001-1005 Only

6. According to your product information summary table [12/29/2015 submission, Module 2.7.1\Summary of Biopharmaceutic Studies and Associated Analytical Methods (Biosummary Tables 1-6 and 9-17), p. 36 of 47], emitted dose as % target for the reference listed drug (RLD) product batch #5ZP9304 is 103% for FP. However, this value is 104% according to its COA (12/29/2015 submission, Module 2.7.1\Certificate of Analysis – RLD batch No. 4ZP9304, p. 1 of 2). Please explain this discrepancy.

Deficiencies Related to Fasting Study MGR001-1014 Only

7. According to your product information summary table [12/29/2015 submission, Module 2.7.1\Summary of Biopharmaceutic Studies and Associated Analytical Methods (Biosummary Tables 1-6 and 9-17), p. 37 of 47], emitted dose as % target for RLD product batch #5ZP9304 is 104% for FP. However, this value is 103% according to its COA (12/29/2015 submission, Module 2.7.1\Certificate of Analysis – RLD batch No. 4ZP9882, p. 1 of 2). Please explain this discrepancy.
8. It is noted that in the ISR reports for FP and salmeterol (12/29/2015 submission, Module 5.3.1.4. mgr001-1014...\MGR001-1014 Bioanalytical Report Appendix 1 – Tables and Attachments, p. 57 and 62 of 1846), you had a footnote note for “Total Evaluable ISR Results”, which said “**Evaluable ISR Result- A sample having an” and the sentence was cut off. Please provide the full sentence of this footnote.

Deficiency Related to Device Orientation Study (MGR000-1004)

9. You did not provide detailed study information about your Device Orientation Study. Please provide the study information using the following table for this study.

Study Number	
Study Title	
Clinical Site (name, street address, phone #, fax #)	
Principal Investigator (name, email)	
Study Dates	

Please provide [REDACTED] (b) (4) as mentioned in c) above for each strength of the drug product.

In Controlled Correspondence 844398, based on your statement of [REDACTED] (b) (4) difference between batches used in the pivotal clinical studies and commercial batches, the Agency recommended you to demonstrate in vitro bioequivalence (BE) according to the *Draft Guidance on Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder at 60 L/min.* [REDACTED] (b) (4)

[REDACTED] please conduct in vitro BE studies [single actuation content (SAC) and aerodynamic particle size distribution (APSD) studies] comparing reference listed drug (RLD) product and the test product with final commercial formulation [REDACTED] (b) (4) device [REDACTED] (b) (4), and manufacturing process [REDACTED] (b) (4), and manufactured [REDACTED] (b) (4) as bridging studies. These studies should be conducted for each strength of the product, and should be conducted according to *Draft Guidance on Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder* (recommended September 2013, will be referred to as product-specific guidance in the rest of this deficiency letter) at **30, 60, and 90 L/min**, and use at least 3 batches each of T and unexpired R products with no fewer than 10 units from each batch.

In the above APSD studies, please include a standard curve and quality control (QC) samples with three validated concentrations in the range of expected study concentrations with each analytical batch, as outlined in the *Guidance for Industry - Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal sprays for Local Actions* (posted April 2003).

2. Please provide COAs for the following RLD batches used in the clinical endpoint study or in vitro BE studies: 4ZP4083 (clinical endpoint study), 5ZP8178, 5ZP8397, 5ZP0114, 4ZP7022, and 5ZP8689 (in vitro studies).

IN VITRO STUDIES

Deficiencies Related to Pre-Study Method Validation for In Vitro Studies

Method Validation – Common to Single Actuation Content (SAC) and Aerodynamic Particle Size Distribution (APSD) Studies

3. It is noted that method validation results for SAC Method # MGR-METH-546070 (Section C of this method) is almost the same as method validation results for Method # MDR-RGMETH-0032 (12/29/2015 submission, Module 3.2.P.5.3\Uniformity of delivered dose Validation Report – MDR-RGMETH-0032). Please clarify if these are the same method validation studies.

Similarly, it is noted that method validation results for APSD Method # MGR-METH-546069 (Section C of this method) is almost the same as method validation results for Method # MDR-RGMETH-0031 (12/29/2015 submission, Module 3.2.P.5.3\Aerodynamic Particle Size Distribution Validation Report – MDR-RGMETH-0031). For the former method validation results, you also included “achievable LOQ of method” that was not reported in the latter method validation report. Please clarify if these are the same method validation studies.

Please provide street address as well as study dates for your method validation studies for each of aforementioned 4 methods. During Office of Study Integrity and Surveillance (OSIS) inspection at (b) (4), it was found out that the analytical methods performed by (b) (4) were developed and validated by Mylan Global Respiratory Group prior to the transfer to (b) (4), according to (b) (4) method transfer protocol. Since the method validation and in vitro BE studies for the 100/50 and 500/50 mcg strengths were conducted at different sites, please provide method transfer report for method transfer from Mylan Global Respiratory Group to (b) (4). Please be advised that if method validation studies were conducted at different sites from any of the in vitro BE studies, then method transfer studies (e.g. precision and accuracy studies for the HPLC method; and precision study for the SAC and APSD method) are needed to support method transfer between different study sites. Please also be advised that method transfer studies for the SAC and APSD methods should be conducted using unexpired RLD product.

4. Please validate accuracy (% recovery at the high and low concentrations) and precision/intermediate precision of the UPLC method that was used in each of the SAC and APSD method. Accuracy and precision should be evaluated with known amounts of fluticasone propionate (FP) and salmeterol (SA) relevant to expected sample concentrations spiked into placebo solution.

Method Validation – SAC Studies only

5. Please provide the flow rate, actuation time and volume of air drawn through the delivery system for the intermediate precision study of SAC.

Method Validation – APSD Studies only

6.

(b) (4)

7. Please provide actuation time and volume of air drawn through the delivery system for the intermediate precision study of APSD.
8. Please provide dose counter number for each of the test and RLD device used in the intermediate precision study of APSD.

9. According to the method validation report of method MDR-RGMETH-0031 (12/29/2015 submission, Module 3.2.P.5.3\Aerodynamic Particle Size Distribution Validation Report – MDR-RGMETH-0031, p. 9 of 26), 3 columns were used in the intermediate precision study of APSD. However, in your test plan table on the same page, only 2 columns were listed. Therefore, please clarify this discrepancy.

Deficiencies Related to Information Common to All In Vitro Studies (057755-02-04, MGR-PRO-2015-080, 057755-02-07, MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093)

Both SAC and APSD Studies

10. According to the study protocols, you used randomization scheme to minimize potential laboratory bias during testing. Please clarify if you used any blinding/unblinding approach during each of the SAC and APSD study. If yes, please provide details on what procedures were taken for blinding/unblinding.
11. In Method #s MGR-METH-546070 (Version 7.0, p. 7 of 38) for SAC study and MGR-METH-546069 (Version 6.0, p. 6 of 37) for APSD study, you stated that during sample preparation, (b) (4). Please also clarify if you did sealing for the RLD device as well.
12. According to Method # MGR-METH-546070 (Version 7.0, p. 8 of 38), for emitted dose test set-up, you stated that when attaching the mouthpiece adaptor to the (b) (4) “ensuring that the raised notch is pointing downwards at the 6 o’clock position. (Diskus/Accuhaler attach the mouthpiece adaptor to the (b) (4), ensuring that the raised notch is pointing horizontally at the 9 o’clock position.)” You also had a similar statement about mouthpiece adapter attachment to the throat in Method # MGR-METH-546069 (Version 6.0, p. 8 of 37) for APSD study. It is unclear what “raised notch” is. Therefore, please provide picture(s) to illustrate how test and RLD devices were set up with the testing apparatus in SAC and APSD studies.
13. According to the study methods, the approximate retention time for SA in your HPLC analysis is 2.00 min [Method # MGR-METH-546070 (Version 7.0, p. 13 of 38)] for SAC study and 1.8 to 2.2 min [Method # MGR-METH-546069 (Version 6.0, p. 16 of 37)] for APSD study. In addition, you also stated in the aforementioned methods that % organic is the main factor affecting SA peak retention time and therefore particular care should be given when diluting the buffer solution component with methanol during preparation of the mobile phase.

However, the chromatograms you provided show a wide range of and/or deviation from expected SA retention time in a few studies. For example:

In contrast, some other studies had SA retention time around the expected retention time (e.g. study MGR-PRO-REP-2015-103). Therefore, please also explain for this inconsistency of SA retention time among different studies. In addition, please specify your approaches taken during sample processing regarding % organic affecting SA peak retention time. Moreover, please explain for wide range of SA retention time as well as deviation from expected SA retention time observed in aforementioned 3 studies, and justify its impact on reliability of sample analysis.

14. According to your cover letter (p. 1-2 of 17) in 9/22/2016 submission, (b) (4) methods ((b) (4) for APSD determination and (b) (4) for SAC) differ from analytical procedures MDR-RGMETH-0032 and MDR-RGMETH-0031 only in the system suitability requirement for the SA retention time. However, methods MDR-RGMETH-0032 (p. 5 of 8), MDR-RGMETH-0031 (p. 4 of 8), Mylan's (p. 13 of 41) and (b) (4) (p. 11 of 40) method MGR-METH-546070, Mylan's (p. 14 of 40) and (b) (4) (p. 14 of 40) method MGR-METH-546070 all had system suitability requirement for SA retention time (b) (4). Therefore, please specify the difference you stated in the aforementioned cover letter.
15. According to the study protocols, SAC studies should be conducted on dose counter #s 60, 30 and 1; while APSD studies should be conducted on dose counter #s 59 and 2. Please list out all SAC and APSD samples that were collected on dose counter numbers other than #s 60, 30 and 1 for SAC studies and #s 59 and 2 for APSD studies. For each of these samples, please provide the detailed reason(s) for using different dose counter numbers, its supporting documents (e.g. investigational report), original actuation data, as well as corrective action taken.
16. Please provide (b) (4) SOP (b) (4) that was effective at the time of the in vitro studies in current application.

APSD Studies

17. According to the study method MGR-METH-546068 (version 6.0, p. 15 of 37), fine particle mass (FPM) is calculated (b) (4) (b) (4) when operated at 60 L/min. However, in study report MGR-REP-2015-096 (version 1.0, p. 14 of 178), you stated that FPM (b) (4) (b) (4). Therefore, please explain why you changed the calculation method for FPM.
18. Please provide detailed calculations for calculating MMAD and GSD.

Deficiencies Related to Information Common to In Vitro Studies 057755-02-04, MGR-PRO-2015-080, and 057755-02-07

Both SAC and APSD Studies

19. It is noted that there are multiple incidences of “alternative blister use” and “replacement device use” in in vitro BE studies. Please explain why there were multiple incidences of them, and the impact of it on in vitro BE studies.

SAC Studies

20. You did not provide actual dose counter numbers and % of label claim in the SAS .xpt dataset for your SAC studies. Therefore, please add a column for actual dose counter number and another column for % of labeled claim in the SAS .xpt file for your SAC studies.

APSD Studies

21. You provided mass balance in the study reports, but did not include it in the SAS .xpt file. Therefore, please add a column for mass balance in your SAS xpt file for APSD studies.

Deficiency Related to Information Common to In Vitro Studies 057755-02-04, 057755-02-07, MGR-REP-2015-092, and MGR-REP-2015-093

22. You provided 100% raw analytical data for SAC and APSD testing in your 9/22/2016 submission (Module 3.2.P.2). However, the raw data format you provided for the 4 studies above is rather granular, as each page only contains information for one sample. Please compile the raw data of each run. An example for this compiled raw data format would be your raw data for study MGR-PRO-2015-080 (9/22/2016 submission, Module 3.2.P.2\Attachment 4-4 – MGR-PRO-2015-080 – 250/50 mcg – APSD Raw Data – Comment 4 – Sequence 0009). The raw data should include all samples (including blank/diluent, standards, etc.) in a run in run sequence order.

Deficiency Related to Information Common to In Vitro Studies MGR-PRO-2015-080, and MGR-PRO-REP-2015-103

23. You provided raw data for the above studies in 9/22/2016 submission, Module 3.2.P.2. However, it is noted that these raw data are incomplete, as there are many instances that the result IDs in the run are not consecutive (e.g. 9/22/2016 submission, Module 3.2.P.2\Attachment 4-4 – MGR-PRO-2015-080 – 250/50 mcg – SAC Raw Data – Comment 4 – Sequence 0009, p. 4 of 740, result IDs 30078, 30088-30077 were missing). In addition, it is noted that raw data for blank/diluent, system suitability S1 or S2, standard check S1 and S2 are not included in raw data for SAC studies. Similarly, blank/diluent, system suitability standard SHL, LOQ, standard check SHL and SLL were not included in raw data for APSD studies. Moreover, raw data for stage 7, stage 8 for many samples (e.g. p. 6 of

aforementioned document) were not included in the raw data for APSD studies. Therefore, please submit 100% raw data (including blank/diluent, standards, etc.) in run sequence order.

Deficiencies Related to In Vitro Equivalence Study 057755-02-04 Only

SAC Study

24. You did not provide reason and supporting document for the rejection of the following sample (p. 8 of 178 of your MGR-REP-2015-096 version 1.0). Therefore, please provide this information.

Product	Batch Number	(b) (4)	Device ID	Mylan Unit	Flow Rate (L/min)
REF	5ZP8397	40		180	60

APSD Study

25. According to study report MGR-REP-2015-096, version 1.0, p. 40 of 178, you stated that “No acceptable data generated for both FP and Sal” for the following sample. Please provide the data obtained as well as supporting document for why this data was not acceptable. Please also provide SOP that pre-defines data acceptability.

Product	Batch Number	Unit	Flow Rate (L/min)	Lifestage
REF	5ZP8178	159	60	BOL

Deficiencies Related to In Vitro Equivalence Study MGR-PRO-2015-080 Only

Both SAC and APSD Studies

26. It is noted that the study protocol MGR-PRO-2015-080 you provided is version 3.0. Please provide the effective date of the 2 previous versions of the protocol.

APSD Study

27. Please provide study dates of the repeated APSD study for the 90 L/min flow rate.

28. For the following 3 samples that were repeated using new devices, you provided the reason for replacement below in study report MGR-PRO-REP-2015-080 version 1.0 (p. 9, 33, 63 of 192).

Number	Product	Batch Number	Unit	Flow Rate (L/min)	Lifestage	Reason for replacement
1	REF	5ZP0114	91R	30	BOL	Error during sampling. Mouth and throat samples were washed into the same volumetric flask.
2	TEST	631-008	37R	30	BOL	
3	REF	5ZP9882	240R	60	BOL	Stage 5 being sampled instead of stage 4.

- a) For sample #s 1 and 2 above, , mouth and throat samples were to be washed into the same flask for each device according to the study method (MDR-RGMETH-0031, Section 6.2.2, step 1). Therefore, please explain why this was considered as an error.
- b) For sample #3 above, please explain how this “stage 5 being sampled instead of stage 4” was found out.

29. For the following sample, the study report showed that it was repeated with a new device [study report MGR-PRO-REP-2015-080 version 1.0 (p. 83 and 95 of 192)], and you stated in your 9/22/2016 submission (Module 1.2\Cover Letter..., p. 2 of 17) that original data was generated. However, you did not provide reason for device replacement in your study report or in your 9/22/2016 submission. Therefore, please explain why its original assay was rejected, and provide supporting documents (e.g. investigational report) for this sample rejection.

Product	Batch Number	Unit	Flow Rate (L/min)	Lifestage
REF	5ZP9304	433R	90	EOL

Deficiency Related to In Vitro Equivalence Study 057755-02-07 Only

30. According to the study report MGR-REP-2015-097 (version 1.0, p. 13 of 178), you stated that “*for units 180 and 221 EOL 60 L/min, no acceptable data will be reported for FP and SA*”. Please provide the data obtained as well as supporting document for why this data was not acceptable. As mentioned above, please also provide SOP that pre-defined data acceptance criteria.

Deficiencies Related to Information Common to In Vitro Studies MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093 (4 kPa fixed pressure drop)

Both SAC and APSD Studies

31. Each of the SAC and APSD studies at 4 kPa fixed pressure drop was conducted on 3 lots of test and 3 lots of RLD product. For each lot, 3 test and 3 RLD devices were tested, with 3 replicates of SAC (beginning, middle, and end lifestages), and 2 replicates of APSD (beginning and end lifestages) collected from each device. You then conducted statistical comparison of geometric mean ratios at 4 kPa vs. 60 L/min. Please repeat the study with 10 test and 10 RLD devices per lot, using 3 lots of test and 3 lots of unexpired RLD product. SAC study should be tested at beginning, middle and end lifestages, while APSD studies should be tested at beginning and end lifestages. Please conduct statistical comparison of test vs. RLD product at 4 kPa pressure drop using population bioequivalence (PBE) analysis. Please refer to *Draft Guidance on Budesonide Inhalation Suspension* for step-wise procedure of the PBE analysis.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf>

Please note that other deficiencies (deficiency #s 10-18, 22, 23, 32, and 33) related to the in vitro studies MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093 (4 kPa fixed pressure drop) are also identified and listed in the current section for IN VITRO STUDIES. Please take them into consideration when you repeat your in vitro studies (4 kPa fixed pressure drop).

32. You did not provide study results in SAS .xpt format for SAC and APSD studies at 4 kPa fixed pressure drop, and thus please provide such for your repeated studies. These SAS datasets should include % of label claim for the SAC study, mass balance (% of label claim) for the APSD study, and dose counter number for both SAC and APSD studies.

Deficiency Related to In Vitro Studies MGR-PRO-REP-2015-103 Only

APSD Study

33. Based on chromatograms provided for the APSD study, it is noted that some runs had run time of 6.5 min while others had 3.5 min (9/22/2016 submission, Module 3.2.P.2\Attachment 3-7..., p. 131 of 238). Therefore, please explain why different run times were used.

PK BE STUDIES

Deficiencies Related to Pre-Study Method Validation

34. It is noted that you performed pre-study method validation on instruments (b) (4). However, additional instruments were used in the pivotal PK study (b) (4) was used in fasting study MGR001-1014; and (b) (4) was used in fasting studies MGR001-1005, MGR001-1006 and MGR001-1014). You did not provide detailed information of these additional instruments used. Therefore, please provide this information, and please be advised that according to *Guidance for Industry – Bioanalytical Method Validation* (draft guidance recommended September 2013), partial validation needs to be conducted for change(s) in instruments and/or software platforms.
35. You stated that assay selectivity was evaluated in 6 sources of human plasma (12/29/2015 submission, Module 5.3.1.4. 15-006 – Validation Study Tagging File\ Project 15-006 Validation Report, p. 6 of 16). However, you only provided representative chromatography to show selectivity. Please provide selectivity results for each of the 6 sources of human plasma.
36. Since your proposed test product has two analytes (i.e., FP and SA), please provide evidence that one analyte does not interfere with analysis of the other analyte (e.g. LQC and HQC samples of FP fortified with SA show no effect on determination of FP, and vice versa).

Deficiency Related to Fasting Studies MGR001-1005 and MGR001-1014

37. For the 2 PK studies you conducted for the 250/50 mcg strength, it is noted that each of the MGR001-1005 and MGR001-1014 studies failed to meet the bioequivalence criteria of

80.00-125.00%. You conducted pooled analysis of these 2 PK studies, and stated that the pooled analysis met the BE criteria. Please be advised that your pooled analysis is not acceptable due to the following reasons:

- a) The pooled analysis consisted of only two studies with opposite findings. It is apparent that by pooling such data together, the differences between the two studies could be balanced out and therefore, yielding a result somewhere toward to the middle and making the pooled study pass bioequivalence.
- b) Study MGR001-1005 failed to show bioequivalence. Study MGR001-1014 also failed to show bioequivalence even though the batch of Advair Diskus® was selected to represent the Advair Diskus® population. Therefore, whether the pooled analysis results can truly represent all the 250/50 mcg strength data is questionable.
- c) The pooled analysis is a post-hoc analysis, not pre-specified in a protocol or a statistical analysis plan. Therefore, the finding from the pooled analysis is viewed as hypothesis generating and is not acceptable from the statistical point of view.
- d) Your statistical model for the pooled analysis included terms for study, subject within study, period within study, treatment, and study by treatment interaction, but did not take sequence-related effects such as sequence within study into consideration. In addition, the batch-to-batch variability was not addressed in the model. Even had the pooled analysis approach/concept been accepted, the suitability of the statistical model is still questionable.

Therefore, the fasting studies MGR001-1005 and MGR001-1014 is unacceptable. Please repeat the PK BE study for the 250/50 mcg strength.

Comments For Future Submissions

38. *Guidance for Industry - Bioanalytical Method Validation* (posted September 2013) states that incurred sample reanalysis (ISR) sample selection should include “*all study subjects*”. However, your ISR studies did not include all study subjects. For your future studies, please be advised to refer to the aforementioned Guidance for ISR sample selection.
39. You submitted IND 118769 for the fasting study of the 250/50 mcg strength, but not for the 500/50 µg strength. Please be advised to submit a bio-IND prior to study commencement for your future study if the dose given in the PK study exceeds the maximum labeled single dose for the evaluation of safety.

FLOW PROFILING STUDY

Deficiencies Related to the Flow Profiling Study (MGR000-1003)

40. According to p. 40 of 321 of the study report, the reference batch (batch # 547-046) used in this study is Accuhaler™. Therefore, the flow profiling study is unacceptable due to the use

of non-US marketed RLD product. Please repeat the flow profiling study using US marketed RLD product.

It is also noted that in the clinical overview (12/29/2015 submission, Module 2.5\Clinical Overview, p. 7 of 21), you stated that “[t]he CRC749 device used in this study was identical in terms of the airway geometry (and therefore airflow paths and device resistance) and the drug-containing discs (and therefore the pharmaceutical performance) remained the same the CRC749 Clinical device used in the pivotal clinical endpoint BE study and PK BE studies with the 100/50 and 500/50 product strengths, and the Commercial device which was included in the pivotal PK BE studies with the 250/50 product strength.” Based on this statement, it appears that you used test device other than the clinical device (b) (4) and commercial device (b) (4). Please use the commercial device for the test product in your repeat flow profiling study.

Please note that other deficiencies (deficiency #s 41-46) related to the flow profiling study are also identified and listed below. Please take them into consideration when you repeat the flow profiling study.

41. According to the Information for Study Participants and Informed Consent Form (12/29/2015 submission, Module 5.3.4.1\IEC IRB Consent Form List, p. 26-27 of 95), both the test and reference devices were placed in the inhaler connecting box (ICB) in the horizontal orientation. Please specify how patients hold ICB for each device (e.g. which orientation). If same orientation was held between T and R devices, please justify the impact of device orientation on subject’s flow profile.
42. According to Figure 3 in the aforementioned Information for Study Participants and Informed Consent Form (12/29/2015 submission, Module 5.3.4.1\IEC IRB Consent Form List, p. 26-27 of 95), you removed mouthpiece cover of the test device. Please justify its impact on device resistance.
43. In the study report (12/29/2015 submission, Module 5.3.4.1\Study Report Body\MGR000-1003 Study Report, p. 40 of 321), you stated that in order to ensure that the resistance of the dry powder inhaler (DPI) was not affected by enclosing it in the ICB, the resistance of the test and reference DPIs was determined before enclosure in the ICB. This experiment was then repeated after enclosure in the ICB. The resistance of the enclosed DPI had to be $\pm 5\%$ of the resistance before the inhaler was put in the IDB; this was a key step in ensuring suitability of the enclosed DPI and the results were recorded in the batch records for the ICBs containing the inhalers. Please provide these results. In addition, please provide details of this study (e.g. study protocol/SOP and study report).
44. It is noted that the concomitant medication SAS .xpt dataset contained drug trade names but not generic names. In addition, route of administration (CM1_ROUT) and frequency was indicated by numbers (e.g. 3, 7, 17 for CM1_ROUT and 1, 5, 9 for CM1_FREQ), and it is unclear what these numbers stand for. Moreover, for start and end time of concomitant medications, you stated in your data definition file that your data format is DDMMYY10. However, values (e.g. 19029, 19640, 4565) listed in the SAS .xpt file does not match this

format. It is also unclear what those numbers in CM1_STA2, CM1_STO2, CM1_ONGO (e.g. 0, 1, 2) stand for. Therefore, please clarify so. In addition, please list out the washout/withhold period between the concomitant medications and study procedures for each subject visit.

45. For pressure drop acceleration rate (kPa/sec), you excluded the multiple values from the summary statistics [e.g. Subject (b) (6) (healthy adult subject) / device: Accuhaler™/Diskus® / manoeuvre 8; Subject (b) (6) (healthy adult subject) / device: CRC749 / manoeuvre 1]. Please provide your pre-specified acceptance criteria (e.g. in an SOP) for pressure drop acceleration rate data at the time of this study.
46. It is noted that although the use of rescue medicine is not mentioned in the study protocol or study report, you provided a SAS .xpt dataset “RESCUE”, which, according to the data definition file, is about “*Salbutamol Intake (Rescue Medication)*”. According to this dataset, multiple subjects took rescue medication. For each of these subjects, please list out the washout period between the rescue medication and study procedures for each visit. Please also justify the impact of rescue medication usage on inhalation profile of these subjects.

DEVICE ORIENTATION STUDY

Deficiency Related to the Device Orientation Study (MGR000-1004)

47. Your proposed Wixela Inhub device has a different device orientation when compared to the reference listed drug (RLD), Advair Diskus. Specifically, your Wixela Inhub device is intended to be held vertically during administration, while the Advair Diskus device is intended to be held horizontally during administration. The Agency has reviewed the Device Orientation Study submitted to your application. The study you submitted does not provide FDA with sufficient information to conclude that proposed product can be substituted with the full expectation that it will produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling, including whether the proposed product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use.

In addressing this deficiency, we refer you to the general principles in FDA’s draft guidance entitled Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA (January 2017) (available at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm536959.pdf>). Although this is draft guidance, it sets forth FDA’s current thinking regarding important principles for evaluating proposed generic combination products submitted in ANDAs. As reflected in that draft guidance, FDA recommends that applicants seek to minimize differences in the user interface of a proposed generic combination product and the RLD. You may consider modifying the design of the user interface for the Wixela Inhub device to minimize differences from the RLD product, specifically with regard to the orientation of your proposed product. To the extent that differences remain between the user interface of the proposed generic combination product and the user interface of the RLD, the guidance provides recommendations on the

identification and assessment of differences in the design of the user interface for a proposed generic combination product when compared to its RLD, including a discussion of when data from a comparative use human factors study may be warranted to address certain identified differences. It would be useful to provide the Agency with the results of the three threshold analyses (e.g., comparative labeling analysis, comparative task analyses, comparison in the design of the delivery device constituent) described in this draft guidance, as well as your overall assessment of the identified differences for your proposed product when compared to the RLD. Please note that the Agency may view the design differences for your proposed presentation as not being minor if these analyses suggest that differences in the user interface of your product as compared to that of the RLD may impact the clinical effect or safety profile of your proposed product as compared to the RLD when the proposed product is substituted for the RLD. In such cases, additional information and/or data, such as data from comparative human factors studies, may be warranted.

The Agency will consider these analyses and any comparative use human factors data or information submitted to evaluate the acceptability of the differences in device and labeling resulting from these differences in user interface, and to evaluate whether your proposed product can be substituted for the RLD with the full expectation that your proposed product will produce the same clinical effect and safety under the conditions specified in labeling when the proposed product is substituted for the RLD. Should you have an alternative approach to addressing this deficiency that you believe would be acceptable, please contact the regulatory project manager (RPM).

CLINICAL ENDPOINT STUDY

Deficiencies Related to the Office of Study Integrity and Surveillance (OSIS) Inspectional Finding for the Clinical Site

48. FDA's *Guidance for Industry - Handling and Retention of BA and BE Testing Samples* (May 2004) states "if additional supplies of the test article and the reference standard will be used by a testing facility to perform the same study or additional studies, the testing facility should retain a sufficient quantity of reserve samples from the **subsequent** shipment." (Emphasis added.) Based on the Office of Study Integrity and Surveillance (OSIS) review of the inspectional findings from FDA's inspection of several clinical sites for Study MGR001-3001, the following clinical sites did not retain reserve samples of test and reference drug products from all shipments used during the study:

Clinical site#	FEI#	Clinical site
3001010	3012251316	Prestige Clinical Research Center, Inc., Miami, FL
3001058	3011200143	AAPRI Research Institute (FKA Kent Surgical Associates, Inc.)
3001018	3009592813	Timber Lane Allergy & Asthma Associates, South Burlington, VT
3001063	3005906303	Allergy and Asthma Research Group, Eugene, OR
3001067	3007013291	Providence Clinical Research, North Hollywood, CA
3001120	3010729442	Linfriz Research Center, Coral Gables, FL

In the absence of these reserve samples, the authenticity of the test and reference products used at these clinical sites could not be verified and, accordingly, the reliability of the data from these clinical sites could not be determined.

We have concerns that the reserve samples retained by the remaining (91) clinical sites for Study MGR001-3001 are not representative of the test and reference products provided by the study sponsor to each clinical site. Therefore, for each of the clinical sites for Study MGR001-3001 not identified above, please provide (1) the number of shipments of test and reference product received from the study sponsor during the course of the study and (2) documentation to support that reserve samples were appropriately retained.

49. The FDA investigators inspected several clinical sites for study MGR001-3001. Form FDA 483 was issued at the close of inspection at Prestige Clinical Research Center, Inc. (PCRC), Miami, FL from 6/7/2016 to 6/10/2016 and 6/13/2016 to 6/15/2016. One of the observations was as follows:

“Failure to retain sealed randomization schedule prior to commencement of subject enrollment. Specifically, a sealed randomization scheme, including blinding codes, was not maintained in the possession of the clinical site prior to the dosing of the initial subject (Run-in placebo on (b) (6) and Randomized dosing on (b) (6) (b) (6) The site completed the study and was closed by the IRB on September 2015; however, the randomization scheme, which was not sealed, was sent to your site from PPD on November 6, 2015.”

It is FDA’s understanding that before the start of study MGR001-3001, the packager (b) (4) (b) (4) did not send the records with subject dosing materials, at the time of the study or before the study started. We believe that this finding applies to all 97 sites. Therefore, to enable tracing the history of actions from the time when blinding codes were assigned to dosing materials until today, please provide a copy of (b) (4) original blinding-packaging records and any log/event history, for all shipments to all 97 clinical sites.

Deficiency Related to Clinical Endpoint Study (MGR001-3001)

50. Your original protocol (dated 11/25/2013) was amended (dated 1/26/2015) during the study. The reviewer could not locate institutional review board (IRB) approval information of the original protocol and its amendment. Therefore, please provide such information.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{ See appended electronic signature page }

Bing V. Li, Ph.D.
Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5.11 Outcome Page

COMPLETED ASSIGNMENT FOR 208891 ID: 30445

Reviewer: Ma, Tian

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Wixela™ Inhub™ (fluticasone propionate and salmeterol xinafoate) Inhalation Powder, 0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ 0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>		
30445	12/29/2015	BIO	ANDA Nasal [2]	2	2	Edit	Delete
30445	12/29/2015	BIO	Consult Review (For Consults to Other Office) [1]	1	1	Edit	Delete
30445	12/29/2015	BIO	Consult Review (For Consults to Other Office) [1]	1	1	Edit	Delete
30445	12/29/2015	BIO	Consult Review (For Consults to Other Office) [1]	1	1	Edit	Delete
30445	12/29/2015	BIO	Consult Review (For Consults to Other Office) [1]	1	1	Edit	Delete
30445	12/29/2015	BIO	OSIS Inspection Report Review [1]	1	1	Edit	Delete
30445	12/29/2015	Parallel	Fasting Study (Full template) [1]	1	1	Edit	Delete
30445	12/29/2015	Parallel	Fasting Study (Full Template - Additional Analyte) [0.25]	0.25	0.25	Edit	Delete
30445	12/29/2015	Parallel	Fasting Study (Full template) [1]	1	1	Edit	Delete
30445	12/29/2015	Parallel	Fasting Study (Full Template - Additional Analyte) [0.25]	0.25	0.25	Edit	Delete
30445	12/29/2015	Parallel	Fasting Study (Full template) [1]	1	1	Edit	Delete
30445	12/29/2015	Parallel	Fasting Study (Full Template - Additional Analyte) [0.25]	0.25	0.25	Edit	Delete
30445	12/29/2015	Parallel	Fasting Study (Full template) [1]	1	1	Edit	Delete

30445	12/29/2015	Parallel	Fasting Study (Full Template - Additional Analyte) [0.25]	0.25	0.25	Edit	Delete
30445	12/29/2015	Parallel	In-Vitro Study (Nasal/Inhaled Dosage Forms) Per Study [0.5]	0.5	0.5	Edit	Delete
30445	12/29/2015	Parallel	In-Vitro Study (Nasal/Inhaled Dosage Forms) Per Study [0.5]	0.5	0.5	Edit	Delete
30445	12/29/2015	Parallel	In-Vitro Study (Nasal/Inhaled Dosage Forms) Per Study [0.5]	0.5	0.5	Edit	Delete
30445	12/29/2015	Parallel	In-Vitro Study (Nasal/Inhaled Dosage Forms) Per Study [0.5]	0.5	0.5	Edit	Delete
30445	12/29/2015	Parallel	In-Vitro Study (Nasal/Inhaled Dosage Forms) Per Study [0.5]	0.5	0.5	Edit	Delete
30445	12/29/2015	Parallel	In-Vitro Study (Nasal/Inhaled Dosage Forms) Per Study [0.5]	0.5	0.5	Edit	Delete
30445	12/29/2015	Parallel	In-Vitro Study (Nasal/Inhaled Dosage Forms) Per Study [0.5]	0.5	0.5	Edit	Delete
30445	12/29/2015	Parallel	In-Vitro Study (Nasal/Inhaled Dosage Forms) Per Study [0.5]	0.5	0.5	Edit	Delete
30445	12/29/2015	Parallel	In-Vitro Study (Nasal/Inhaled Dosage Forms) Per Study [0.5]	0.5	0.5	Edit	Delete
30445	12/29/2015	Parallel	In-Vitro Study (Nasal/Inhaled Dosage Forms) Per Study [0.5]	0.5	0.5	Edit	Delete
30445	12/29/2015	Parallel	In-Vitro Study (Nasal/Inhaled Dosage Forms) Per Study [0.5]	0.5	0.5	Edit	Delete
30445	12/29/2015	Parallel	In-Vitro Study (Nasal/Inhaled Dosage Forms) Per Study [0.5]	0.5	0.5	Edit	Delete
30445	12/29/2015	Parallel	In-Vitro Study (Nasal/Inhaled Dosage Forms) Per Study [0.5]	0.5	0.5	Edit	Delete
30445	12/29/2015	Parallel	PD Study Using Dose Scale Method [2]	2	2	Edit	Delete
30445	12/29/2015	Parallel	Anything Else Not Listed	1	1	Edit	Delete

			(Discuss With Management) [1]				
30445	12/29/2015	Parallel	Anything Else Not Listed (Discuss With Management) [1]	1	1	Edit	Delete
30445	12/29/2015	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1	Edit	Delete
30445	12/29/2015	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1	Edit	Delete
30445	12/29/2015	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1	Edit	Delete
30445	12/29/2015	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1	Edit	Delete
30445	12/29/2015	Parallel	OSIS Inspection Report: Review of Parent (Per application) [1]	1	1	Edit	Delete
				Total:	27		

Easily Correctable Deficiency (ECD)

ANDA No.	208891			
Drug Product Name	Wixela™ Inhub™ (fluticasone propionate and salmeterol Xinafoate) Inhalation Powder			
Strength(s)	0.1 mg/EQ 0.05 mg base per inhalation, 0.25 mg/EQ 0.05 mg base per inhalation, and 0.5 mg/EQ 0.05 mg base per inhalation			
Applicant Name	Mylan Pharmaceuticals Inc.			
Applicant Address	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310			
US Agent Name and the mailing address	Joseph J. SobECKi, Head of Regulatory Affairs - North America			
US agent's Telephone Number	(304) 599-2595 x 6429			
US Agent's Fax Number	(304) 285-6407			
US Agent's Email Address	joseph.SobECKi@mylan.com			
Original Submission Date(s)	December 29, 2015			
Submission Date(s) of Amendment(s) Under Review	February 15, 2016 (concentration data, graphs and SAS output for pharmacokinetic studies; tabular listing of all clinical studies; information on unblinding, randomization and datasets for the clinical endpoint study)			
Reviewer	Tian Ma, Ph.D.			
Study Number (s)	MGR001-1006	MGR001-1007	MGR001-1005	MGR001-1014
Study Type (s)	Fasting	Fasting	Fasting (failed, but was used in pooled analysis with MGR001-1014)	Fasting (failed, but was used in pooled analysis with MGR001-1005)
Strength (s)	0.1 mg/EQ 0.05 mg base per inhalation	0.5 mg/EQ 0.05 mg base per inhalation	0.25 mg/EQ 0.05 mg base per inhalation	0.25 mg/EQ 0.05 mg base per inhalation
Clinical Site	Worldwide Clinical Trials Early Phase Services, LLC			
Clinical Site Address	2455 NE Loop 410, Suite 150 San Antonio, Texas 78217			
Analytical Site	Mylan Pharmaceuticals Inc.			
Analytical Site Address	Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505			
Study Number (s)	057755-02-04	MGF-PRO-2015-080	057755-02-07	
Study Type (s)	In Vitro BE [single actuation content (SAC) and aerodynamic particle size distribution (APSD)]	In Vitro BE (SAC and APSD)	In Vitro BE (SAC and APSD)	
Strength (s)	0.1 mg/EQ 0.05 mg base per inhalation	0.25 mg/EQ 0.05 mg base per inhalation	0.5 mg/EQ 0.05 mg base per inhalation	

Analytical Site	(b) (4)	Mylan Global Respiratory Group	(b) (4)
Analytical Site Address		Sandwich, Kent. UK	
Study Number (s)	MGR-REP-2015-092	MGR-PRO-REP-2015-103	MGR-REP-2015-093
Study Type (s)	Pressure Differential (4 kPa) (SAC and APSD)	Pressure Differential (4 kPa) (SAC and APSD)	Pressure Differential (4 kPa) (SAC and APSD)
Strength (s)	0.1 mg/EQ 0.05 mg base per inhalation	0.25 mg/EQ 0.05 mg base per inhalation	0.5 mg/EQ 0.05 mg base per inhalation
Analytical Site	(b) (4)	Mylan Global Respiratory Group	(b) (4)
Analytical Site Address		Sandwich, Kent. UK	
Study Number (s)	MGR001-3001		
Study Type (s)	Clinical Endpoint		
Strength (s)	0.1 mg/EQ 0.05 mg base per inhalation		
Clinical Site	Site Number	Principal Investigator and Location	Address
	3001001	Idalia A. Acosta, Miami, FL 33015	5941 NW 173 Dr, Ste 1 Miami, FL 33015
	3001002	Niran J. Amar, Waco, TX 76712	333 Londonderry Dr, Ste 110 Waco, TX 76712
	3001003	James W. Baker, Portland, OR 97223	9495 SW Locust St Portland, OR 97223
	3001004	G Daniel Brooks, Bellevue, NE 68123-4303	3503 Samson Way, Ste 108 Bellevue, NE 68123-4303
	3001006	Warner W. Carr, Mission Viejo, CA 92691	27800 Medical Center Rd, #240/#244 Mission Viejo, CA 92691
	3001007	Jonathan Corren, Los Angeles, CA 90025	10780 Santa Monica Blvd Ste 280 Los Angeles, CA 90025
	3001008	David Cypcar, Asheville, NC 28801	14 McDowell St Asheville, NC 28801
	3001009	Joseph D. Diaz, San Antonio, TX 78229	2414 Babcock Rd, Ste 108-109 San Antonio, TX 78229
	3001010	Manuel A. Franco, Miami, FL 33133	2720 SW 37 Ave Miami, FL 33133
	3001011	Sherwin A. Gillman, Orange, CA 92868	725 West La Veta Ave, Ste 100 Orange, CA 92868
	3001012	John T. Given, Canton, OH 44718	Allergy, Respiratory & Sleep Center 4048 Dressier Rd NW, Ste 100 Canton, OH 44718

3001013	Stanley Goldstein, Rockville Centre, NY 11570	242 Merrick Rd, Ste 401 Rockville Centre, NY 11570
3001014	Richard G. Gower, Spokane, WA 99202	324 S Sherman St Spokane, WA 99202
3001015	Leon S. Greos, Centennial, CO 80112	14000 E. Arapahoe Rd, Ste 260 Centennial, CO 80112
3001016	Amina Z. Haggag, Anaheim, CA 92801	Anaheim Clinical Trials, LLC 1085 N. Harbor Blvd Anaheim, CA 92801
3001017	Frank C. Hampel Jr., New Braunfels, TX 78130	705-A Landa St New Braunfels, TX 78130
3001018	Edward Francis Kent Jr., South Burlington, VT 05403	Timber Lane Allergy & Asthma Research, LLC 54 Timber Lane South Burlington, VT 05403
3001019	Phillip E. Korenblat, St. Louis, MO 63141	1040 N Mason Rd, Ste 112 St. Louis, MO 63141
3001020	Craig Fred LaForce, Raleigh, NC 27607	North Carolina Clinical Research 2615 Lake Dr, Ste 301 Raleigh, NC 27607
3001022	Edward E. Lisberg, River Forest, IL 60305	7420 Central Ave, Ste 2020 River Forest, IL 60305
3001023	Stephen Maddock, Lenexa, KS 66219	Analab Clinical Research Inc 15335 W 95th St Lenexa, KS 66219
3001024	Lyndon E. Mansfield, El Paso, TX 79903	2121 Wyoming Ave El Paso, TX 79903
3001025	Jonathan Matz, Baltimore, MD 21236	Chesapeake Clinical Research, Inc 7939 Honeygo Blvd, Ste 219 Baltimore, MD 21236
3001026	Curtis J. Mello, North Dartmouth, MA 02747	370 Faunce Corner Rd 2nd Fl North Dartmouth, MA 02747
3001027	S. David Miller, North Dartmouth, MA 02747	Northeast Medical Research Associates, Inc. 49 State Rd Watuppa Bldg, Ste 202 North Dartmouth, MA 02747
3001028	Anthony Montanaro, Portland, OR 97202	6327 SE Milwaukie Ave, 2nd Floor Portland, OR 97202
3001029	Nancy K. Ostrom, San Diego, CA 92123	5776 Ruffin Rd San Diego, CA 92123

3001031	Amit I. Patel, Riverside, CA 92506	Integrated Research Group, Inc. 4646 Brockton Ave, Ste 202-3 Riverside, CA 92506
3001032	David S. Pearlman, Denver, CO 80230	125 Rampart Way, Ste 150 Denver, CO 80230
3001033	Andrew J. Pedinoff, Skillman, NJ 08558	Montgomery Professional Center 24 Vreeland Dr Skillman, NJ 08558
3001034	Warren William Pleskow, Encinitas, CA 92024	317 N El Camino Real, Ste 506 Encinitas, CA 92024
3001035	Larry S. Posner, Napa, CA 94558	1100 Pear Tree Lane Napa, CA 94558
3001036	Gordon D. Raphael, Bethesda, MD 20814	4915 Auburn Ave, Ste 202 Bethesda, MD 20814
3001037	Paul H. Ratner, San Antonio, TX 78229	7711 Louis Pasteur Dr, Ste 406 San Antonio, TX 78229
3001038	Syed M. Rehman, Toledo, OH 43617	7247 W. Central Ave, Ste A Toledo, OH 43617
3001039	Michael E. Ruff, Dallas, TX 75231	5499 Glen Lakes Dr, Ste 200 Dallas, TX 75231
3001040	Russell A. Settipane, East Providence, RI 02914	450 Veterans Memorial Pkwy #15 East Providence, RI 02914
3001041	Ellen R. Sher, Ocean, NJ 07712	802 West Park Ave, Ste 213 Ocean, NJ 07712
3001042	Lawrence D. Sher, Rolling Hills Estates, CA 90274	550 Deep Valley Dr, Ste 317 Rolling Hills Estates, CA 90274
3001045	Stephen A. Tilles, Seattle, WA 98115	9725 Third Ave NE, Ste 500 Seattle, WA 98115
3001046	Mark L. Vandewalker, Columbia, MO 65203	601 W Nifong Bldg 2-A Columbia, MO 65203
3001047	David P. Chen, Bozeman, MT 59718	950 Stoneridge Dr, Ste 1 Bozeman, MT 59718
*3001048	Patrick H. Win, Shiloh, IL 62269	325 Tamarack Lane Shiloh, IL 62269
3001049	John A. Winder, Sylvania, OH 43560	5800 Monroe St, Ste A-9 Sylvania, OH 43560
3001050	James D. Wolfe, San Jose, CA 95117	4050 Moorpark Ave, Ste 6 San Jose, CA 95117
3001051	Robert N. Wolfe, Los Angeles, CA 90048	Southern California Institute For Respiratory Diseases, Inc. 8635 West 3rd St, Ste 965-W Los Angeles, CA 90048
3001053	Thomas R. Murphy, N. Charleston, SC 29420	7555 Northside Dr N. Charleston, SC 29420

3001054	David I. Bernstein, Cincinnati, OH 45231	Bernstein Clinical Research Center, LLC 8444 Winton Rd Cincinnati, OH 45231
3001055	Charles M. Fogarty, Spartanburg, SC 29303	485 Simuel Rd Spartanburg, SC 29303
3001056	Philip C. Halverson, Minneapolis, MN 55402	825 Nicollet Mall, Ste 1135 Minneapolis, MN 55402
3001057	Sanchayita "Ita" Tripathy, Rolla, MO 65401	509 East 10th St Rolla, MO 65401
3001058	John F. Zwetchkenbaum, Warwick, RI 02886	470 Toll Gate Rd, Ste 203 Warwick, RI 02886
3001059	Dario D. Altamirano, Hialeah, FL 33012	900 W 49th St, Ste 430 Hialeah, FL 33012
3001060	Philip A. Emrie, Wheat Ridge, CO 80033	8550 W 38th Ave, Ste 202 Wheat Ridge, CO 80033
3001061	Timothy Harrison Elder, Gainesville, FL 32607	4343 W Newberry Rd, Ste 17 Gainesville, FL 32607
3001062	Gregory J. Feldman, Spartanburg, SC 29303	141 Harold Fleming Court Spartanburg, SC 29303
3001063	Jason H. Friesen, Eugene, OR 97401	Allergy and Asthma Research Group 1488 Oak St Eugene, OR 97401
3001064	Gregory M. Gottschlich, Cincinnati, OH 45242	9395 Kenwood Rd, Ste 101 Cincinnati, OH 45242
3001065	James Lawrence Pearle, Fullerton, CA 92835	301 W Bastanchury Rd, Ste 220 Fullerton, CA 92835
*3001066	Ronald H. Saff, Tallahassee, FL 32308	Allergy & Asthma Diagnostic Treatment Center 2300 Centerville Rd Tallahassee, FL 32308
3001067	Teresa S. Sligh, North Hollywood, CA 91606	6400 Laurel Canyon Blvd, Ste 300A North Hollywood, CA 91606
3001068	Kurt W. Jensen, Tacoma, WA 98405	Pulmonary Consultants, PLLC 1708 S. Yakima Ave, Ste 300 Tacoma, WA 98405
3001069	Edward M. Kerwin, Medford, OR 97504	Clinical Research Institute of Southern Oregon, PC 3860 Crater Lake Ave, Ste B Medford, OR 97504
3001071	Daniel F. Soteres, Colorado Springs, CO 80907	2709 North Tejon St Colorado Springs, CO 80907
3001074	William R. Lumry, Dallas, TX 75231	10100 N Central Expressway, Ste 125 Dallas, TX 75231
3001075	Mikhail Palatnik, Gold River, CA 95670	2485 Sunrise Blvd Gold River, CA 95670

3001076	Paul Y. Qaqundah, Huntington Beach, CA 92647	17822 Beach Blvd, Ste 278 Huntington Beach, CA 92647
3001077	Weily Soong, Birmingham, AL 35209	504 Brookwood Blvd, Ste 250 Birmingham, AL 35209
3001078	Selwyn Spangenthal, Charlotte, NC 28207	1918 Randolph Rd, Ste 440 Charlotte, NC 28207
*3001079	William W. Storms, Colorado Springs, CO 80907	1625 Medical Center Point, Ste 190 Colorado Springs, CO 80907
3001080	Martha V. White, Wheaton, MD 20902	11002 Veirs Mill Rd, Ste 414 Wheaton, MD 20902
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3001082	Vosudesh K. Pai, Lawrenceville, GA 30046	555 Old Norcross Rd, Ste 250 Lawrenceville, GA 30046
3001083	Paul A. Shapero, Bangor, ME 04401	700 Mt. Hope Ave, Ste 430 Bangor, ME 04401
3001084	Daniel Sousa, Fall River, MA 02720	373 New Boston Rd Fall River, MA 02720
3001085	Sheldon Spector, Los Angeles, CA 90025	11645 Wilshire Blvd, Ste 1155 Los Angeles, CA 90025
3001086	Gary C. Steven, Greenfield, WI 53228	8585 W Forest Home Ave, Ste 200 Greenfield, WI 53228
3001087	Manuel A. Fernandez- Gonzalez, Miami, FL 33135	590 SW 27th Ave Miami, FL 33135
3001088	Agustin J. Latorre, Miami, FL 33155	6850 Coral Way, Ste 409 Miami, FL 33155
3001089	Robert S. Call, Henrico, VA 23233	9920 Independence Park Dr, Ste 101 Henrico, VA 23233
3001090	Marcy Jo Gousse, Smithfield, PA 15478	100 Ridge View Dr, Ste 3 Smithfield, PA 15478
3001091	Anoshie Ratnayake, Costa Mesa, CA 92626	3545 Howard Way Costa Mesa, CA 92626
3001092	Marvin Kalafer, Jenkintown, PA 19046	815 Greenwood Ave, Ste 12 Jenkintown, PA 19046
3001093	Santiago Reyes, Oklahoma City, OK 73112	3366 NW Expressway, Bldg D, Ste 330 Oklahoma City, OK 73112
3001095	Karl V. Sitz, Little Rock, AR 72205	18 Corporate Hill, Ste 110 Little Rock, AR 72205
3001096	Stephen G. Basheda, Pittsburgh, PA 15243	1050 Bower Hill Rd, Ste 307 Pittsburgh, PA 15243
3001097	Ifikhar Hussain, Tulsa, OK 74136	7307 S. Yale Ave, Ste 200 Tulsa, OK 74136

	3001100	Manav Singla, White Marsh, MD 21162	Asthma Allergy & Sinus Center 5430 Campbell Blvd, Ste 103 White Marsh, MD 21162
	3001102	Daniel Rodriguez, New Port Richey, FL 34653	Advanced Research Institute, Inc. 7114 Congress St New Port Richey, FL 34653
	3001104	Edward Joseph Campbell, Provo, UT 84604	2230 North at University Pkwy Cottontree Square, Bldg 6A Provo, UT 84604
	3001107	Stephen Ryan, Tacoma, WA 98405	316 Martin Luther King Jr. Way, Ste 401 Tacoma, WA 98405
	3001108	Tonny Tanus, Bakersfield, CA 93301	2116 17th St Bakersfield, CA 93301
	3001109	Carl Thornblade, Missoula, MT 59808	2683 Palmer St, Ste B Missoula, MT 59808
	3001111	Miguel E. Trevino, Clearwater, FL 33756	1573 South Fort Harrison Ave Clearwater, FL 33756
	3001112	Steven F. Weinstein, Huntington Beach, CA 92647	Allergy and Asthma Specialists Medical Group 17742 Beach Blvd, Ste 310 Huntington Beach, CA 92647
	3001114	David Fuentes, Boerne, TX 78006	1420 River Rd, Ste 100 Boerne, TX 78006
	3001115	Susan L. Andrew, Dickinson, TX 77539	914 FM 517 Road West Dickinson, TX 77539
	*3001116	William L. Ebbeling, Fresno, CA 93720	1646 E. Herndon Ave, Ste 106 Fresno, CA 93720
	3001119	Bruce A. DeCotiis, Brick, NJ 08724	1673 Hwy 88 West Brick, NJ 08724
	3001120	Ernesto Diaz, Coral Gables, FL 33134	5200 SW 8th St, Ste 119-120 Coral Gables, FL 33134
	3001122	Lawrence P. Landwehr, Warrensburg, MO 64093	407A East Russell Ave, Ste 3 Warrensburg, MO 64093
	Clinical Site Address	Please see table above	
Study Number (s)	MGR000-1003		
Study Type (s)	Flow Profiling		
Strength (s)	N/A (empty inhaler which did not contain drug or placebo)		
Clinical Site	Site	Principal Investigator	Address
	1	Dominik Kappeler	Inamed Clinical Unit, 82131 Gauting, Germany
	2	Isabelle Schenkenberger	Clinical Research Berlin GbR; 10787 Berlin, Germany

	3	Prof. Dr. med. Walter Dorsch	Practice for Child and Adolescent Medicine, Allergy, Pediatric Pulmonology, Naturopathic, 81379 Munich, Germany
	4	Dr. med. Manfred Praun	Practice for Child and Adolescent Medicine Dr. Praun & Dr. Stiebing, 82205 Gilching, Germany
	5 (not activated)	Prof. Dr. med. Stefan Zielen	University Hospital Johann Wolfgang Goethe-Universität Frankfurt/Main, Centre for children and adolescents, Departement of paediatric pneumology, allergology and cystic fibrosis, 60590 Frankfurt/Main, Germany
Clinical Site Address	Please see table above		
Study Number (s)	MGR000-1004		
Study Type (s)	Device Orientation		
Strength (s)	N/A (empty inhaler which did not contain drug or placebo)		
Clinical Site	Not provided		
Clinical Site Address	Not provided		
OSIS Status	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete		<u>Year 3 ANDAs</u> ☒ To Be Determined by OSIS ☐ Pending For Cause Inspection
OVERALL REVIEW RESULT	INADEQUATE		
REVISED/NEW DRAFT GUIDANCE INCLUDED	NO		
COMMUNICATION	☒ ECD ☐ IR ☐ NOT APPLICABLE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1,2	Fasting	0.1 mg/EQ 0.05 mg base per inhalation	INADEQUATE
1,2	Fasting	0.5 mg/EQ	INADEQUATE

		0.05 mg base per inhalation	
1,2	Fasting (failed, but was used in pooled analysis with MGR001-1014)	0.25 mg/EQ 0.05 mg base per inhalation	INADEQUATE
1,2	Fasting (failed, but was used in pooled analysis with MGR001-1005)	0.25 mg/EQ 0.05 mg base per inhalation	INADEQUATE
1	In Vitro BE (SAC and APSD)	0.1 mg/EQ 0.05 mg base per inhalation	INADEQUATE
1	In Vitro BE (SAC and APSD)	0.25 mg/EQ 0.05 mg base per inhalation	INADEQUATE
1	In Vitro BE (SAC and APSD)	0.5 mg/EQ 0.05 mg base per inhalation	INADEQUATE
1	Pressure Differential (4 kPa) (SAC and APSD)	0.1 mg/EQ 0.05 mg base per inhalation	INADEQUATE
1	Pressure Differential (4 kPa) (SAC and APSD)	0.25 mg/EQ 0.05 mg base per inhalation	INADEQUATE
1	Pressure Differential (4 kPa) (SAC and APSD)	0.5 mg/EQ 0.05 mg base per inhalation	INADEQUATE
1,2	Clinical Endpoint	0.1 mg/EQ 0.05 mg base per inhalation	INADEQUATE
1,2	Flow Profiling Study	N/A (empty inhaler which did not contain drug or placebo)	INADEQUATE
1	Device Orientation	N/A (empty inhaler which did not contain drug or placebo)	INADEQUATE

* The firm stated that these sites screened subjects but did not enroll any subjects.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCY* identified during the full ANDA review and the current ANDA review cycle will remain open. The following comment should be communicated to the firm.

Deficiencies Related to Information Common to All In Vitro Studies (057755-02-04, MGF-PRO-2015-080, 057755-02-07, MGR-REP-2015-092, MGR-PRO-REP-2015-103, and MGR-REP-2015-093)

1. Please provide MGR-METH-546070 (v. 7.0) [test method for the emitted dose study], and MGR-METH-546069 (v. 6.0) [test method of the aerodynamic particle size distribution (APSD) study].
2. You provided your single actuation content (SAC) and APSD study results in pdf format. Please provide it in SAS .xpt format.

In addition, it is noticed that you have repeats using a new device for multiple units in Studies 057755-02-04, MGF-PRO-2015-080 and 057755-02-07. Please provide the study results with their original value in one SAS .xpt file, and with their repeat values in a separate SAS .xpt file.

3. Please provide 20% serial chromatograms for each of your SAC and APSD study.
4. For each of your SAC and APSD study, you did not provide 100% raw numerical data (analyst's printouts) for all analytical runs (accepted and rejected) conducted during the UPLC sample analysis of these studies. The raw numerical data should include the data of peak area/height for the drug, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all samples, calibration standard samples, and quality control samples.

Deficiency Related to In Vitro Equivalence Studies 057755-02-04 and 057755-02-07

5. According to your study reports of the aforementioned studies, it is noted that you repeated several samples in your SAC and APSD study (e.g. 12/29/2015 submission, Module 3.2.P.2. Pharmaceutical Development\In Vitro Bio Equivalence Report – 100/50mcg – MGR-REP-2015-096, p. 5 of 181, (b) (4) device ID 115, Mylan unit 1R; 12/29/2015 submission, Module 3.2.P.2. Pharmaceutical Development\In Vitro Bio Equivalence Report – 500/50mcg – MGR-REP-2015-097, p. 6 of 181, (b) (4) device ID 111, Mylan unit 34R). For each of these repeat samples, please explain why their original assay was rejected, and please provide supporting documents (e.g. investigational report) for these sample rejections.

Deficiencies Related to In Vitro Equivalence Study MGF-PRO-2015-080 Only

6. According to your study report, the original samples of the following repeat samples were rejected due to poor chromatography. Please provide the rejected chromatograms of their

original samples as well as rejected and/or accepted chromatograms of these repeat samples.

Study	Flow Rate (L/min)	Lifestage	Analyte	Product (T/R)	Lot	Repeat Unit
APSD	60	Beginning	Fluticasone propionate (FP)	R	5ZP9304	198R
APSD	60	Beginning	Salmeterol	R	5ZP9304	198R
APSD	90 (original testing)	Beginning	FP	T	631-007	248R
APSD	90 (original testing)	Beginning	Salmeterol	T	631-007	248R

- In your study report, you stated that after completion of the initial testing for the study, *“it was discovered that the flow meter used for the APSD testing at 90 L/min failed its calibration and was subsequently reading incorrect flow values. Therefore the APSD testing was repeated for the 90 L/min flow rate (MGR-PRO-2015-080 v3.0).”* Please provide supporting documentation of the flow meter failure, the incorrect flow values measured, and corrective actions taken.

Deficiencies Related to All Pivotal Fasting Studies (MGR001-1006, MGR001-1007, MGR001-1005 and MGR001-1014)

- Please provide documentation demonstrating if the quality control samples (QCs) and calibration curve standards (CCs) were processed along with the subject samples in the same processing batch prior to analysis on LC-MS/MS.
- It is noticed that for samples identified for reassay, many of their original concentrations were listed as “not reportable”, “ALQ” or “BLQ”. Please provide their original concentration numbers (e.g. 12.34 pg/mL instead of “not reportable”) for each of the samples identified for reassay.

Deficiencies Related to Fasting Study MGR001-1006 Only

- For the 2 samples (Subject (b) (6), Period 2, 3 hrs; and Subject (b) (6), Period 1, 24 hrs) that were reassayed for FP and salmeterol due to poor chromatography, you provided their rejected chromatograms. Please also provide the accepted chromatograms of these reassay samples.
- In your bioanalytical report, you stated that the reassay of sample Subject (b) (6), Period 1, 0.08 hr for FP and salmeterol failed due to *“documented sample processing error – insufficient volume in Aliquot 1, Aliquot 2 was utilized for re-assay in Run 78”*.

According to your numerical raw data, the response for internal standard (IS) was acceptable (within 40%-180% of mean IS of its run as per SOP MGWBIO-SOP-BIO-GEN-0020). Therefore, please explain this discrepancy (you stated that there was insufficient volume, but IS response of this sample was acceptable) and explain how and when insufficient volume in Aliquot 1 was identified.

12. For Subject (b) (6) reinjection (Run ID 63) that had a run status as “N/A”, you stated that the run was “*not imported into (b) (4) due to analyst error (incorrect plate was injected)*”. You did not provide numerical raw data for this run. Please provide this information, and please also clarify which plate was incorrectly injected, and how it was identified.

Deficiencies Related to Fasting Study MGR001-1007 Only

13. For Subject (b) (6), Period 2, 3 hrs that were reassayed for FP due to “documented sample processing error – broken vial”, this sample still meets acceptance criteria for IS. Please explain this discrepancy (you stated that vial was broken, but IS response of this sample was acceptable) and explain how and when broken vial was identified.
14. You stated that the salmeterol run for Subject (b) (6) (Run #23) was rejected due to poor chromatography for salmeterol. Please provide the rejected chromatograms of this run and the accepted chromatograms of its repeat run.

Deficiencies Related to Fasting Study MGR001-1005 Only

15. Three (3) samples (Subject (b) (6), Period 2, 0.03 hr, 0.08 hr and 8 hrs) were reassayed for FP and salmeterol due to “documented sample processing error – insufficient sample volume”. According to the numerical raw data, the response for IS of these samples was acceptable (within 40%-180% of mean IS of its run). Therefore, please explain this discrepancy (you stated that there was insufficient volume, but IS response of these samples was acceptable) and explain how and when insufficient volume was identified.
16. For sample Subject (b) (6) Period 1, 0.08 hr that was reassayed for FP and salmeterol due to poor chromatography, please provide the rejected and accepted chromatograms of this sample.
17. You stated that the FP and salmeterol runs for Subjects (b) (6) (Run #s 23 and 34) were rejected due to “*sample processing/analyst error-plate was lost during assay procedure*”. Please provide numerical raw data of the original runs, as well as investigational report of this plate lost and corrective actions taken.

Deficiencies Related to Fasting Study MGR001-1014 Only

18. In your bioanalytical report, you stated that in Run #27, the carry-over check blank slightly exceeded 20% of the LLOQ peak response ratio for FP (23.6%). This carryover check blank sample was then re-injected to determine whether the initial result was due to autosampler carryover or to a small amount of FP present in the sample. You stated that

the re-injection confirmed the presence of the FP peak, “*indicating that there had been no significant carryover in the run*” (12/29/2015 submission, Module 5.3.1.4. mgr001-1014 – Bioanalytical Study Tagging File\Legacy Clinical Study Report\MGR001-1014 Bioanalytical Report, p. 9-10 of 13). Please explain how this conclusion was made, given that FP peak was present.

19. You stated that the FP and salmeterol run for Subject (b) (6) and Subject (b) (6) (Period 1) (Run # 50) was rejected because “*plate was lost during assay procedure (leaking (b) (4) tip)*”. You did not provide numerical raw data for this run. Therefore, please provide so, and please also provide investigational report of this plate lost and corrective actions taken.
20. You stated that the FP reassay run (Run # 48) was rejected because it did not meet batch acceptance criteria for FP QCs. However, among the 14 QCs included in this run, only 2 (1 mid QC “FZ CX 1” and 1 high QC “FZ D1”) were not within 15% of the theoretical value for FP. Therefore, please explain why this run was rejected.

Deficiencies Related to the Flow Profiling Study (MGR000-1003)

21. You provided your inhaled flow rate study datasets (e.g. “flow profile”, “adverse event”, “medication”, and “analysis sets and CIP violators”) in pdf format. Please also provide them in SAS .xpt format.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 208891

STATISTICAL REVIEW

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

ANDA/Sequence Number: 208891/0021 (Amendment 22)

Drug Name: Fluticasone Propionate and Salmeterol Inhalation Powder, 100/50 µg, 250/50 µg, and 500/50 µg

Applicant: Mylan Pharmaceuticals Inc.

Reference Listed Drug: Advair Diskus[®] 100/50 µg, 250/50 µg, and 500/50 µg (NDA 021077)

Indication: Treatment of asthma in patients aged 4 years and older and maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease

Date(s): FDA Received Date: 8/28/2017
Review Assignment Date: 12/5/2017
Mid Cycle Date: 2/25/2018
Review Goal Date: 6/12/2018

Biometrics Division: DBVIII

Statistical Primary Reviewer: Youngsook Lee, Ph.D.

Statistical Secondary Reviewer: Yu-Te Wu, Ph.D.

Division of Clinical Review: OGD/OB/DCR

Clinical Primary Reviewer: Michael Spagnola, MD

Clinical Secondary Reviewer: Carol Kim, Pharm.D.

Keywords: Asthma, FEV₁, AUEC₀₋₁₂, Equivalence Test, Two One-Sided Tests, Fieller's Theorem, Superiority Test

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1 EXECUTIVE SUMMARY

The purpose of this review is to provide statistical assessment of clinical endpoint study MGR001-3001 of Mylan Pharmaceuticals Inc. The aim of the study is to confirm the local bioequivalence of the test product, MGR001 100/50 (fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder) versus the reference listed drug (RLD), Advair Diskus[®] 100/50 after oral inhalation of single and multiple doses (twice a day for 4 weeks). This statistical review will aid FDA Office of Generic Drugs in making an informed decision on approval of the test product.

1.1 Conclusions and Recommendations

Equivalence is established between the test product and RLD in FDA Day 1 PP population and FDA Day 29 PP population. For FDA PP population which excludes subjects with protocol violations affecting either Day 1 endpoint or Day 29 endpoint, equivalence is not established for Day 1 endpoint but established for Day 29 endpoint. For both primary endpoints, the test product and RLD are superior to placebo.

1.2 Brief Overview

The applicant developed MGR001, fluticasone propionate and salmeterol inhalation powder, pre-dispensed in a multi-dose dry powder inhaler, CRC749 as a generic version of Advair Diskus[®]. Advair Diskus[®] was approved by FDA in 2000 for treatment of asthma in patients aged 4 years and older and maintenance treatment of airflow obstruction. The applicant submitted the clinical study report and data of clinical endpoint study MGR001-3001 in the original Abbreviated New Drug Application (ANDA) 208891 on 12/29/2015, seeking approval of the test product.

Study MGR001-3001 is a multi-center, randomized, double-blind, double-dummy, placebo-controlled, parallel group study to determine the local equivalence of multiple doses of MGR001 to Advair Diskus[®] administered via oral inhalation in male or female subjects aged 18 years or older with asthma. The study consists of two periods: 4-week Single-Blind Placebo Run-in Period and 4-week Double-Blind Treatment Period. During Single-Blind Placebo Run-in Period, subjects received the CRC749 inhaler containing placebo. During Double-Blind Treatment Period, subjects were randomly assigned to receive one of the 3 treatments: test, RLD, and placebo (5:5:1). In order to maintain the double-blind, double-dummy dosing technique was utilized and subjects were required to make one inhalation twice a day from each of 2 inhalers, CRC749 and Diskus[®], containing active or placebo for each study treatment.

The FDA co-primary endpoints are: change from baseline for FEV₁ AUEC₀₋₁₂ on Day 1 (Day 1 endpoint) and change from baseline for FEV₁ trough on Day 29 (Day 29 endpoint).

The FDA equivalence analyses use three FDA Per-Protocol (PP) populations: FDA Day 1 PP, FDA Day 29 PP, and FDA PP. FDA Day 1 PP is used for Day 1 endpoint analysis and FDA 29 PP is used for Day 29 endpoint. FDA PP is used for both endpoints.

The FDA superiority analyses use the FDA modified Intent-to-Treat (mITT) population which includes all randomized subjects who took at least one dose of study product.

1.3 Statistical Findings and Issues

No major statistical issue that affects primary endpoint analysis results is found during the review. The differences in equivalence analysis results between the applicant and FDA are mainly caused by the differences in the PP populations. The applicant's PP population excludes a subject who had significant protocol violations which affect both primary endpoints. FDA defines a PP population separately for each of the primary endpoints (FDA Day 1 PP and FDA Day 29 PP) and excludes subject who had protocol violations which affect only the corresponding primary endpoint. FDA also defines a single PP population (FDA PP) and excludes subjects who had a protocol violation which affects either of the primary endpoints.

2 INTRODUCTION

The purpose of this review is to provide statistical assessment of clinical endpoint study MGR001-3001 of Mylan Pharmaceuticals Inc. The aim of the study is to confirm the local bioequivalence of the test product, MGR001 100/50 (fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder) versus the reference listed drug (RLD), Advair Diskus[®] 100/50 after oral inhalation of single and multiple doses (twice a day for 4 weeks). This statistical review will aid FDA Office of Generic Drugs in making an informed decision on approval of the test product.

2.1 Overview

Asthma

Asthma is a chronic disease involving the airways in the lungs. These airways (bronchial tubes) allow air to come in and out of the lungs. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. For some people, asthma is a minor nuisance. For others, it can be a major problem that interferes with daily activities and may lead to a life-threatening asthma attack. Asthma affects people of all ages, but it most often starts during childhood. In the United States, more than 25 million people are known to have asthma. About 7 million of these people are children.

Regulatory Background

Advair Diskus[®] (GlaxoSmithKline, NDA 021077) was approved by FDA in 2000 and is a fixed-dose combination of fluticasone propionate/salmeterol powder for oral inhalation that uses a multi-dose, pre-dispensed dry powder inhaler, Diskus[®]. Advair Diskus[®] is available in 3 strengths (100/50 µg, 250/50 µg, and 500/50 µg). All 3 strengths are indicated for the twice a day prophylactic treatment of asthma in patients who are 4 years and older while the 250/50 µg strength is also indicated for twice a day maintenance treatment of chronic obstructive pulmonary disease.

Mylan Pharmaceuticals Inc. (the applicant) submitted an original Abbreviated New Drug Application (ANDA) 208891 on 12/29/2015, seeking approval of the test product, MGR001 as a generic version of RLD, Advair Diskus[®]. The applicant developed MGR001, fluticasone propionate and salmeterol inhalation powder, pre-dispensed in a multi-dose dry powder inhaler, CRC749. The applicant aims to demonstrate that the test product meets the requirements of therapeutic equivalence, including in vivo local bioequivalence using clinical endpoints as specified in the FDA Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate (recommended Sep 2013).

The original submission contains the clinical study report and data from the clinical endpoint study MGR001-3001. During the first review cycle in 2016, Dr. Cynthia Liu, the primary statistical reviewer in DBVIII/OB/OTS¹ at that time, conducted a statistical evaluation of

¹ Division of Biometrics VIII/Office of Biostatistics/ Office of Translational Sciences

MGR001-3001, as per the consult request from the agency's DBI/OB/OGD². The reviewer verified the applicant's statistical analysis results using their statistical method and analysis populations. The statistical evaluation completed by Dr. Cynthia Liu was completed without any per protocol population recommendations from a FDA clinical reviewer. The reviewer identified some minor statistical issues but concluded that those issues don't affect the applicant's primary analysis results.

The agency issued a Complete Response (CR) letter to the applicant because the original ANDA was not approvable due to several deficiencies on 3/28/2017. The applicant submitted Major Complete Response Amendment, Amendment 22 (sequence 0021), which addressed the deficiencies described in the agency's CR letter and provides the information requested by the agency's review disciplines. Because a new study was not submitted, we reviewed the clinical study report and data in the original submission as well as the new data and information in this amendment and other amendments (Information Request responses) submitted during the current review cycle.

2.2 Data Sources

The applicant's submissions, including the clinical study reports, the data, and Information Request responses are in Electronic Document Room (EDR). EDR locations of the materials reviewed in this report are given below.

Clinical Study Report:

<\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-report-body.pdf>

Statistical Analysis Plan:

<\\cdsesub1\evsprod\anda208891\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\mgr001-3001\mgr001-3001-statistical.pdf>

Original Data Submissions:

ADSL.xpt – <\\cdsesub1\evsprod\anda208891\0000\m5\datasets\mgr001-3001\analysis\adam\datasets\adsl.xpt>

ADRE.xpt – <\\cdsesub1\evsprod\anda208891\0000\m5\datasets\mgr001-3001\analysis\adam\datasets\adre.xpt>

ADEFF.xpt - <\\cdsesub1\evsprod\anda208891\0000\m5\datasets\mgr001-3001\analysis\adam\datasets\adeff.xpt>

Additional Data Submissions:

² Division of Bioequivalence I/Office of Bioequivalence/Office of Generic Drugs

[ADCM1.xpt - \\cdsesub1\evsprod\anda208891\0021\m5\datasets\mgr001-3001\analysis\legacy\datasets\adcm1.xpt](#)

[IR12FL.xpt - \\cdsesub1\evsprod\anda208891\0027\m5\datasets\mgr001-3001\analysis\legacy\datasets\ir12fl.xpt](#)

[ADRE21.xpt - \\cdsesub1\evsprod\anda208891\0028\m5\datasets\mgr001-3001\analysis\legacy\datasets\adre21.xpt](#)

[ADRE31.xpt - \\cdsesub1\evsprod\anda208891\0032\m5\datasets\mgr001-3001\analysis\legacy\datasets\adre31.xpt](#)

Complete Response Amendment:

[\\cdsesub1\evsprod\anda208891\0021\m1\us\12-cover-letters\cover-letter-0021-resubmission-major-complete-response-amend.pdf](#) (Sequence 0021; received on 8/28/2017)

Information Request Responses:

[\\cdsesub1\evsprod\anda208891\0027\m1\us\12-cover-letters\cover-letter-0027-clinical-information-request-response-2018.pdf](#) (Sequence 0027; received on 2/26/2018)

[\\cdsesub1\evsprod\anda208891\0028\m1\us\12-cover-letters\cover-letter-0028-biostats-information-request-response-2018.pdf](#) (Sequence 0028; received on 2/26/2018)

[\\cdsesub1\evsprod\anda208891\0032\m1\us\12-cover-letters\cover-letter-0032-information-request-clinical-20180322.pdf](#) (Sequence 0032; received on 3/22/2018)

3 STATISTICAL EVALUATION OF STUDY MGR001-3001

This section provides the reviewers' statistical evaluation of Study MGR001-3001.

3.1 Overview

Study Title

A randomized, double-blind, double-dummy, placebo-controlled, parallel group study to determine the local equivalence of multiple doses of MGR001 to Advair Diskus® administered via oral inhalation in male or female subjects aged 18 years or older with asthma

Study Objectives

To confirm the local bioequivalence of MGR001 100/50 (the test product) versus Advair Diskus® 100/50 (RLD) after oral inhalation of single and multiple doses (twice a day for 4 weeks) using clinical endpoints

Study Sites

A multicenter study conducted at 101 sites in the United States, of which 97 sites screened and enrolled subjects, 3 sites screened but did not enroll any subjects, and 1 site neither screened nor enrolled any subjects but received investigational product.

Study Period

From 10/22/2014 (first subject first visit) to 7/10/2015 (last subject last visit)

Study Products

Details of each study product are summarized in the following table.

Table 1 - Study Products

.....

Expirat

Inhaler

FP = fluticasone propionate

*Source: Applicant’s Table 3-3 in Clinical Study Report (page 58 of 811)

3.2 Study Design and Endpoints

Study Design

The study consists of two periods:

- 4-week Single-Blind Placebo Run-in Period (28 days -7/+2 days), encompassing the following visits: a Screening visit at approximately 4 weeks prior to randomization (Visit 1) and a Run-in visit at 3 to 7 days prior to randomization (Visit 2)
- 4-week Double-Blind Treatment Period, encompassing the following visits: Day 1 (Visit 3/Randomization), Day 15 (± 2 days, visit 4), and Day 29 (± 2 days, Visit 5/End of Treatment)

During Single-Blind Placebo Run-in Period, subjects received the CRC749 inhaler containing placebo.

During Double-Blind Treatment Period, on Day 1 (Visit 3), subjects were randomly assigned to receive one of the 3 treatments: test, RLD, and placebo (5:5:1). In order to maintain the double-blind, double-dummy dosing technique was utilized and subjects were required to make one inhalation twice a day from each of 2 inhalers, CRC749 and Diskus®, containing active or placebo for each study treatment.

Details of each visit are given in the following table:

Table 2 - Visit Schedule

	Visit 1 Screening Visit (28 [-7/+2] ^a Days Pre-Visit 3)	Visit 2 Run-In Visit (3 to 7 Days Pre-Visit 3)	Visit 3 Day 1											Visit 4 Day 15 (±2 Days)	Visit 5 Day 29 (±2 Days) EOT and Follow-			
			-30 min	0 h	0.5 h	1 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h		-30 min	0 h	Post Spirometr	
Informed consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IVRS/IWRS registration/entry	X	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Medical history (including asthma/atopy) and demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Concomitant medication	X	X	X	-	-	-	-	-	-	-	-	-	-	X	X	-	-	-
Full physical examination (including height and weight at Screening)	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Inclusion/exclusion criteria	X	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Confirm no SABA for 6 hours and other background medications that day	X	X	X	-	-	-	-	-	-	-	-	-	-	X	X	-	-	X
12-Lead ECG/BP/PR	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Spirometry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
FEV ₁ reversibility	X	X ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Laboratory safety tests (blood and urine) including FSH ^c	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Urine pregnancy test (if applicable)	X	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Inhaler training	X	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Dispense PEFR meter and diary and rescue medication	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PEFR and complete daily diary	X																	X
Diary data review	-	X	X	-	-	-	-	-	-	-	-	-	-	X	X	-	-	-
Placebo run-in	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Compliance/accountability	-	X	X	-	-	-	-	-	-	-	-	-	-	X	X	-	-	-
Randomization	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Subject takes study drug in clinic	X	X	-	X	-	-	-	-	-	-	-	-	X ^d	X	-	-	-	
Device questionnaire	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	
Review adverse events	-	X	X										X	X	X	-	X	

Abbreviations: BP, blood pressure; ECG, electrocardiogram; EOT, end of treatment; FEV₁, forced expiratory volume in 1 second; FSH, follicle stimulating hormone; h, hour; IVRS/IWRS, Interactive Voice Response/Web Response system; min, minutes; PEFR, peak expiratory flow rate; PR, pulse rate; SABA, short-acting β₂-agonists.

^a Screening can start 21 days up to 30 days prior to randomization.

^b Only if not assessed or <12% reversible at screening visit.

^c Screening only.

^d Evening dose may have been taken in clinic after completion of 12-hour spirometry.

*Source: Applicant’s Table 3-4 in Clinical Study Report (page 64 – 65 of 811)

Study Endpoints

Study MGR001-3001 compared the effect of test and RLD on 1) forced expiratory volume in one second (FEV₁) area under the effect curve over 12 hours post-dose (AUEC₀₋₁₂) after the first dose on Day 1 (Visit 3) to assess the salmeterol component and on 2) trough FEV₁ on Day 29

(±2 days; Visit 5) after 4 weeks of twice daily dosing to assess the fluticasone propionate component. Therefore, the study has the following co-primary endpoints:

- Day 1 endpoint: change from baseline in FEV₁ AUEC₀₋₁₂ on Day 1
- Day 29 endpoint: change from baseline in trough FEV₁ on Day 29

Day 1 endpoint

Day 1 endpoint was calculated from FEV₁ measurements collected 30 minutes prior to morning dose, 0 minutes prior to morning dose, and at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours following completion of dosing with the second inhaler on Day 1.

The baseline for Day 1 endpoint was defined by the applicant as the mean of the 2 pre-dose FEV₁ measures on Day 1. If either 30 minute or 0 hour pre-dose FEV₁ value was missing, then the mean was set equal to non-missing value. If both pre-dose FEV₁ values are missing, then the baseline was set to missing and the Day 1 endpoint was also set to missing.

The applicant estimated Day 1 endpoint by the linear trapezoidal rule and corrected for the baseline. The AUEC₀₋₁₂ formula was defined as:

$$AUEC_{0-12} = \int_{t_0}^{t_{12}} (c_i - c_0) dt_i$$

where t_i is the actual time of collection corresponding to the i^{th} FEV₁ measurement on Day 1 with t_0 being the time at the start of dosing and c_i is the change from baseline in FEV₁ at time t_i on Day 1 with c_0 being 0 for all subjects.

If a subject took albuterol during the 0 to 12 hours post-dose spirometry assessments, all serial spirometry data collected after the albuterol use were set to missing for the equivalence analysis using per-protocol set (PPS) but were analyzed “as is” for the superiority analysis using full analysis set (FAS).

The rules for handling of missing data for the AUEC₀₋₁₂ calculation, prespecified in the Statistical Analysis Plan (SAP; page 21 of 4448), are as follows:

- For missing data within the first 3 hours post-dose:
 - A single missing FEV₁ value between two time points that had non-missing FEV₁ values was imputed by linear interpolation.
 - Two or more adjacent missing FEV₁ values were not imputed and AUEC₀₋₁₂ was set to missing.
- For missing data on or after 4 hours post-dose:
 - A single missing FEV₁ value between two time points that had non-missing FEV₁ values was imputed by linear interpolation.
 - If the 4-hour and 12-hour time points were non-missing, then any combination of missing values between these two time points was imputed by linear interpolation.

- If the 10-hour and 12-hour time points were missing and the 6-hour and 8-hour time points were non-missing, then linear extrapolation was used to impute these missing FEV₁ values. Linear extrapolation was also applied if the 12-hour time point was missing and the 8-hour and 10-hour time points were non-missing.
- If the FEV₁ value at either 3-hour or 4-hour post-dose time point was missing, and the time point at which the missing value occurred was between two time points that had FEV₁ values, then linear interpolation was used to impute the missing value. If both the FEV₁ values at the 3-hour and 4-hour post-dose time points were missing, the values were not imputed.

Reviewer's Comments: We verified that the applicant calculated Day 1 endpoint and handled the missing data for the baseline and for the AUEC₀₋₁₂ as the way that they prespecified in the protocol and SAP.

Day 29 endpoint

Day 29 endpoint was based on two FEV₁ measurements performed 30 minutes apart on Day 29 (± 2 days). Trough FEV₁ on Day 29 was calculated as the mean of the 2 FEV₁ values. If either of two FEV₁ measurements was missing, then the non-missing value was used. If both FEV₁ measurements were missing, then the non-missing FEV₁ value measured on Day 15 (Visit 4) was carried forward. This approach was implemented for both equivalence and superiority analyses.

Reviewer's Comments: The applicant used the Last Observation Carried Forward (LOCF) method for both equivalence and superiority analyses, regardless of reason for discontinuation. However, the current practice of Office of Generic Drugs (OGD) is to use LOCF only for superiority analysis using the modified Intent-to-Treat (mITT) population, not for the equivalence analysis using Per Protocol (PP) population except for the discontinuation due to lack of efficacy (treatment failure). For our analyses, we followed the OGD's current practice. More details are discussed in Section 3.3.2.

The applicant calculated the baseline for Day 29 endpoint by taking the average of [1 prebronchodilator FEV₁ measure at Visit 2, and the mean of the 2 pre-dose FEV₁ measures on Day 1 (Visit 3)]. If either of the 2 pre-dose Day 1 FEV₁ values was missing, then the Day 1 pre-dose FEV₁ mean was set equal to non-missing value. If both values are missing, the Day 1 pre-dose FEV₁ mean was set to missing. If either the Visit 2 prebronchodilator FEV₁ or the mean of the 2 pre-dose FEV₁ measures on Day 1 was missing, then baseline was set equal to the non-missing value. If all 3 values were missing, then the baseline value was set to missing and the Day 29 endpoint was also set to missing.

Reviewer's Comments: The applicant defined two different baselines for two primary endpoints. Both applicant's definitions are different from the definition in FDA Draft Guidance (2013). The guidance defines the baseline for two primary endpoints as the average of pre-dose FEV₁ values of at least two time points on Day 1. If one of two pre-dose FEV₁ values is missing, the applicant used the single non-missing value for the calculation of the mean on Day 1. However, the guidance recommended at least two values for the calculation of the mean on Day 1; therefore,

the clinical reviewers in DCR/OB/OGD³ recommend the baselines for both endpoints should be set to missing if one of two pre-dose FEV₁ values on Day 1 is missing. The baselines for FDA analyses are calculated according to this recommendation.

3.3 Statistical Methods

This section describes the applicant's and the FDA's statistical methods used for statistical analyses of the data from Study MGR001-3001.

3.3.1 Applicant Statistical Methods

Blinded Sample Size Re-estimation

The pre-specified Blinded Sample Size Re-estimation (BSSR) was conducted after 286 subjects had completed Visit 5 and had provided data for both primary endpoints on 3/17/2015. Assumptions for the coefficient covariance for Day 29 endpoint were not supported by the aggregated data; therefore, the sample size needed to be increased in order for the study to have adequate power for demonstrating equivalence between test and RLD treatments. Total sample size was revised from 836 completers to 990 completers (test:RLD:placebo = 450:450:90), the maximum allowed in the protocol, which requires at least 1100 subjects to be randomized, assuming a 10% discontinuation rate.

Reviewer's Comments: The BSSR in the original protocol allowed the BSSR to occur after approximately 300 subjects. A protocol amendment issued on 1/26/2015, before the BSSR being performed, allowed the BSSR to occur after approximately 250-300 subjects instead of 300 subjects so that the BSSR can take place earlier in the recruitment process. This minor protocol change is acceptable.

Pooled Sites

Because the number of subjects was small in some sites, sites were clustered by the 4 geographic regions: USA-Northeast, USA-Midwest, USA-South, and USA-West, based on US Census Bureau clustering. These 4 regions were used in the statistical analysis model.

Reviewer's Comments: Pooling sites based on geographical regions is acceptable.

Equivalence Analysis

For each of co-primary endpoints, an analysis of covariance (ANCOVA) model with treatment (test and RLD) and region (Northeast, Midwest, South, and West) as fixed effects and with the corresponding baseline as a covariate was used to obtain the least squares (LS) means for the treatment groups. Then Fieller's theorem was used to construct the two-sided 90% confidence interval for the LS mean ratio of the test product to RLD. Clinical equivalence between test and RLD was to be established if the 90% confidence interval of the LS mean ratio, for both

³ Division of Clinical Review in Office of Bioequivalence in Office of Generic Drugs

endpoints, were contained within the interval of [0.80, 1.25]. The primary analysis population for the equivalence test was the PPS. The analysis on the FAS was used as supportive.

Superiority Analysis

For each of co-primary endpoints, the same ANCOVA model with treatment (test, RLD, and placebo) and region (Northeast, Midwest, South, and West) as fixed effects and with the corresponding baseline as a covariate was used to obtain the LS mean differences for test vs. placebo and for RLD vs. placebo. Superiority of test and RLD over placebo was considered confirmed if the p-values for all four comparisons were less than 0.05. The primary analysis population for the superiority test was FAS. The analysis on PPS was used as supportive.

3.3.2 FDA's Statistical Methods

Equivalence Analysis

To establish equivalence of the test product to RLD, the 90% confidence interval for the test/RLD ratio of the means must be contained within the equivalence limit of [0.80, 1.25] prespecified in FDA Draft Guidance (2013), using the FDA PP population.

The compound hypothesis to be tested is:

$$H_0: \mu_T / \mu_R \leq \theta_1 \text{ or } \mu_T / \mu_R \geq \theta_2 \text{ versus } H_A: \theta_1 < \mu_T / \mu_R < \theta_2,$$

where μ_T = mean of test and μ_R = mean of RLD.

We reject H_0 with a type I error $\alpha = 0.05$, if the 90% confidence interval for μ_T / μ_R , the ratio of the test mean over the RLD mean is contained within the prespecified equivalence limit of [80%, 125%]. This procedure corresponds to the two one-sided tests (TOST) approach proposed by Schuirmann (1987), where rejection of the null hypothesis supports the conclusion of equivalence of the two products.

The 90% confidence interval for μ_T / μ_R is constructed using Fieller's theorem (Fieller, 1940). Details on Fieller's theorem can be found in Section 5.1 in Appendix.

Superiority Analysis

For missing data for Day 29 endpoint, if one of two pre-dose FEV₁ measurements on Day 29 is missing, the non-missing value was used to calculate the endpoint. LOCF method is used if both pre-dose FEV₁ measurements on Day 29 are missing but a pre-dose FEV₁ measurement on Day 15 is available. If a pre-dose FEV₁ measurement on Day 15 is also missing but baseline is available, the baseline observation carried forward (BOCF) method is used to calculate the endpoint.

To determine adequate study sensitivity, both the test product and RLD should be statistically superior to placebo (p-value of < 0.05) using the FDA mITT population and LOCF/BOCF. We will conduct the tests separately, i.e., test vs. placebo and RLD vs. placebo.

3.4 Subject Disposition

Applicant Analysis Populations

Safety Set

The applicant's Safety Set was defined as all randomized subjects who had taken at least one dose of study drug and for whom post-dose safety data were available. Safety Set was used for the applicant's safety analysis.

Full Analysis Set (FAS)

The applicant's FAS was defined as all randomized subjects who had taken at least one dose of study drug and had provided data for either of co-primary endpoints. FAS was used for the applicant's primary analysis for assay sensitivity (superiority).

Reviewer's Comments: In Original Protocol, FAS was defined as "all randomized subjects who have taken study medication and have provided data for at least the FEV₁ AUEC₀₋₁₂ primary endpoint measured on Day 1 (Day 1 endpoint)". The definition was changed as above in Amendment 1. The changed definition doesn't exclude more subjects as no subject was excluded from the applicant's FAS due to not having a primary endpoint. Therefore, this change did not affect the analysis population for the superiority analysis.

Per Protocol Set (PPS)

The applicant's PPS was defined as all subjects in FAS who did not have significant protocol deviation impacting both co-primary endpoints. PPS was used for the applicant's primary analysis for bioequivalence.

Reviewer's Comment: The applicant did not pre-specify the definition of "significant protocol deviation" in the protocol and only excluded 17 subjects in applicant's PPS from the FAS population. We found many subjects in applicant's PPS population violated the study inclusion/exclusion criteria. These subjects are excluded from the FDA PP populations.

FDA Analysis Populations

modified Intent-to-Treat (mITT)

The FDA mITT population includes all randomized subjects who took at least one dose of study product. FDA mITT is used for the FDA's superiority analysis.

Reviewer's Comment: Although the definitions are different, the FDA's mITT population and the applicant's FAS are essentially the same because no subject was excluded from the applicant's FAS due to not having both co-primary endpoints. Both populations exclude 6 subjects: 1 subject who didn't receive study drug and 5 subjects who were randomized into the study twice (subject IDs for the second entry were excluded and those for the first entry were included in the analysis).

Per Protocol (PP)

The primary clinical reviewer provided the recommendations for FDA's PP populations. As there are two primary endpoints, three sets of FDA PP populations were recommended: FDA Day 1 PP, FDA Day 29 PP, and FDA PP. FDA Day 1 PP excludes subjects who had protocol violations that affect Day 1 endpoint only. FDA Day 29 PP excludes subjects who had protocol violations that affect Day 29 endpoint only. FDA PP excludes subjects who had protocol violations that affect either Day 1 endpoint or Day 29 endpoint.

Reviewer's Comments: As the FDA's Draft Guidance (2013) does not provide the definition of PP population, we collaborated with the clinical reviewers to identify the subjects who violated the protocol and need to be excluded from the FDA PP populations. During this collaboration, we sent several Information Request (IR) letters together and separately to the applicant for clarification, or additional information or data. This review uses the information and datasets that the applicant submitted in responses to those agency's IR letters.

Some protocol violations are applicable to both co-primary endpoints, which lead to exclusions from all three PP populations. Others are only applicable to one of two endpoints, which lead to exclusions from either FDA Day 1 PP or FDA Day 29 PP.

1) Exclusion from all three FDA PP populations

a. Exclusion from Applicant's PPS

A total of 17 subjects in FAS were excluded from PPS because of significant protocol deviations. Details for the reasons for exclusion are provided in the applicant's Listing 16.2.2-1.2 in Section 16.2.3 of Clinical Study Report.

b. Unacceptable FEV₁ Measurements

The FEV₁ measurements with a Pulmonary Function Test grade of "Unacceptable" don't meet American Thoracic Society standard and should not be used in primary endpoint analyses or for determining whether to meet inclusion/exclusion criteria. In Section 4.1.4.2.1 (page 81 of Clinical Study Report), the applicant stated the "Unacceptable" FEV₁ measurements were excluded from efficacy analyses but some were used for the calculation of bronchodilator reversibility. We confirmed this statement using the dataset (adre31.xpt) in IR response submitted on 3/22/2018 (sequence 0032). We set all "Unacceptable" FEV₁ measurements (total of 142 measurements from 124 subjects) to missing and don't use them in any of our analyses.

c. Inclusion Criterion 5 - % Predicted FEV₁

To be enrolled into the study, subjects have to meet Inclusion Criterion 5. In the study protocol, Inclusion Criterion 5 is stated that 1) a Visit 1 pre-bronchodilator FEV₁ be 50% to 85% (55% to 95% for subjects taking ICS or LABA prior to screening), 2) a Visit 2 pre-bronchodilator FEV₁ be 50% to 85%, and 3) the mean of pre-dose Visit 3 FEV₁ be 50% to 85% of predicted values according to age, height, race, and sex using NHANES III⁴ predicted values, following abstinence from SABA for minimum of 6 hours and withholding restricted medications prior to visits.

Although the applicant's inclusion criterion requires that subjects need to meet the criterion at Visit 1, Visit 2, and Visit 3, subjects are included in FDA PP populations if they met the criterion at Visit 3 and at either Visit 1 or Visit 2. This is recommended by the clinical reviewers' recommendation because FDA Draft Guidance (2013) recommends only FEV₁ measures at Visit 1 and Visit 3 be in the specific range (between 40% and 85%). We identified 6 subjects who didn't meet the criterion but were included in the applicant's PPS. These subjects are excluded from all three FDA PP populations.

Reviewer's Comments: We independently calculated % predicted FEV₁ values using the demographic information (age, height, race and sex) and the formulas in NHANES III. We compared our calculations with the % predicted FEV₁ values in the applicant's dataset and found many discrepancies between them. Regarding this issue, we sent an IR letter to the applicant on 2/16/2018. In their response (sequence 0028; 2/26/2018), the applicant explained that those discrepancies happened because the demographic information for some subjects were incorrectly entered into the spirometry equipment which calculated % predicted FEV₁ value based on the entered demographic information, in a real time. The % predicted FEV₁ values in the applicant's dataset were from this spirometry equipment, not programmatically calculated by the applicant. The applicant calculated the predicted FEV₁ values using the correct demographic information and submitted them to the agency (adre21.xpt) in the response. We verified that the applicant's calculated values match with ours.

d. Inclusion Criterion 6 - % Reversibility

In the study protocol, Inclusion Criterion 6 is stated as the subjects are eligible for enrollment if subjects had post-bronchodilator reversibility of at least 12% within 30 minutes following 360 mg albuterol from a pMDI and space at either Visit 1 or, if necessary (i.e., if not assessed at Visit 1 or if assessed and reversibility was less than 12%), at Visit 2.

A reversibility test is made to distinguish asthma from other causes of obstructive lung disease. A significant rise in FEV₁ (i.e., higher % reversibility) is diagnostic for asthma. Although the FDA Draft Guidance (2013) recommends reversibility of at least 15% for

⁴ <https://www.atsjournals.org/doi/full/10.1164/ajrccm.159.1.9712108>

inclusion criterion, the clinical reviewers recommended subjects with a reversibility of at least 12% after rounding (i.e., 11.5% or higher is acceptable) to be included in the FDA PP populations because the reversibility of 12% is also widely considered as a significant rise. The clinical reviewers also recommend considering reversibility at additional visits such as SCREENING_R1 or RUN_IN_R1 when identifying subjects.

From the applicant's PPS, we identified a total of 51 subjects who don't have reversibility of at least 11.5% at Visit 1, Visit 2, or any of the additional visits mentioned above. These subjects are excluded from all three FDA PP populations.

Reviewer's Comments: Any reversibility derived using "Unacceptable" prebronchodilator or post-bronchodilator FEV₁ values were not used (i.e., set to missing) when identifying above subjects.

e. Missing Baseline

We identified one subject who has only one pre-dose FEV₁ value on Day 1 and was included in the applicant's PPS. We set this subject's baselines for both endpoints to missing. Because baselines are missing for both primary endpoints, this subject is excluded from all three FDA PP populations.

2) Exclusion from FDA Day 1 PP and FDA PP populations

a. Insufficient Data

In Section 16.1.9.4.3.6 of Clinical Study Report, the applicant reported that a total of 20 subjects had insufficient data to calculate Day 1 endpoint. Among 20 subjects, 18 subjects used albuterol at multiple time points during the 12-hour spirometry assessment on Day 1; therefore, FEV₁ data at those time points were set to missing for equivalence analysis, which resulted in insufficient data to calculate Day 1 Endpoint. Other 2 subjects had multiple missing post-dose FEV₁ data. Details for these subjects were provided in the applicant's table, which can be found in Appendix (Table 11).

Although these subjects were not included in the applicant's equivalence analysis but were included in the applicant's PPS. All these subjects are excluded from FDA Day 1 PP and FDA PP but not excluded from FDA Day 29 PP because this issue doesn't affect Day 29 endpoint.

3) Exclusion from FDA Day 29 PP and FDA PP populations

a. Treatment Compliance

A subject is considered compliant if the overall study drug compliance is greater than or equal to 75% and less than or equal to 125% during Double-Blind Treatment Period. The details on how the overall study drug compliance is calculated are in Appendix (Section 5.3).

We identified 59 subjects (test = 27, RLD = 25, placebo = 7) who were not compliant but were included in the applicant's PPS. These subjects are excluded from the FDA Day 29 PP and FDA PP but not excluded from FDA Day 1 PP because treatment compliance issue doesn't affect Day 1 endpoint.

b. Day 29 (Visit 5) Out of Visit Window

Visit window for Visit 5 is Day 29 ± 2 days (Day 27 to Day 31). From the applicant PPS, we identified 74 subjects (test = 30, RLD = 35, placebo = 9) who visited the study center for Visit 5 outside of this visit window or didn't have FEV₁ at Visit 5. These subjects are excluded from FDA Day 29 PP and FDA PP but not excluded from FDA Day 1 PP because this issue doesn't affect Day 1 endpoint.

c. Day 29 Out of Time Window Spirometry Assessments

In SAP, the subjects with out-of-time window spirometry assessments were defined as Day 29 (Visit 5) average pre-dose time was not within ± 2 hours of Day 1 (Visit 3) average pre-dose times and/or pre-dose assessments at Visit 2, Visit 3, and Visit 5 completed after 12 pm.

We identified 208 subjects (test = 94, RLD = 95, placebo = 19) who had out-of-time window spirometry assessments but were included in the applicant's PPS. These subjects are excluded from FDA Day 29 PP and FDA PP but not excluded from FDA Day 1 PP because this issue doesn't affect Day 1 endpoint.

Reviewer's Comments: In the protocol, it is stated that the Day 29 spirometry should be performed within a ± 1 hour time window. Regarding the different definitions of time window used in SAP and protocol, the applicant explained in the IR response on 2/26/2018 (sequence 0027) that the protocol definition was stated in a way to provide direction to the investigator sites to complete the spirometry assessments at a similar time of day to the Day 1 measures. After the practical consideration, ± 2 hour time window was specified in SAP to allow the situation that some patients would attend the clinic earlier or later. The clinical primary reviewer recommended excluding subjects from FDA Day 29 PP based on the ± 2 hour time window prespecified in SAP.

Key reasons for exclusion from three FDA PP populations are listed above. Other reasons such as concomitant medication are not listed. The complete list of subjects who are excluded from FDA PP populations and the reasons for exclusion can be found in the FDA PP recommendation document from the primary clinical reviewer on 5/9/2018 (A208891N000DCR_RecStat5.9.doc).

Subject Disposition Table

Table 3 presents the number of subjects in each study population by treatment group and reason for exclusion from each population.

Table 3 – Subject Disposition Table

	Applicant				FDA			
	Test	RLD	Placebo	Total	Test	RLD	Placebo	Total
Randomized	512	513	103	1128	512	513	103	1128
Safety population	512	512	103	1127	512	512	103	1127
Total exclusion	0	1	0	1	0	1	0	1
Reasons for exclusion								
Did not take any study medication	0	1	0	1	0	1	0	1
Applicant FAS/FDA mITT population	509	511	102	1122	509	511	102	1122
Total exclusion	3	2	1	6	3	2	1	6
Reason for exclusion								
Did not take any study medication	0	1	0	1	0	1	0	1
Entered into study twice	3	1	1	5	3	1	1	5
FDA Day 1 PP population					475	463	90	1028
Total exclusion					37	50	13	100
Reason for exclusion								
Excluded from the mITT Population					3	2	1	6
Subject has at least one significant protocol deviation impacting both endpoints					7	9	1	17
Did not meet inclusion criterion 5					2	4	0	6
Did not meet inclusion criterion 6					20	27	4	51
Missing Baseline					0	1	0	1
Insufficient Data for Day 1 Endpoint					5	7	7	19
FDA Day 29 PP population					357	350	68	775
Total exclusion					155	163	35	353
Reason for exclusion								
Excluded from the mITT Population					3	2	1	6
Subject has at least one significant protocol deviation impacting both endpoints					7	9	1	17
Did not meet inclusion criterion 5					2	4	0	6
Did not meet inclusion criterion 6					20	27	4	51
Missing Baseline					0	1	0	1
Concomitant medication after Day 1					4	3	2	9
Not compliant					22	21	4	47
Day 29/Visit 5 out of visit window					22	24	6	52
Day 29 out of time window spirometry assessments					74	71	17	162
Dosed before completion of pre-dose spirometry assessments at Visit 5					1	1	0	2
Applicant PPS/FDA PP population	502	502	101	1105¹⁾	354	348	63	765
Total exclusion	10	11	2	23	158	165	40	363
Reason for exclusion								
Excluded from the mITT Population	3	2	1	6	3	2	1	6

Subject has at least one significant protocol deviation impacting both endpoints	7	9	1	17	7	9	1	17
Did not meet inclusion criterion 5					2	4	0	6
Did not meet inclusion criterion 6					20	27	4	51
Missing Baseline					0	1	0	1
Concomitant medication after Day 1					4	3	2	9
Not compliant					22	21	4	47
Day 29/Visit 5 out of visit window					22	24	6	52
Day 29 out of time window spirometry assessments					74	71	17	162
Dosed before completion of pre-dose spirometry assessments at Visit 5					1	1	0	2
Insufficient Data for Day 1 Endpoint					3	2	5	10

¹⁾ Applicant’s PPS contained 1105 subjects. Applicant’s equivalence analysis for Day 1 endpoint contained 1085 subjects and applicant’s equivalence analysis for Day 29 endpoint contained 1094 subjects. See below Reviewer’s Comments for more details.

*Source: Reviewer’s Analysis

Reviewer’s Comments: We observed the number of subjects included in the applicant’s PPS and the actual number of subjects included in the applicant’s equivalence analyses are different. Less subjects were used in the analyses. The applicant did not explain why different number of subjects were included in the equivalence analyses.

3.5 Demographics and Baseline Characteristics

We examine comparability of demographic and other baseline characteristics – age, gender, race, body mass index, duration of asthma, geographical region, pre-bronchodilator FEV₁ at Screening visit (Visit 1) – across the treatment groups in the FDA mITT population. Treatment groups appear to be comparable regarding those demographic and baseline characteristics. The results are summarized in Table 4.

Overall, the mean age was 43 years. There were more females (60%) than males (40%). The majority of study population was White (73%) followed by Black or African American (19%). More subjects were enrolled in the South and West regions than in the Northeast and Midwest regions. The mean body mass index was about 29 kg/m². The mean duration of asthma was 27 years. The mean pre-bronchodilator FEV₁ at Screening visit was 2.41 L.

Table 4 – Demographics and Baseline Characteristics in FDA mITT population

Category	Test n = 509	RLD n = 511	Placebo n = 102	Total n = 1122
Age (years)				
Mean ± SD	42.6 ± 14.1	42.5 ± 14.2	43.5 ± 13.9	42.7 ± 14.1
Median (Range)	43 (18 – 84)	43 (18 – 84)	43 (18 – 84)	43 (18 – 84)
Gender, n (%)				
Female	305 (59.9)	308 (60.3)	64 (62.8)	677 (60.3)
Male	204 (40.1)	203 (39.7)	38 (37.3)	445 (39.7)
Race, n (%)				

White	377 (74.1)	371 (72.6)	73 (71.6)	821 (73.2)
Black or African American	91 (17.9)	98? (19.2)	21 (20.6)	210 (18.7)
Asian	10 (2.0)	11 (2.2)	1 (1.0)	22 (2.0)
Native Hawaiian or Other Pacific Islander	1 (0.2)	0 (0.0)	1 (1.0)	2 (0.2)
Other	30 (5.9)	31 (6.1)	6 (5.9)	67 (6.0)
Region, n (%)				
Midwest	82 (16.1)	93 (18.2)	11 (10.8)	186 (16.6)
Northeast	67 (13.2)	70 (13.7)	14 (13.7)	151 (13.5)
South	174 (34.2)	145 (28.4)	43 (42.2)	362 (32.3)
West	186 (36.5)	203 (39.7)	34 (33.3)	423 (37.7)
Body Mass Index (kg/m²)				
Mean ± SD	29.4 ± 6.0	29.1 ± 5.9	29.4 ± 5.9	29.3 ± 5.9
Median (Range)	28.3 (18.0 – 44.9)	28.4 (17.8 – 45.0)	29.1 (18.6 – 44.7)	28.5 (17.8 – 45.0)
Duration of Asthma (years)				
Mean ± SD	27.0 ± 14.1	27.1 ± 15.0	28.1 ± 14.7	27.1 ± 14.6
Median (Range)	24.8 (0.3 – 79.8)	24.5 (0.8 – 70.7)	26.2 (0.6 – 65.8)	24.8 (0.3 – 79.8)
Pre-Bronchodilator FEV₁ at Screening Visit (L)				
n	495	497	98	1090
Mean ± SD	2.43 ± 0.62	2.38 ± 0.61	2.42 ± 0.66	2.41 ± 0.62
Median (Range)	2.40 (0.93 – 4.40)	2.34 (0.92 – 4.23)	2.41 (1.21 – 4.29)	2.37 (0.92 – 4.40)

*Source: Reviewer’s Analysis

3.6 Applicant’s Analysis Results

This section summarizes the applicant’s statistical analysis results in Clinical Study Report for MGR3001-001.

Primary Endpoint Analysis

The applicant’s statistical analysis results for Day 1 endpoint are summarized in Table 5 and the results for Day 29 endpoint are summarized in Table 6.

Table 5 - Applicant's Primary Endpoint Analysis Results – Day 1 Endpoint

	Treatment		
	Test	RLD	Placebo
Equivalence Analysis			
PPS Population (n)	497	494	94
LS Mean (SE)	3.9734 (0.1704)	3.5411 (0.1593)	
90% CI for LS Mean Ratio of Test/RLD	(101.6% , 123.7%)		
Superiority Analysis			

FAS Population (n)	508	511	102
LS Mean difference from placebo (SE)	3.1343 (0.3760)	2.6773 (0.3769)	
P-value for difference from placebo	<0.0001	<0.0001	

LS Mean = Least Square Mean; SE = Standard Error; CI = Confidence Interval

*Source: Applicant’s Table 6-1 and Table 6-2 in Clinical Study Report (page 133 and 135 of 811)

Table 6 - Applicant's Primary Endpoint Analysis Results – Day 29 Endpoint

	Treatment		
	Test	RLD	Placebo
Equivalence Analysis			
PPS Population (n)	498	497	99
LS Mean (SE)	0.2911 (0.0163)	0.2728 (0.0162)	
90% CI for Test/RLD LS Mean Ratio	(93.8% , 122.0%)		
Superiority Analysis			
FAS Population (n)	504	505	102
LS Mean difference from Placebo (SE)	0.2352 (0.0380)	0.2145 (0.0381)	
P-value for difference from Placebo	<0.0001	<0.0001	

LS Mean = Least Square Mean; SE = Standard Error; CI = Confidence Interval

*Source: Applicant’s Table 6-3 and Table 6-4 in Clinical Study Report (page 142 and 144 of 811)

The applicant concluded that 1) assay sensitivity was established as both test and RLD were statistically significantly superior to placebo (p-value<0.0001) and 2) bioequivalence of test and RLD was established as the ratios of LS means and the 90% confidence intervals were wholly contained within the acceptance limits of 80% - 125% for both co-primary endpoints

Reviewer’s Comments: Although the applicant defined a common PPS for both endpoints, the numbers of subjects used for equivalence analysis for each primary endpoint are different. The reason is unknown because the applicant did not specify the reasons for exclusion from the analysis for each subject. For some subjects, this happens because of missing endpoints. For example, if a subject has a missing Day 1 endpoint but has a Day 29 endpoint, the subject is included in PPS but not included in the equivalence analysis for Day 1 endpoint. Similarly, although one FAS population was defined for both endpoints, the numbers of subjects used for superiority analysis for each primary endpoint are different.

3.7 Reviewer’s Assessments

This section provides the reviewer’s statistical analysis results and conclusions using the FDA analysis populations and statistical methods described in Section 3.3.2.

The FDA co-primary endpoints are:

- 1) Day 1 endpoint: change from baseline in FEV₁ AUEC₀₋₁₂ on Day 1,
- 2) Day 29 endpoint: change from baseline for FEV₁ trough on Day 29.

Equivalence Analyses

The FDA's equivalence analyses use the FDA's PP populations: FDA Day 1 PP, FDA Day 29 PP, and FDA PP. For Day 1 endpoint, FDA Day 1 PP and FDA PP are used. For Day 29 endpoint, FDA Day 29 PP and FDA PP are used.

As no subject was discontinued due to lack of efficacy, LOCF/BOCF is not used for equivalence analyses.

Day 1 Endpoint

Using FDA Day 1 PP, equivalence between test and RLD is established as the 90% confidence interval for the test/RLD ratio is (100.7%, 122.2%), entirely contained within the prespecified equivalence limit of [80%, 125%].

However, equivalence of test and RLD is not established using FDA PP, as the 90% confidence interval for the test/RLD ratio is (101.1%, 126.8%), fallen outside of the equivalence limit of [80%, 125%].

Day 29 Endpoint

Using both FDA Day 29 PP and FDA PP, equivalence between test and RLD is established as the 90% confidence intervals for the test/RLD ratio are (92.0%, 122.4%) and (91.5%, 122.1%), entirely contained in the prespecified equivalence limit of [80%, 125%].

Superiority Analyses

The FDA's superiority analyses use the FDA's mITT population.

Day 1 Endpoint

For the missing data, we followed the applicant's method for handling missing data. A total of three subjects' missing data points cannot be imputed and their Day 1 endpoints were set to missing.

Using the FDA mITT population, it is demonstrated that each active treatment is statistically superior than placebo as the p-values for the difference from placebo are less than 0.05.

Day 29 Endpoint

For the missing Day 29 data, the Day 15 data were carried forward for three (3) subjects and the baseline data were carried forward for 13 subjects.

Using the FDA mITT population and LOCF/BOCF, it is demonstrated that each active treatment is statistically superior than placebo as the p-values for the difference from placebo are less than 0.05.

The summary of the reviewer’s primary endpoint analysis results is presented in the following tables: Table 7 for Day 1 endpoint and Table 8 for Day 29 endpoint.

Table 7 - Reviewer's Primary Endpoint Analysis Results – Day 1 Endpoint

	Treatment		
	Test	RLD	Placebo
Equivalence Analysis			
FDA Day 1 PP Population (n)	475	463	90
LS Mean (SE)	3.9315 (0.1610)	3.5459 (0.1619)	
90% CI for LS Mean ratio of Test/RLD	(100.7% ,122.2%)		
FDA PP Population (n)	354	348	63
LS Mean (SE)	3.810 (0.1797)	3.3690 (0.1801)	
90% CI for LS Mean ratio of Test/RLD	(101.1% ,126.8%)		
Superiority Analysis			
FDA mITT Population (n)	509 ¹⁾	511 ²⁾	102
LS Mean difference from placebo (SE)	3.1325 (0.3826)	2.6758 (0.3657)	
P-value for difference from placebo	<0.0001	<0.0001	

LS Mean = Least Square Mean; SE = Standard Error; CI = Confidence Interval

¹⁾ 1 subject (# (b) (6)) is not included because of a missing baseline.

²⁾ 2 subjects (b) (6) are not included because of missing data.

*Source: Reviewer’s Analysis

Table 8 - Reviewer's Primary Endpoint Analysis Results – Day 29 Endpoint

	Treatment		
	Test	RLD	Placebo
Equivalence Analysis			
FDA Day 29 PP Population (n)	357	350	68
LS Mean (SE)	0.2912 (0.0179)	0.2746 (0.0180)	
90% CI for LS Mean ratio of Test/RLD	(92.0% ,122.4%)		
FDA PP Population (n)	354	348	63
LS Mean (SE)	0.2905 (0.0181)	0.2750 (0.0181)	
90% CI for LS Mean ratio of Test/RLD	(91.5% ,122.1%)		
Superiority Analysis			
FDA mITT Population (n)	509 ¹⁾	511	102

LS Mean difference from placebo (SE)	0.2346 (0.0381)	0.2143 (0.0366)
P-value for difference from placebo	<0.0001	<0.0001

LS Mean = Least Square Mean; SE = Standard Error; CI = Confidence Interval

¹⁾ 1 subject (# (b) (6)) is not included because of a missing baseline.

*Source: Reviewer’s Analysis

Exploratory Analyses

Per clinical reviewers’ request, we conducted exploratory statistical analyses for the subjects who received study product from the first shipment only. The results can be found in the Appendix (Section 5.4).

4 SUMMMARY AND CONCLUSIONS

This section provides the summary of statistical evaluation of Study MGR3001-001 and overall statistical conclusion.

4.1 Side by Side Tables for DCR Reviewers

The side by side table of subject disposition is provided in Section 3.4 (Table 3).

The side by side table of the applicant’s and FDA’s primary endpoint analysis results is given below.

Table 9 - Primary Endpoint Analysis – Day 1 Endpoint (per Applicant and FDA Statistical Reviewer)

	Applicant			FDA		
	Test	RLD	Placebo	Test	RLD	Placebo
Equivalence Analysis						
PPS/FDA Day 1 PP population (n)	497	494	94	475	463	90
LS Mean	3.9734	3.5411		3.9315	3.5459	
90% CI for LS Mean T/R ratio	(101.6% , 123.7%)			(100.7% , 122.2%)		
FDA PP population (n)				354	348	63
LS Mean (SE)				3.8100	3.3690	
90% CI for LS Mean T/R ratio				(101.1% , 126.8%)		
Superiority Analysis						
mITT population (n)	508	511	102	509 ¹⁾	511 ²⁾	102
LS Mean difference from Placebo	3.1343	2.6773		3.1325	2.6758	
P-value for difference	<0.0001	<0.0001		<0.0001	<0.0001	

LS Mean = Least Squares Mean; CI = Confidence Interval

¹⁾ 1 subject ((b) (6)) is not included because of a missing baseline.

²⁾ 2 subjects (b) (6) are not included because of missing data.

Table 10 - Primary Endpoint Analysis – Day 29 Endpoint (per Applicant and FDA Statistical Reviewer)

	Applicant			FDA		
	Test	RLD	Placebo	Test	RLD	Placebo
Equivalence Analysis						
PPS/FDA Day 29 PP population (n)	498	497	99	357	350	68
LS Mean	0.2911	0.2728		0.2912	0.2746	
90% CI for LS Mean T/R ratio	(93.8% ,122.0%)			(92.0% ,122.4%)		
FDA PP population (n)				354	348	63
LS Mean (SE)				0.2905	0.2750	
90% CI for LS Mean T/R ratio				(91.5% ,122.1%)		
Superiority Analysis						
mITT population (n)	504	505	102	509 ¹⁾	511	102
LS Mean difference from Placebo	0.2352	0.2145		0.2346	0.2143	
P-value for difference	<0.0001	<0.0001		<0.0001	<0.0001	

LS Mean = Least Squares Mean; CI = Confidence Interval

¹⁾ 1 subject (b) (6) is not included because of a missing baseline.

4.2 Statistical Issues

No major statistical issue that affects primary endpoint analyses is found during the review.

The differences in equivalence analysis results between the applicant and FDA are mainly caused by the differences in the PP populations. The applicant’s PPS excludes subjects who had a significant protocol violation only if it affects both primary endpoints. The definition of significant protocol violation is not clearly stated in the protocol. However, FDA defines a PP population separately for each of two primary endpoints (FDA Day 1 PP and FDA Day 29 PP) by excluding subjects who had protocol violations which affect the corresponding primary endpoint only. FDA also defines a single PP population (FDA PP) by excluding subjects who had protocol violations which affect either of the primary endpoints.

The slight differences in superiority analysis results between the applicant and FDA are caused by the differences in the baseline definitions and in the missing data imputation method. Both pre-dose FEV₁ values in the morning of Day 1 need to be non-missing for the baseline calculation in the FDA analyses while a baseline can be calculated although one value is missing in the applicant’s analyses. When the Day 29 data are missing, FDA use BOCF as well as LOCF while the applicant used only LOCF for superiority analyses.

4.3 Conclusions and Recommendations

Day 1 Endpoint

Equivalence between test and RLD is established using FDA Day 1 PP, as the 90% confidence interval for the test/RLD ratio is (100.7%, 122.2%), entirely contained within the prespecified equivalence limit of [80%, 125%].

Equivalence between test and RLD is not established using FDA PP, as the 90% confidence interval for the test/RLD ratio is (101.1%, 126.8%), fallen outside of the equivalence limit of [80%, 125%].

Using the FDA mITT population, it is demonstrated that each active treatment is statistically superior than placebo as the p-values for the difference from placebo are less than 0.05.

Day 29 Endpoint

Equivalence between test and RLD is established using FDA Day 29 PP and FDA PP, as the 90% confidence intervals for the test/RLD ratio are (92.0%, 122.4%) and (91.5%, 122.1%) respectively, entirely contained in the prespecified equivalence limit of [80%, 125%].

Using the FDA mITT population and LOCF/BOCF, it is demonstrated that each active treatment is statistically superior than placebo as the p-values for the difference from placebo are less than 0.05.

5 APPENDIX

5.1 Fieller’s Theorem

Let the random variables X and Y be jointly normal with $E(X) = \mu_X$ and $E(Y) = \mu_Y$ and let $\eta = \mu_X / \mu_Y$.

Let $W = X - \eta Y$. Then W is a normally distributed random variable, with $E(W)=0$ and $Var(W) = Var(X) - 2\eta Cov(X,Y) + \eta^2 Var(Y)$.

If S_{XX} , S_{YY} , and S_{XY} are sample estimates of $Var(X)$, $Var(Y)$, and $Cov(X,Y)$ with m degrees of freedom, then the statistic T is defined by

$$T = \frac{\bar{X} - \eta \bar{Y}}{\sqrt{S_{XX} - 2\eta S_{XY} + \eta^2 S_{YY}}}$$

T is a pivotal statistic with a t distribution with m degrees of freedom. Let t be an upper $\alpha/2$ percentile point for the t distribution with m degrees of freedom. Solve the inequality $T \leq t$ for η to get

$$\frac{(\bar{X}\bar{Y} - t^2 S_{XY}) \pm \sqrt{(\bar{X}\bar{Y} - t^2 S_{XY})^2 - (\bar{Y}^2 - t^2 S_{YY})(\bar{X}^2 - t^2 S_{XX})}}{(\bar{Y}^2 - t^2 S_{YY})}$$

as $(1 - \alpha)100\%$ confidence limits for η . Note that the solution to the inequality may not exist and may not be an interval.

5.2 Exclusions from FDA Day 1 PP – Insufficient Data

Table 11 – Subjects with Insufficient Post-dose FEV₁ Data on Day 1

Identification	Group	Comments
(b) (6)	Advair® Diskus® 100/50	Subject took albuterol starting at the 6-hours post-dose time point.
	Advair® Diskus® 100/50	Subject took albuterol starting at the 2-hours post-dose time point.
	Advair® Diskus® 100/50	Subject took albuterol starting at the 8-hours post-dose time point.
	Advair® Diskus® 100/50	Subject took albuterol starting at the 30-minutes post-dose time point.
	Advair® Diskus® 100/50	Subject took albuterol starting at the 6-hours post-dose time point.
	Advair® Diskus® 100/50	Subject only have post-dose data up to the 6-hours post-dose time point.
	Advair® Diskus® 100/50	Subject took albuterol starting at the 30-minutes post-dose time point.
	Advair® Diskus® 100/50	Subject took albuterol starting at the 3-hours post-dose time point.
MGR001	100/50	Subject took albuterol starting at the 8-hours post-dose time point.
MGR001	100/50	Subject took albuterol starting at the 30-minutes post-dose time point.
MGR001	100/50	Subject took albuterol starting at the 8-hours post-dose time point.
MGR001	100/50	Subject took albuterol starting at the 30-minutes post-dose time point.
MGR001	100/50	Subject is missing data for the 2 hours to 6 hours post-dose time points
	Placebo	Subject took albuterol starting at the 8-hours post-dose time point.
	Placebo	Subject took albuterol starting at the 8-hours post-dose time point.
	Placebo	Subject took albuterol starting at the 1-hour post-dose time point.
	Placebo	Subject took albuterol starting at the 30-minutes post-dose time point.
	Placebo	Subject took albuterol starting at the 30-minutes post-dose time point.
	Placebo	Subject took albuterol starting at the 4-hours post-dose time point.
	Placebo	Subject took albuterol starting at the 4-hours post-dose time point.

*Applicant’s Table 2 in Section 16.1.9.3.4.6 of Clinical Study Report (page 231 of 4448)

5.3 Treatment Compliance During Double Blind Treatment Period

Because of a double-dummy dosing, compliance during the double-blind treatment period for each of the active treatment and matching placebo components of the treatment group was calculated separately for each of the four components: Placebo MGR001, Active MGR001, Placebo Advair® and Active Advair®. The overall compliance for the active treatment groups was derived from the corresponding active inhaler component. The overall compliance for the Placebo treatment was calculated as follows:

- If the compliance for the two inhalers are both less than 100% then overall compliance = minimum of [Placebo Advair® compliance, Placebo MGR001 compliance]
- If the compliance for the two inhalers are both greater than 100% then overall compliance = maximum of [Placebo Advair® compliance, Placebo MGR001 compliance]
- If the compliance for the two inhalers are on either side of 100% then overall compliance is determined as follows:
 - If absolute deviation from 100% is not equal, report the compliance with the greatest absolute deviation from 100%.
 - If absolute deviation from 100% is equal, report the overall compliance as minimum of [Placebo Advair® compliance, Placebo MGR001 compliance]

Overall compliance information was used to categorize subjects as being either compliant or not. A subject is considered compliant if the overall study drug compliance is greater than or equal to 75% and less than or equal to 125%.

The applicant calculated the treatment compliance for each inhaler type as:

- Compliance (%) = (total actual dose administered / total expected dose)*100, where
 - total actual dose = number of dose counter before first dose from inhaler – number in dose counter upon return of the inhaler
 - if the dose counter information is (are) missing due to unreturned or lost inhaler(s), the total actual dose = total actual dose taken from AM3g™ for lost inhaler(s) + total actual dose from returned inhaler(s)
 - total expected dose = 2*(date of expected last dose – date of first dose + 1)
 - date of first dose = the date the dose was first administered in clinic on Day 1 (Visit 3) as indicated in the date recorded by the site in ERT's Masterscope™ CT. If the date is missing, the earliest date from the Randomized Study Drug accountability page in the eCRF is used.
 - for subjects who completed Day 29, date of expected last dose = the day prior to Day 29 (Visit 5)
 - for the subjects who terminated from the study early, date of expected last dose = the actual date of last dose

However, we don't agree with the applicant on using actual dates when calculating total expected dose, which will lead to the over-estimation of expected dose. For example, if a subject terminated from the study in the morning of Day 15 (Visit 4) and the total actual dose by the morning of Day 15 was 28. The compliance rate for this subject will be 100% if we follow the applicant's way of calculating the compliance. This subject's compliance rate should be 50% because the total expected dose for double-blind treatment period is 56 (=2 doses per day * 28 days) regardless of whether or not the subject completed the study. We used the fixed dose of 56 as the total expected dose to calculate the treatment compliance. That is,

$$\text{Compliance} = (\text{total actual dose administered} / 56) * 100$$

5.4 Exploratory Analyses with First Shipment Only

The summary of the reviewer’s exploratory statistical analysis results using data from first shipment only is presented in the following tables: Table 12 for Day 1 endpoint and Table 13 for Day 29 endpoint.

Table 12 - Reviewer's Exploratory Analysis Results – Day 1 Endpoint (First Shipment Only)

	Treatment		
	Test	RLD	Placebo
Equivalence Analysis			
FDA Day 1 PP Population (n)	236	60	7
LS Mean (SE)	4.0602 (0.2212)	3.3562 (0.4054)	
90% CI for LS Mean ratio of Test/RLD	(99.0% , 152.6%)		
FDA PP Population (n)	181	43	5
LS Mean (SE)	3.8891 (0.2345)	2.9753 (0.4504)	
90% CI for LS Mean ratio of Test/RLD	(102.8% , 176.5%)		
Superiority Analysis			
FDA mITT Population (n)	255 ¹⁾	64	9
LS Mean for difference from placebo (SE)	4.4318 (1.0538)	3.6105	
P-value for difference from placebo	<0.0001	0.0009	

1) 1 subject (b) (6) is not included because of missing data.

*Source: Reviewer’s Analysis

Table 13 - Reviewer's Exploratory Analysis Results – Day 29 Endpoint (First Shipment Only)

	Treatment		
	Test	RLD	Placebo
Equivalence Analysis			
FDA Day 29 PP Population (n)	184	43	6
LS Mean (SE)	0.2915 (0.0237)	0.2753 (0.0458)	
90% CI for LS Mean Ratio of Test/RLD	(80.2% , 148.5%)		
FDA PP Population (n)	181	43	5
LS Mean (SE)	0.2903 (0.0239)	0.2756 (0.0459)	
90% CI for LS Mean Ratio of Test/RLD	(79.7% , 147.8%)		
Superiority Analysis			
FDA mITT Population (n)	255	64	9
LS Mean for difference from Placebo (SE)	0.2248 (0.1143)	0.2081 (0.1108)	

P-value for difference from Placebo	0.0503	0.0647

*Source: Reviewer's Analysis

6 REFERENCE

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Hankinson at al., "Spirometric Reference Values from a Sample of the General U.S. population." *American Journal of Respiratory and Critical Care Medicine* Vol. 159, No. 1 (Jan 01, 1999)



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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 208891

OTHER REVIEW(s)

Clinical Review of Drug-Device Combination Product Addendum

ANDA number	208891
Drug Product	Fluticasone Propionate and Salmeterol Inhalation Powder 100/50µg and 250/50µg
Applicant Name	Mylan Pharmaceuticals Inc.
Treatment Indication	1) Treatment of asthma in patients aged 4 years and older 2) Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD)
Reference Listed Drug (RLD)	Advair Diskus® (Fluticasone Propionate and Salmeterol Xinafoate) 100/50µg, 250/50µg, and 500/50µg
NDA number for RLD	NDA 021077 (approved on 8/24/2000)
RLD Applicant Name	Glaxo Group LTD
Original Submission Date	December 29, 2015
Materials Reviewed	• Original ANDA submission: 12/29/2015 • ANDA amendment: 8/11/2016 (Easily Correctable Deficiency Response to Division of Bioequivalence), 9/28/2016 (Easily Correctable Deficiency Response to Division of Bioequivalence), 4/3/2017 (Request for a Post Complete Response Scientific Meeting), 4/4/2017 (Post Complete Response Clarification Request Written Responses Requested), 5/19/2017 (Response to Agency's Request for Clarification Regarding Mylan's Meeting Request), 8/7/2017 (Sponsor Minutes – Post Complete Response Scientific Meeting), 8/28/2017 (Resubmission – 1st Major Complete Response Amendment), 12/18/2017 (Information Request Response to Division of Clinical Review), 2/26/2018 (Discipline Review Letter Response to Division of Labeling Review), 12/13/2018 (Discipline Review Letter Response to Division of Labeling Review), 12/17/2018 (Amendment to Discipline Review Letter Response to Division of Labeling Review) • Clinical Review of Drug-Device Combination Product Review by Michael Spagnola, M.D. completed on June 26, 2018 • DMEPA Device Orientation Study Review by Lissa C. Owens, Pharm.D. completed on March 16, 2017 • DMEPA Device Orientation Study Review Memorandum by Mishale Mistry, Pharm.D., MPH completed on June 26, 2018 • Labeling review by JuWon Lee, Pharm.D. completed on June 11, 2018 • Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry, Published January 2017 • FDA Draft Product Specific Guidance for Fluticasone Propionate; Salmeterol Xinafoate, Recommended September 2013
Primary Reviewer	Michael Spagnola, M.D. Medical Officer Division of Clinical Review (DCR), Office of Bioequivalence (OB), Office of

	Generic Drugs (OGD)
Secondary Reviewer	Carol Kim, Pharm.D. Acting ANDA Team Leader, DCR, OB, OGD
Tertiary Reviewer	Mark Ritter, M.D. Associate Division Director, DCR, OB, OGD
Date of Completion	January 28, 2019
DCR Conclusion	DCR concludes that the differences in Step 2 and Step 4 of the IFU for Mylan's Wixela Inhub (CRC749) inhaler are acceptable minor design differences due to permissible differences in device design and manufacturing. The overall conclusions and recommendations remain the same as stated in the Clinical Review of Drug-Device Combination Product Review completed on June 26, 2018.
Deficiency Classification	☐ Major ☐ Minor ☒ N/A (Review is Adequate)

1 INTRODUCTION AND BACKGROUND

This is an addendum to the Clinical Review of Drug-Device Combination Product completed by Michael Spagnola, M.D. on June 26, 2018 and in response to the Division of Labeling Review consult requesting a clinical review of the proposed Instructions for Use (IFU) submitted by Mylan for ANDA 208891. The addendum provides clarification for Step 2 and Step 4 of the Instructions for Use in Section 2.3 (“Labeling Comparison”) of the Clinical Review of Drug-Device Combination Product Review completed on June 26, 2018.

On December 29, 2015, the Applicant (Mylan) submitted ANDA 208891 for Fluticasone Propionate and Salmeterol Inhalation Powder 100/50µg, 250/50µg, and 500/50µg as a generic version of the RLD, Advair Diskus® Fluticasone Propionate and Salmeterol Xinafoate 100/50µg, 250/50µg, and 500/50µg. On April 18, 2018, the Division of Labeling Review sent a consult to the Division of Clinical Review requesting a clinical review of the proposed Instructions for Use (IFU) submitted by Mylan for ANDA 208891. On June 26, 2018, the Division of Clinical Review completed their consult response and the review was adequate from DCR’s perspective.¹ In the consult response, DCR concluded “there are acceptable differences between the Wixela Inhub (CRC749) inhaler and the RLD, Advair Diskus® inhaler. The data submitted supports that the Wixela Inhub (CRC749) inhaler will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling.” On December 13, 2018 and December 17, 2018, Mylan submitted a response to the Division of Labeling Review’s Discipline Review letter and an amendment to their response that included updated labeling and Instructions for Use.

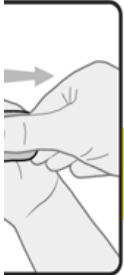
2 REVIEW OF COMPARATIVE THRESHOLD ANALYSES

2.1 Labeling Comparison

Figures 1 through 2 provide a comparison and justification from Mylan for any differences in Step 2 and Step 4 of the Instructions for Use for their proposed generic product compared to the RLD.

¹ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881b37e29>

Figure 1: Mylan's Comparison of Instructions for Use (Step 2) Between CRC749 Inhaler and Advair Diskus® Inhaler

REFERENCE LISTED DRUG APPROVED LABELING ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder) 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg/50 mcg APPROVED DECEMBER 20, 2017	MYLAN'S PROPOSED OUTSERT TEXT Wixela™ Inhub™ (fluticasone propionate and salmeterol inhalation powder, USP) 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg/50 mcg (MDR:FPSX:R8; Revised: 12/2018)
Step 2. Slide the lever until you hear it click. Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the lever away from the mouthpiece as far as it will go until it clicks. See Figure C.	hand on the grip lower the mouthpiece cover from top to bottom. See Figure C.
 Figure B	 Figure C
- The number on the counter will count down by 1. The DISKUS is now ready to use. Follow the instructions below so you will not accidentally waste a dose: Do not close the DISKUS. Do not tilt the DISKUS. Do not move the lever on the DISKUS.	Step 2. Push down the lever: - Hold the INHUB in the vertical position. Push the yellow lever down to the end of the purple arrows (you may hear a click). See Figure D. - The INHUB is now ready to use. Follow the instructions below so you will not accidentally waste a dose: Do not close the INHUB. Do not move the lever on the INHUB once pushed down.

Source: Annotated Comparison with Listed Drug (Labeling), eCTD Sequence 0053, Module 1.14.3.1, p. 69

Reviewer's Comments: *The removal of the text that informs users "that the number of the counter will count down by 1" from Step 2 of the IFU for Mylan's proposed generic inhaler is an acceptable minor design difference and is due to permissible differences in device design and manufacturing. (b) (4) moved the statement that informs users that "the dose counter will count down by one dose" to Step 4 of (b) (4)*

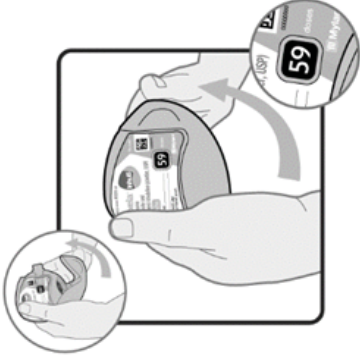
(b) (4) The difference in the timing of when the dose counter counts down by one dose is acceptable as users of both inhalers are appropriately informed of the number of remaining doses in the inhaler before they need to take the next dose of medication.

Unlike the Advair Diskus inhaler, the Wixela Inhub (CRC749) inhaler may not make an audible "click" when the lever has been pushed to the correct position. This difference in the device was previously determined to be acceptable. Thus, it is acceptable for the Applicant to remove the text in the heading for Step 2 that references sliding the lever until it clicks and to replace it with text informing users to push down the lever.

*There is an acceptable minor design difference in the instructions provided to the user to avoid accidentally wasting a dose. The IFU for the Wixela Inhub (CRC749) inhaler informs users to "**Do not** move the lever on the INHUB once pushed down" and the IFU for the RLD informs user to "**Do not** move the lever on the DISKUS." The addition of the words "once pushed down" in the IFU for Wixela Inhub (CRC749) inhaler is acceptable due to permissible differences in device design and to accurately provide instructions to the user.*

These differences would not impact the conclusion that the generic product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling.

Figure 2: Mylan's Comparison of Instructions for Use (Step 4) Between CRC749 Inhaler and Advair Diskus® Inhaler

REFERENCE LISTED DRUG-APPROVED LABELING ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder) 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg/50 mcg APPROVED DECEMBER 20, 2017	MYLAN'S PROPOSED OUTSERT TEXT Wixela™ Inhub™ (fluticasone propionate and salmeterol inhalation powder, USP) 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg/50 mcg (MDR:FPSX:R8; Revised: 12/2018)
Step 4. Close the DISKUS. - Place your thumb in the thumb grip and slide it back towards you as far as it will go. See Figure F. Make sure the DISKUS clicks shut and you cannot see the mouthpiece.  Figure F - The DISKUS is now ready for you to take your next scheduled dose in about 12 hours. When you are ready to take your next dose, repeat Steps 1 through 4.	Step 4. Close the INHUB. - Push the mouthpiece cover up to the closed position, this will automatically return the yellow lever to the start position. See Figure G. Make sure the INHUB is shut and you cannot see the mouthpiece. - The dose counter will count down 1 dose as you close the mouthpiece cover. This will now tell you how many doses are left. The INHUB is now ready for you to take your next scheduled dose in about 12 hours. When you are ready to take your next dose, repeat Steps 1 through 4.  Figure G

Source: Annotated Comparison with Listed Drug (Labeling), eCTD Sequence 0053, Module 1.1.4.3.1, p. 72

Reviewer's Comments: *The addition of the text that informs users that “the dose counter will count down by one dose” to Step 4 of the IFU for Mylan’s proposed generic inhaler is an acceptable minor design difference and due to permissible differences in device design and manufacturing. Including this statement in Step 4 of the IFU for Mylan’s Wixela Inhub (CRC749) inhaler accurately reflects when the device counter counts down by one. In the Advair Diskus® inhaler (RLD), the dose counter counts down by one dose when the lever is slid until it clicks and for Mylan’s Wixela Inhub (CRC749) inhaler, the dose counter counts down by one when the mouthpiece cover is closed. The addition of the text that informs users that the dose counter will count down by one dose to Step 4 of the IFU is acceptable and would not impact the full expectation that the proposed device inhaler will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling when the proposed device inhaler is substituted for the RLD.*

3 CONCLUSION

DCR concludes that the differences in Step 2 and Step 4 of the IFU for Mylan’s Wixela Inhub (CRC749) inhaler are acceptable minor design differences due to permissible differences in device design and manufacturing.

The three differences identified in this addendum would not impact the full expectation that the proposed device inhaler will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling when the proposed device inhaler is substituted for the RLD.

The overall conclusions and recommendations remain the same as stated in the Clinical Review of Drug-Device Combination Product Review completed on June 26, 2018.



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Clinical Review of Drug-Device Combination Product

ANDA number	208891
Drug Product	Fluticasone Propionate and Salmeterol Inhalation Powder 100/50µg and 250/50µg
Applicant Name	Mylan Pharmaceuticals Inc.
Treatment Indication	1) Treatment of asthma in patients aged 4 years and older 2) Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD)
Reference Listed Drug (RLD)	Advair Diskus® (Fluticasone Propionate and Salmeterol Xinafoate) 100/50µg, 250/50µg, and 500/50µg
NDA number for RLD	NDA 021077 (approved on 8/24/2000)
RLD Applicant Name	Glaxo Group LTD
Original Submission Date	December 29, 2015
Materials Reviewed	• Original ANDA submission: 12/29/2015 • ANDA amendment: 8/11/2016 (Easily Correctable Deficiency Response to Division of Bioequivalence), 9/28/2016 (Easily Correctable Deficiency Response to Division of Bioequivalence), 4/3/2017 (Request for a Post Complete Response Scientific Meeting), 4/4/2017 (Post Complete Response Clarification Request Written Responses Requested), 5/19/2017 (Response to Agency's Request for Clarification Regarding Mylan's Meeting Request), 8/7/2017 (Sponsor Minutes – Post Complete Response Scientific Meeting), 8/28/2017 (Resubmission – 1st Major Complete Response Amendment), 12/18/2017 (Information Request Response to Division of Clinical Review), 2/26/2018 (Discipline Review Response to Division of Labeling Review) • FDA Complete Response letter signed by Denise Toyer McKan on 3/28/2017 • FDA Face-to-Face Meeting Minutes for Post Complete Response Scientific Meeting held on 7/13/2017 • Division of Bioequivalence Review for Dry Powder Inhaler Products by Tian Ma, Ph.D. completed on 3/22/2017 • DMEPA Device Orientation Study Review by Lissa C. Owens, Pharm.D. completed on March 16, 2017 • Response to Consult Request by Denise S. Conti, Ph.D. completed on March 20, 2017 • OPQ Consult Response by Fang Yuan, Ph.D. completed on February 27, 2018 • DMEPA Device Orientation Study Review Memorandum by Mishale Mistry, Pharm.D., MPH completed on June 26, 2018 • Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry, Published January 2017 • FDA Draft Product Specific Guidance for Fluticasone Propionate; Salmeterol Xinafoate, Recommended September 2013
Primary Reviewer	Michael Spagnola, M.D.

	Medical Officer Division of Clinical Review (DCR), Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Secondary Reviewer	Carol Kim, Pharm.D. Acting ANDA Team Leader, DCR, OB, OGD
Tertiary Reviewer	Mark Ritter, M.D. Associate Division Director, DCR, OB, OGD
Date of Completion	June 26, 2018
GDUFA Goal Date	June 27, 2018
DCR Conclusion	DCR concludes that there are acceptable differences between the Wixela Inhub (CRC749) inhaler and the RLD, Advair Diskus® inhaler. The data submitted supports that the Wixela Inhub (CRC749) inhaler will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling.
Deficiency Classification	☐ Major ☐ Minor ☒ N/A (Review is Adequate)

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1 INTRODUCTION AND BACKGROUND

1.1 Summary of Drug Information Pertinent to Review

On December 29, 2015, the Applicant (Mylan) submitted ANDA 208891 for Fluticasone Propionate and Salmeterol Inhalation Powder 100/50µg, 250/50µg, and 500/50µg as a generic version of the RLD, Advair Diskus® Fluticasone Propionate and Salmeterol Xinafoate 100/50µg, 250/50µg, and 500/50µg. On March 28, 2017, the Agency issued a Complete Response (CR) letter to the Applicant for ANDA 208891 and the Applicant submitted a Major Complete Response Amendment on August 28, 2017. To date, there is one other pending ANDA (ANDA 203433 – West-Ward Pharmaceuticals International Limited) and no approved ANDAs for Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder.

In support of an approval for this ANDA, Mylan submitted a non-dosing human factors study (MGR000-1004), also called a device orientation study, in their original ANDA submitted on December 29, 2015. Mylan also submitted a comparative threshold analyses consisting of a labeling comparison, comparative task analysis, and physical comparison of the delivery device. According to the Applicant, the outcome of their Comparative Threshold Analyses of the User Interface for all differences identified was minor. Mylan asserted that the identified differences were “minor, relative to the risk profile of the product, such that the design differences do not involve any critical design attributes that impact the substitution of the RLD with the Wixela Inhub (CRC749) inhaler when there is no additional training or healthcare intervention.” On April 18, 2018, the Division of Clinical Review received a consult request from the Division of Labeling Review (DLR) requesting a review of Mylan’s revised Instructions for Use (IFU) submitted by Mylan.

This review evaluates the Comparative Threshold Analyses, Device Orientation Study (MGR000-1004), Assessment of Orientation of Use on Uniformity of Emitted Dose Study, Impact of Potential Powder Buildup on Device Functionality Study, and the revised Instructions for Use (IFU) submitted by Mylan for ANDA 208891. This review also serves as a consult response to the Division of Labeling Review’s consult sent to the Division of Clinical Review on April 18, 2018.

1.1.1 Product Labeling

The current product labeling for Advair Diskus (Fluticasone Propionate and Salmeterol Xinafoate) 100/50µg, 250/50µg, and 500/50µg was approved on December 20, 2017. In addition to the Prescribing Information, the Advair Diskus product labeling also includes Patient Counseling Information, Medication Guide, and Instructions for Use (IFU). The following information is taken from the latest approved product labeling, available at the Drugs@FDA webpage.¹

1.1.1.1 Indication

Advair Diskus is a drug-device combination product containing a corticosteroid and a long-acting beta₂-adrenergic agonist (LABA) indicated for 1) treatment of asthma in patients aged 4 years and older and 2) maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). An important limitation of use is that Advair is not indicated for relief of acute bronchospasm.

¹ https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021077s056s057lbl.pdf

1.1.1.2 Dosage Forms and Strengths

Inhalation Powder: Inhaler containing a foil blister strip of powder formulation for oral inhalation. The strip contains combination of fluticasone propionate 100, 250, or 500 mcg and salmeterol 50 mcg per blister.

1.1.1.3 Dosage/Administration

- For oral inhalation only
- Treatment of asthma in patients aged 12 years and older: 1 inhalation of Advair Diskus 100/50, Advair Diskus 250/50, or Advair Diskus 500/50 twice daily. Starting dosage is based on asthma severity.
- Treatment of asthma in patients aged 4 to 11 years: 1 inhalation of Advair Diskus 100/50 twice daily.
- Maintenance treatment of COPD: 1 inhalation of Advair Diskus 250/50 twice daily.

Advair Diskus should be administered as 1 inhalation twice daily by the orally inhaled route only. After inhalation, the patient should rinse his/her mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis. More frequent administration or a greater number of inhalations (more than 1 inhalation twice daily) of the prescribed strength of Advair Diskus is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. Patients using Advair Diskus should not use additional LABA for any reason.

1.1.1.4 How Supplied

Advair Diskus is supplied as a disposable purple plastic inhaler containing a foil blister strip with 60 blisters. The inhaler is packaged in a plastic-coated, moisture-protective foil pouch. Advair Diskus is also supplied in an institutional pack containing 14 blisters.

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F and 86°F (15°C and 30°C). Store in a dry place away from direct heat or sunlight. Keep out of reach of children.

Advair Diskus should be stored inside the unopened moisture-protective foil pouch and only removed from the pouch immediately before initial use. Discard Advair Diskus 1 month after opening the foil pouch or when the counter reads “0” (after all blisters have been used), whichever comes first. The inhaler is not reusable. Do not attempt to take the inhaler apart.

Reviewer’s Comments: *On December 20, 2017, the Boxed Warning about asthma-related death was removed from the drug label of Advair® after a review of four large clinical safety trials showed that treating asthma with long-acting beta agonists in combination with inhaled corticosteroids does not result in significantly more serious asthma-related side effects than treatment with inhaled corticosteroids alone.*

1.2 Pertinent Regulatory Background

In general, generic drug products classified as therapeutically equivalent to their RLD can be expected to produce the same clinical effect and safety profile as the RLD when substituted under the conditions specified in the product labeling. In assessing the TE of a proposed generic combination product, FDA considers whether the proposed generic can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use. While FDA does not expect

that the user interface for a proposed generic be identical to the user interface for its RLD, any identified differences between the proposed generic and its RLD should be adequately analyzed, scientifically justified, and not preclude approval under an ANDA. In certain instances, additional information and/or data, such as data from comparative use human factors studies, may be warranted to further assess differences identified in the user interface may impact the clinical effect or safety profile of the generic combination product when the generic is substituted for the RLD.² FDA recently set forth its current thinking in draft guidance on “Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA” (2017).

1.3 Generic Drug Product Development

The Applicant submitted multiple controlled correspondences and had multiple meetings (face-to-face and teleconference) with the Agency during the development of their proposed product:

- December 3, 2009: Face-to-face meeting between FDA and Pfizer (company who was leading the development of the CRC749 inhaler before it was acquired by Mylan);³
- May 12, 2010: Face-to-face meeting between FDA and Pfizer;⁴
- December 12, 2012: Type C Meeting between FDA and Mylan;⁵
- September 27, 2013: Type C Meeting between FDA and Mylan;⁶
- August 4, 2014: Mylan’s Protocol Assessment Request (Protocol Number 26230) for proposed study MGR000-1004 “A non-dosing inhaler development study to assess the use of the 4 key operational steps of CRC749 and the likelihood of orientation-related errors by representative users, including Advair® Diskus ® patients”; and⁷

² <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf>

³ FDA Meeting Minutes (available at <\\fda.gov\wodc\CDER\OGD\OGDS11\ScienceGroup\MeetingswithFirms\Pfizer>, FDA OGD minutes - Pfizer FINAL Dec 22 2009.doc).

⁴ FDA Meeting Minutes (available at <\\fda.gov\wodc\CDER\OGD\OGDS11\ScienceGroup\MeetingswithFirms\Pfizer>, Pfizer_Fluticasone_Propionate;Salmeterol_Xinafoate_FDA meetingmins_12may2010).

⁵ <http://panorama.fda.gov/document/preview?versionID=5408c2ed000a7ba25da7eff1d3cece37&ID=5408c2ed000a7ba13ead3f0553f12828>. See also Control Correspondence 12-0731, Request for Type C Meeting (July 30, 2012) (available at <\\fda.gov\wodc\CDER\OGD\OGDS6\Controls\2012-docs>, 12-0731.pdf) and Control Correspondence 12-0850, Mylan’s Meeting Minutes from Type C Meeting (available at <\\fda.gov\wodc\CDER\OGD\OGDS6\Controls\2012-docs>, 12-0850.pdf).

⁶ <http://mercado.fda.gov/search/resources/panorama/documentum/Panorama/090026f8806f745d?includeRequestSystem=false>. See also Control Correspondence 13-0422, Request for Type C Meeting (May 22, 2013) (available at <\\fda.gov\wodc\CDER\OGD\OGDS6\Controls\2013-docs>, 13-0422.pdf) and Control Correspondence 13-0422A, Updated Request for Type C Meeting (July 16, 2013) (available at <\\fda.gov\wodc\CDER\OGD\OGDS6\Controls\2013-docs>, 13-0422A.pdf).

⁷ August 26, 2014 Cover Letter (available at <http://panorama.fda.gov/document/preview?versionID=53fde4dd0007ef05ef0ef11915ec1126&ID=53fde4dd0007ef04a3048dd7f7797ee6>); Protocol Assessment Request (available at <http://panorama.fda.gov/document/preview?versionID=53fde4dd0007ef07263462a3b4b00cae&ID=53fde4dd0007ef0627b739c421f5c608>). See also DMEPA, Human Factors Study Protocol Memorandum (December 4, 2014) (available at <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f880894f0c>) and ORS Review for

- October 22, 2015: Face-to-face meeting between FDA and Mylan.⁸

1.4 Other Relevant Information

On December 29, 2015, the Applicant submitted ANDA 208891 for Fluticasone Propionate and Salmeterol Inhalation Powder 100/50µg, 250/50µg, and 500/50µg as a generic version of the RLD, Advair Diskus® Fluticasone Propionate and Salmeterol Xinafoate 100/50µg, 250/50µg, and 500/50µg. This review assesses the non-dosing human factors study (MGR000-1004), also called the device orientation study, and the Comparative Threshold Analyses. The flow profiling study (MGR000-1003) and the device robustness study (MGR001-1010) were not evaluated in this review.

The Division of Bioequivalence I (DB I) in the Office of Generic Drugs initially had primary review responsibilities of the clinical endpoint bioequivalence study and the device orientation study for the original ANDA submission. The primary review responsibility for the review from a clinical perspective of the drug-device combination product was transferred to DCR from DB I after the submission of the Major Complete Response Amendment dated August 28, 2017.

On April 18, 2018, the Division of Clinical Review received a consult request from the Division of Labeling Review (DLR) requesting a review of Mylan's revised Instructions for Use (IFU) submitted by Mylan. DLR noted that on April 1, 2016, they previously consulted the Division of Therapeutic Performance (DTP) to review the proposed Instructions for Use.⁹

The following list summarizes the information considered by DCR in this review:

- Division of Bioequivalence I (DB I) consult request (June 30, 2016) and DMEPA consult response (March 16, 2017)
 - DMEPA ECD (August 10, 2016) and Mylan ECD response (August 11, 2016)
 - DMEPA ECD (September 22, 2016) and Mylan ECD response (September 28, 2016)
- DB I Review (March 22, 2017)
- Bioequivalence Deficiency 47, FDA Complete Response Letter (March 28, 2017)
- Mylan Request for Post Complete Response Scientific Meeting (April 4, 2017)
- FDA Request for Additional Information to Update Meeting Request Package (May 10, 2017) and Mylan Response (May 19, 2017)
- FDA Meeting Minutes from July 13, 017 Post Complete Response Scientific Meeting
- Mylan Complete Response Amendment (August 28, 2017)
- FDA Discipline Review Letter (DRL) – Labeling (February 12, 2018) and Mylan DRL Response (February 26, 2018)
- Division of Labeling Review consult request (April 18, 2018)
 - Division of Labeling Review consult request (April 1, 2016) and Division of Therapeutic Performance consult response (May 13, 2016)
- FDA Information Request (IR) (June 18, 2018) and Mylan IR Response (June 19, 2018)
- DMEPA Device Orientation Study Review Memorandum (June 26, 2018)

Control No. 26230 (available at

<http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f8809038bc>).

⁸ FDA Meeting Minutes (available at <http://panorama.fda.gov/task/view?ID=5595768a00f7bc4f56c280ebc473538b>). See also ORS Review for Control No. 844398 (available at

<http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f880bf27b1>).

⁹ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f880cf3448>

2 REVIEW OF COMPARATIVE THRESHOLD ANALYSES

2.1 Physical Comparison of Delivery Device Constituent Part

Mylan conducted a physical comparison of delivery device constituent parts between the CRC749 inhaler and the Advair Diskus inhaler. According to Mylan's Comparative Threshold Analyses, all differences identified in the physical comparison between the two inhalers were minor and none of the design differences identified would impact the clinical effect or safety profile of the Wixela Inhub (CRC749) inhaler compared to the RLD.

Reviewer's Comments: *Actual device inhalers were evaluated for comparison after the Applicant sent the Agency one sample of the finished (to-be-marketed) Wixela Inhub (CRC749) inhaler and one sample of the RLD, Advair Diskus inhaler, in an ECD response. The Applicant's description of the Wixela Inhub (CRC749) inhaler and Advair Diskus inhaler were accurate and verified through visual inspection of the samples provided by the Applicant in their ECD response.*

(b) (4)

(b) (4)

4 CONCLUSION

DCR concludes that there are acceptable differences between the Wixela Inhub (CRC749) inhaler and the RLD, Advair Diskus® inhaler. The data submitted supports that the Wixela Inhub (CRC749) inhaler will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling.

5 CLINICAL COMMENTS TO BE PROVIDED TO THE APPLICANT

The Clinical Discipline has completed its clinical review of the drug-device combination product and has no comments at this time.



Michael
Spagnola

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Date: 6/26/2018 01:18:18PM
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Mark
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DEVICE ORIENTATION STUDY REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: March 16, 2017
Requesting Office or Division: Division of Bioequivalence (DBI)
Application Type and Number: ANDA 208891
Product Name and Strength: Wixela Inhub (fluticasone propionate and salmeterol xinafoate) Inhalation Powder
Product Type: Drug-Device Combination Product
Rx or OTC: Rx
Applicant/Sponsor Name: Mylan Pharmaceuticals Inc.
Submission Date: February 16, 2016
OSE RCM #: 2016-1503
DMEPA Primary Reviewer: Lissa Owens, PharmD
DMEPA Team Leader: Mishale Mistry, PharmD, MPH
DMEPA Associate Director for Human Factors: QuynhNhu Nguyen, MS
OMEPRM Acting Deputy Director: Lubna Merchant, PharmD, MS

1 REASON FOR REVIEW

This review evaluates the results of the device orientation study conducted by Mylan and submitted on February 16, 2016 for their proposed product, Wixela Inhub, a proposed generic for Advair Diskus. The Division of Bioequivalence (DBI) within the Office of Generic Drugs (OGD) requested that DMEPA review the device orientation study.

2 REGULATORY HISTORY

During a December 12, 2012 meeting with the Applicant^a, OGD expressed concern regarding the difference in the orientation of use between the proposed Wixela Inhub device and the currently marketed Advair Diskus device. There were concerns that patients may use the proposed product in a horizontal orientation, as they would with the Advair Diskus which may result in incomplete lip sealing around the mouthpiece resulting in an incomplete dose. Additionally, it was thought that holding the proposed inhaler horizontally may lead to a different air flow pattern through the inhaler compared to when the proposed device is used vertically. Hence, the Agency recommended that the firm demonstrate one of the following:^b

- Low likelihood of the orientation-related errors when the MGR001 (Wixela Inhub device) is used by the patients including prior RLD users.
- Inhalation profiles through inhaler [i.e. peak inhalation flow rate (PIFR) and total inhalation volume through inhaler] when used by the patients and the device retention (i.e. amount of drug retains in the device and air channel following inhalation) are comparable at both the (vertical and horizontal) orientation

DMEPA reviewed the device orientation study protocol, submitted on August 27, 2014 under the IND, in OSE RCM 2014-2270^c which included recommendations to the study design prior to its implementation. We note that the Applicant incorporated our recommendations to the study protocol.

The Applicant submitted the results of the device orientation study on February 16, 2016, which noted that 10 participants inhaled from the inhaler in the horizontal position at some point throughout the 3 tasks. On August 10, 2016, DMEPA sent an easily correctible deficiency (ECD) to the Applicant requesting information on the breakdown in which task each participant executed the error. In addition, DMEPA requested that the Applicant specify which participants were Advair users and which were Advair/DPI naïve users. The Applicant responded to the ECD on August 11, 2016. Subsequently, based on input from the clinical team, DMEPA sent an additional ECD to the Applicant on September 22, 2016 regarding 1) whether powder build-up or other device related issues could occur if the device was continually used in the horizontal

^a <\\cdsnas\OGDS6\CONTROLS\2012-docs\12-0731.pdf> p. 32-33 of 34, Question 8

^b Letter to G.Geba (OGD) from S. Talton (Mylan) re: "MGR001 (fluticasone propionate plus salmeterol xinafoate inhalation powder in CRC749 inhaler), Meeting Minutes from Type C Meeting Held on December 12, 2012" (January 28, 2013).

^c Owens, L. Human Factors Memo Review for MGR001 (Powder) in CRC749 (Inhaler) (IND118769). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 Dec 4. RCM No.: 2014-2270

orientation, and 2) how would continual use of the device in the horizontal orientation affect the delivery of subsequent doses. The Applicant responded to the ECD on September 28, 2016.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study (HFS)	C
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F
Labels and Labeling	G-N/A

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We considered the human factors study report submitted by the Applicant on February 16, 2016, along with the design of the RLD device and the currently proposed Wixela Inhub device.

We note that the proposed product under ANDA 208891 has the same active ingredient, route of administration, dosage form, and strength(s) as the RLD, Advair Diskus. Both products are dry powder inhalers containing 60 doses. In addition, both the RLD product and the ANDA product require similar steps for administration: Step 1 Open the device, Step 3 Inhale the medication, and Step 4 Close the device (see Appendix F for details). However, one key difference between the Wixela Inhub device and the RLD is the proposed orientation of use. Specifically, the Wixela Inhub is intended to be held vertically during administration whereas the RLD is intended to be held horizontally during administration. In addition, the second step in using the devices is different due to the difference in orientation. The RLD instructs patients to slide the lever until you hear a click whereas the proposed product instructs patients to “push the yellow lever down to the end of the purple arrows (you may hear a click).”

FDA had previously raised concerns that patients may use the proposed product in a horizontal orientation, as they would with the RLD. Although we reviewed the device orientation study protocol, submitted on August 27, 2014 and made recommendations to the study design, we note that this study was not designed to assess the differences in use error rates between this ANDA product and the RLD.

When differences in design are identified between an ANDA product and RLD, our current approach is to recommend that the Applicant analyze and describe these user interface differences between the ANDA product and RLD. Based on the outcome of these comparative analyses, an Applicant may need to provide additional data, such as data from a comparative use human factors study to address whether the proposed product can be substituted for the RLD with the full expectation that it will produce the same clinical and safety profile as the RLD under the conditions specified in the labeling.^d

We note that the Applicant conducted a non-comparative HFS. The Applicant has not provided data, such as data from a comparative use human factors study that assesses the differences in use error rates between the proposed product and the RLD. Such data may be warranted to assess the acceptability of the differences in device and labeling resulting from these differences in user interface between the proposed product and the RLD and to help evaluate whether the proposed product can be substituted for the RLD with the full expectation that the proposed product will produce the same clinical effect and safety under the conditions specified in labeling.

Below is our review of the human factors data the Applicant submitted, although we note that it is not a comparative use human factors study and therefore generally does not provide sufficient data and information to evaluate the acceptability in an ANDA of the differences in the proposed product's device as compared to the RLD.

DMEPA reviewed the results of the device orientation study. The following errors occurred in the study:

1. Wrong orientation (n=10)
2. Lever not pushed fully (n=1)
3. Inhalation step not complete before lever pushed fully (n=2)

Three participants committed use errors related to failure to fully push down the lever (1 DPI naïve participant) and failure to complete the inhalation step before the lever is pushed fully (1 DPI naïve participant and 1 Advair user), which would result in missed doses.

- Lever not pushed fully (n=1): After completion of the task, the participant recognized on her own that the dose counter did not decrease, meaning she did not receive the dose. However, the participant thought that this was because there was no actual drug product in the device. The participant reported that in actual use, she would re-read the IFU if this situation occurred.

^d For example, FDA recommends that sponsors consider designing a comparative use human factors study to provide sufficient data to confirm that the use error rate, for the critical task(s) as impacted by the differing external critical design attribute of the delivery device constituent part for the proposed generic combination product, is not worse than the corresponding use error rate for the RLD when used by patients and caregivers in representative use scenarios and use environments consistent with the labeled conditions of use. See Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA (January 2017) (available at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm536959.pdf>).

- Inhalation step not complete before lever pushed fully (n=2): One Advair-experienced participant deliberately inhaled as she pushed down on the lever; she stated that she used the inhaler the same way she uses her Advair Diskus as this was easier for her. Therefore, this use error does not appear to be unique to the proposed product as these participants reported using their Advair Diskus in the same way. A DPI-naïve participant appeared to be pushing the lever down and inhaling at the same time (the participant's mother was instructing the participant throughout the session as they would do at home). The participant's mother reported that they thought the medication would come out as you push down on the lever. However, the mother re-read the IFU and understood the use error that occurred.

In order to activate the dose, the lever must be pushed fully before inhaling the medication. This sequential order is identical between the ANDA and the RLD.

We note that of the 110 participants, which consisted of Advair users and Advair/DPI naïve users, 10 participants used the device horizontally at some point over the three tasks. Of the 10 participants, nine (n=9) were Advair users and one (n=1) was a DPI naïve user (see Appendix C table 2). However, per their inhalation profile, nine of these 10 participants received the target delivered dose. Specifically, the inhalation profile of these nine participants was assessed through a CRC749 inhaler, where their mean peak inhalation flow rate (PIFR) was >30 L/min and mean total inhaled volume (TIV) was >1 over three inhalations. One participant reported a low PIFR and TIV, which could potentially indicate an underdose, but this participant experienced challenges with the lung function test and did not achieve the required volumes when using the device correctly with a vertical orientation. Therefore, per the Applicant, this error is not considered a true device related use error. DMEPA and the clinical team agreed with the Applicant's assessment.

Additionally, per the analysis of the inhalation profiles among participants who used the proposed product in the wrong orientation, it appears that the device may be used in the vertical or horizontal position.

However, we had concerns about a potential build-up of powder and other device-related issues if the device was used continually in the horizontal orientation. The Applicant submitted data to demonstrate that the mechanical function of the device is maintained regardless of the orientation of the device during use and that potential powder build-up would not impact mechanical function of the device through its life.

(b) (4)

(b) (4)

5 CONCLUSION

The proposed Wixela Inhub device has a different device orientation when compared to the RLD, Advair Diskus. The Applicant has not submitted supporting data, such as data from a comparative use human factors study that assesses the differences in use error rates between this product and the RLD as a result of design differences between the two products.

Such data may be warranted to assess the acceptability of the differences in device and labeling resulting from differences in user interface between the proposed product and the RLD and to help evaluate whether the proposed product can be substituted for the RLD with the full expectation that the proposed product will produce the same clinical effect and safety under the conditions specified in labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Wixela Inhub that Mylan submitted in their proprietary name submission on September 2, 2015.

Table 2. Relevant Product Information for Wixela Inhub	
Initial Approval Date	N/A
Active Ingredient	Fluticasone Propionate and Salmeterol
Indication	Treatment of asthma in patients four (4) years and older, maintenance treatment of airflow obstruction and reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD)
Route of Administration	Oral Inhalation
Dosage Form	Dry powder inhaler
Strength	100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg
Dose and Frequency	1 inhalation twice a day
How Supplied	Pre-metered, multi-dose, disposable dry powder inhaler; a plastic container containing two (2) 30-dose disks with pre-metered individual doses
Storage	20° to 25°C (68° to 77°F). Keep in a dry place away from direct heat and sunlight.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On August 5, 2016, we searched the L:drive and AIMS using the terms, CRC749 to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous human factors review^e and we confirmed that our previous recommendations were implemented.

^e Owens, L. Human Factors Memo Review for MGR001 (Powder) in CRC749 (Inhaler) (IND118769). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 Dec 4. RCM No.: 2014-2270

APPENDIX C. HUMAN FACTORS STUDY

This Device Orientation study was designed to identify whether a participant who inhaled through the inhaler horizontally would successfully achieve a flow profile that demonstrates their ability to deliver a therapeutic dose of MGR001 in a real-life dosing scenario. Once the patient has prepared the dose (open, push down), inhalation of a therapeutic dose will be achieved with a PIFR of >30 L/min. The acceptance criteria of 30L/min was determined through the in-vitro flow rate dependency data (described in Section 3.2.P.2.04) which showed reproducibility of the target delivered dose (ED/aPSD) at flow rates ranging from 30-90 L/min.

Participants

Table 3.2.P.7-62: User Groups and Recruitment Criteria

Age Group	Number of Advair® Diskus® patients	Number of DPI naïve patients with asthma and/or COPD
12-17	15	15
18-64	25	25
≥65	15	15
Total per user group	55	55
Inclusion/Exclusion Criteria	• have been using Advair® Diskus® for a minimum of 3 months. • have been diagnosed with asthma and/or COPD. • are 12 years old or older. • currently take their medication regularly (1 inhalation twice a day). • has not participated in a paid research study relating to the medical inhaler or pharma industry in the last 6 months.	• have been diagnosed with asthma and/or COPD • are 12 years old or older. • have no personal experience of using a dry powder inhaler to administer a dose to themselves or another. • has not participated in a paid research study relating to the medical inhaler or pharma industry in the last 6 months.

Table 3.2.P.7-63: Demography of Users

Number of Advair® Diskus® patients	Number of DPI naïve patients with asthma and/or COPD
• 53 Right handed/2 Left handed • 10 Manual Dexterity issues in hands or fingers • 29 Male/26 Female	• 46 Right handed/7 Left handed/2 Ambidextrous • 6 Manual Dexterity issues in hands or fingers • 28 Male/27 Female

Error Categories

Table 3.2.P.7-64: Error definitions

Error Type	Description of Error
Orientation Related Use Error	A participant inhales from the inhaler in the horizontal orientation however achieves a PIFR of >30 L/min and TIV >1 L.
Device Use Error	A participant inhales from the inhaler in the horizontal orientation and does not achieve a PIFR of >30 L/min and TIV >1 L
Use Error: Other	An action or lack of action from the participant not related to orientation of use that leads to a different result than that intended.

Any participant who held the CRC749 in the horizontal orientation during the inhalation step in any of the first three tasks was asked to demonstrate their inhalation profile (with the inhaler held in the horizontal orientation) through a CRC749 inhaler connected to the Inhalation Profiling System (IPS) which assessed the participant's inhalation profile. Their mean peak inhalation flow rate (PIFR) and mean total inhaled volume (TIV) were recorded over three inhalations and assessed against the assessment criteria. If the mean data from the 3 inhalations were <30 L/min PIFR and <1L TIV respectively then the participant was asked to demonstrate one further inhalation vertically to enable an assessment of whether the root cause was device related.

Tasks

Task 1- CRC749 Participant is given the CRC749 (no active or lactose) in its intended packaging (inhaler in foil pouch in a carton with IFU) and asked to take a dose.

Task 2- CRC749 Using the same inhaler participant is asked to take another dose.

Task 3- CRC749 Using the same inhaler participant is asked to take another dose.

Criteria

Table 3.2.P.7-66: Assessment Criteria

Success Criteria		Description of criteria
A	User is able to open the Mouthpiece Cover.	The user must be able to open the Mouthpiece Cover.
B	User pushes the lever as far as it will go.	The user pushes the lever all the way to the end of the purple arrows (if the lever was pushed far enough to open the Pocket the inhaler dose counter number will decrement).
C	User leaves the lever fully pushed during inhalation.	It is acceptable for the lever to be pushed as the participant inhales or for the participant to return the lever as they inhale (success) It is unacceptable for the participant to push the lever, return the lever and then inhale (failure).
Di	User holds the inhaler in the vertical orientation	If the user inhales from the inhaler in the horizontal position this will be scored as an orientation-related use error. The participant must then go on to complete task Dii for overall criteria D success/fail.
Dii	If the user holds the inhaler in the horizontal orientation they will achieve inhaled flow rates of > 30 L/min and inhaled volumes of > 1 L (Orientation-related use error only)	Only participants who have held the inhaler horizontally should complete this criteria. The user must achieve a mean inhaled flow rate of > 30 L/min and mean total inhaled volume of >1 L.
E	User fully closes the Mouthpiece Cover for storage.	The user must close the Mouthpiece Cover fully after use for storage.
F	User does not injure themselves during use of the inhaler.	Any injuries are to be reported.

Results

3.2.P.7.2.6.1.5 Study Results - Orientation Related Use Error

10 participants inhaled from the inhaler in the horizontal position at some point throughout the 3 tasks. All 10 demonstrated their use of the inhaler horizontally using the IPS and of those 10, 9 achieved a PIFR of >30 L/min and TIV >1 L and therefore would have received a full dose. Given the participant would have received a therapeutic dose as defined by the study objective, these 9 observations were classed as an Orientation Related Use Error in line with the pre-study criteria defined in Table 3.2.P.7-66.

3.2.P.7.2.6.1.6 Study Results - Device Related Use Error

Of the 10 participants who inhaled with the inhaler in the horizontal position, 1 participant did not achieve a PIFR of >30 L/min and TIV >1 L and therefore there is a potential that this participant may not have received a full dose. The description of the error and root cause analysis for this Device Use Error is provided in Table 3.2.P.7-67. The risk assessment for this Device Use Error is provided in Table 3.2.P.7-70.

Table 3.2.P.7-67: Device Related Use Error Description and Root Cause Analysis

Description of Device Related Use Error	Root Cause Analysis	Demography
<u>Low inhaled flow rate and total inhaled volume</u> The participant held the inhaler horizontally on all 3 tasks and was therefore subsequently asked to inhale 3 times using the instrumented CRC749 inhaler. (b) (4)	Prior to the beginning of the task the participant indicated that she had an issue with the lung function test¹ at her physician's office. She stated 'the ball that goes up and down, I can't make it move'. The low inhaled flow rate and total inhaled volume achieved in both orientations of inhalation demonstrates that this is not due to the orientation of use of the device.	This was a female Advair® Diskus® user in the 65+ age group (age:82) <u>Additional information</u> (b) (6)

¹ Performance on the lung function test was not part of the study inclusion criteria.

Table 3.2.P.7-68: Use Error: Description and Root Cause Analysis

Description of Use Error: Other	Root Cause Analysis	Demography
<u>Lever not pushed fully</u> The participant did not push the lever fully on Task 3 and therefore the dose counter did not decrement.	The participant noticed that the dose counter had not decremented after the task. During the post session interview to determine root cause analysis she explained she thought it was because there was no medication in the inhaler. Once the moderator explained that the inhaler was working as it would in a real life scenario the participant said that it (the dose counter) had only moved once and so she didn't think she got a dose. She indicated that she would reread the IFU at home in this situation. The participant then reread the IFU and realised that she had not pushed the lever fully and would correct this during home use.	This was a female DPI naïve user in the 65+ age group who used a Proventil® HFA inhaler.
<u>Inhalation step not complete before the lever pushed fully</u> It was not clear whether the lever had been pushed fully before the participant stopped inhaling. He appeared to inhale as he was pushing the lever down during previous tasks and self-reported pushing the lever down and inhaling at the same time. To ensure all potential risk is captured this has been assessed as the worst case scenario - no dose.	The mother was instructing the child throughout the session as they would do at home. The mother said she used the inhaler as she has used and seen other (pMDI) inhalers: 'in my mind the medication would come out as you are pushing down on the lever'. When the mother reread the IFU she understood the intended use and the error that had been made.	This was a male DPI naïve user in the 12-17 age group who used a (b) (6) HFA inhaler. He also had previous experience with other HFAs.
<u>Inhalation step not complete before the lever pushed fully</u> The participant did not leave the lever fully pushed during inhalation. The participant inhaled as she pushed the lever down however the lever was not at the end of the purple arrows until after she finished inhaling and therefore the participant would not have received a dose.	'Deliberate Misuse' When the moderator asked the participant about how she knew when to push the lever and when to breathe, she indicated that, although she knew the instructions indicated that the lever should be pushed down before inhaling, she has always inhaled as she pushed the lever because it was easier to remember: "It's easier for me. It's easier to remember to push [the lever] down and breathe in at the same time...[I tried it] how the instructions said to do it...pull down, breathe in, take a deep breath out...no, no, no, I found my own way to do it...I wanted to do it my way, I found an easier way The participant stated she used the inhaler the same way as she used her Diskus®, as this was an easier way for her. Her mother was aware that she used her current medication incorrectly but that it was what was easier for her.	This was a female Advair® Diskus® user, Female, aged 12-17 The participant stated she 'was supposed to wear glasses but didn't wear them' Throughout the session participant demonstrated behaviors indicative of a potential social and/or psychological disorder. This was not an exclusion for recruitment. Mother stated towards end of session that the participant was on (b) (6)

3.2.P.7.2.6.1.8 Study Results -Assessment of Risk to Patient Dosing

Of the 4 reported errors only 2 were clearly attributable to the participants understanding of how to use the inhaler. Of the remaining 2 errors, one was based on deliberate misuse where the participant self-reported that she whilst she understood the intended use of the inhaler she was choosing to use the inhaler differently and was also non-compliant with instructions for use of her current inhaler (RLD). The remaining error was based on the participants poor lung function and therefore not attributable to the inhaler. All errors that could have a potential to impact patient dosing are reported through the Risk Management program (Section 3.2.P.7.2.7), taking into account the worst case scenario and are presented in Table 3.2.P.7-69, Table 3.2.P.7-70 and Table 3.2.P.7-71. Each error is discussed in terms of the severity of potential harm to the patient and occurrence levels are assigned based on evidence from the entire study population, as defined in Table 3.2.P.7-77 and Table 3.2.P.7-

Table 3.2.P.7-69: Summary of recorded errors

Error Type	Number of errors
Device Use Error	1
Use Error: Other	3

Table 3.2.P.7-70: Risk Assessment of Device Related Use Error

Description of Device Related Use Error	Risk Assessment
Low inhaled flow rate and total inhaled volume	This Device Related Use error was assessed through the User FMEA. With a peak inhaled flow rate of <30L/min and a total inhaled volume of <1L the patient may get an underdose. It is assumed that an inability to achieve this flow profile would be consistent and therefore it can be assumed that the patient would receive an underdose for more than seven consecutive dosing days. According to the MGR001 Medical Hazard Assessment (refer to Section 3.2.P.7.2.7) this underdosing scenario is scored as a severity level of 2 (defined in the risk management program as; results in temporary injury or impairment not requiring professional medical intervention) however given the patient inferred her challenges with the lung function test in her physician's office and did not achieve the required volumes in either orientation this shows that it was not as a result of the device design or orientation in which she inhaled. The occurrence level was scored as O2 (unlikely to occur with minimum history of occurrence) and the risk was deemed as acceptable.

Description of Use Error: Other	Risk Assessment
Lever not pushed fully (1 participant)	When the lever is not pushed to the point where the Pocket is prodded a dose would not be available. Upon completion of task, the participant noticed the visual cue of the dose counter and understood that as it had not decremented this meant she would not have received a dose. This prompted her to read the IFU and correct her actions. This was deemed an acceptable risk as, in accordance with the MGR001 Medical Hazard Assessment, if one dose is missed then it would be scored a severity level of 1 (inconvenience or temporary discomfort). The occurrence level was scored as O2.
Inhalation step not complete before the lever pushed fully (2 participants)	In the worst case scenario of this use error, a user who pushes the lever whilst inhaling and completes their inhalation before the lever reaches the end of the stroke may not receive a dose because, there is a potential that the dose does not become available until their inhalation is complete. This participant exhibited an inconsistent dosing technique through all 3 tasks that would not result in >7 consecutive days of missed dose. Therefore this was deemed an acceptable risk as, in accordance with the MGR001 Medical Hazard Assessment, if one dose is missed then it would be scored a severity level of 1 (inconvenience or temporary discomfort). The occurrence level was scored as O2.

Table 3.2.P.7-73: Number of Errors by User Group and Error Type

Group	Error Type		Total
	Use Error	Device Use Error	
Advair® Diskus® Users	1	1	2
DPI Naïve	2	0	2

Table 2 Breakdown of the Orientation Related Use Errors for Task 3

Participant Number	Task Number	Orientation of Inhalation	User Group	Age Group	Dominant Hand	Gender	Advair® dose	Time Using Advair® Diskus® (Years)	Other Inhaler(s) used by participant
(b) (6)	1	Horizontal	Advair® Diskus®	18 to 64	Right	Male	100/50	7	ProAir® HFA, Qvar™
	2	Horizontal							
	3	Horizontal							
	1	Horizontal	Advair® Diskus®	18 to 64	Right	Female	250/50	7	ProAir® HFA
	2	Horizontal							
	3	Horizontal							
	1	Horizontal	Advair® Diskus®	18 to 64	Right	Female	250/50	14	ProAir® HFA
	2	Horizontal							
	3	Horizontal							
	1	Vertical	Advair® Diskus®	12 to 17	Right	Male	250/50	3.5	Proventil® HFA
	2	Vertical							
	3	Horizontal							
	1	Horizontal	Advair® Diskus®	18 to 64	Left	Female	500/50	1.5	Flovent®
	2	Horizontal							
	3	Horizontal							
	1	Horizontal	DPI Naive	18 to 64	Right	Female	n/a	n/a	ProAir® HFA
	2	Horizontal							
	3	Horizontal							
	1	Horizontal	Advair® Diskus®	65+	Right	Male	100/50	4	Spiriva®
	2	Horizontal							
	3	Horizontal							
	1	Horizontal	Advair® Diskus®	65+	Right	Female	100/50	0.5	Symbicort®
	2	Horizontal							
	3	Horizontal							
	1	Horizontal	Advair® Diskus®	65+	Right	Female	250/50	1	n/a
	2	Horizontal							
	3	Horizontal							
	1	Horizontal	Advair® Diskus®	12 to 17	Right	Male	250/50	5	Ventolin® HFA
	2	Horizontal							
	3	Horizontal							

(b) (4)

APPENDIX F: OTHER



Acrobat
Document.pdf



cover-letter-001...



cover-letter-000...

Comparison of the RLD and the ANDA



annotated-com...

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LISSA C OWENS
03/16/2017

QUYNHNHU T NGUYEN
03/16/2017

LUBNA A MERCHANT
03/16/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 208891

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 60225	Version: 03
Document Status: Effective		
Title: Approval Routing Summary Form	Author: Kevin Denny	

Approval Type: FULL APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH)

RPM: Frank Giannandrea Team Leader: Bui

PI PII PIII PIV (eligible for 180 day exclusivity Yes No) MOU RX or OTC

ANDA #: **208891** Applicant: **Mylan Pharmaceuticals, Inc.**

Established Product Name: **Wixela Inhub (Fluticasone Propionate and Salmeterol Inhalation Powder USP), 100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg**

Basis of Submission (RLD): **NDA # 21077, Advair Diskus, GlaxoSmithKline**

Basis Of Submission Discontinued? Yes No

If yes, has FR published indicating the Agency determined the product was not withdrawn for reasons of safety or effectiveness?

Yes FR Notice dated _____; Document Citation _____; FR. _____ (Example: 78 FR 67365)

No Consult completed but not yet published in FR

(Is ANDA based on an approved Suitability Petition? Yes No, if yes, use SP language in template)

Does the ANDA contain REMS? Yes No (If YES, initiate approval action 6 weeks prior to target action date)

Regulatory Project Manager Evaluation:

Date: **1/9/2019**

Date (Received) Acceptable for Filing -- Date **12/29/2015**

Date last Complete Response (CR) letter was issued -- Date **6/27/2018**

Previously reviewed and tentatively approved (if applicable) --- Date **N/A**

YES	NO			
☒	☐	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A)		
		<table border="1"> <tr> <td> Date of Acceptable Bioequivalence 1/29/2019 - Date of BE Guidance (if any) 9/2013 Date of Acceptable Labeling 1/29/2019 - Date of last RLD labeling update 1/7/2019 Date of Acceptable Quality 1/30/2019 - DMF No(s). (b) (4) Date(s) Acceptable 8/20/18 & 5/11/18 - No outstanding DMF review amendments ☒ - Date of Acceptable Overall Manufacturing Inspection 7/18/2018 </td> <td> If applicable: Date of Acceptable Microbiology N/A Date of Acceptable Clinical Review 1/29/2019 Date of Acceptable Dissolution N/A Date of Acceptable REMS N/A </td> </tr> </table>	Date of Acceptable Bioequivalence 1/29/2019 - Date of BE Guidance (if any) 9/2013 Date of Acceptable Labeling 1/29/2019 - Date of last RLD labeling update 1/7/2019 Date of Acceptable Quality 1/30/2019 - DMF No(s). (b) (4) Date(s) Acceptable 8/20/18 & 5/11/18 - No outstanding DMF review amendments ☒ - Date of Acceptable Overall Manufacturing Inspection 7/18/2018	If applicable: Date of Acceptable Microbiology N/A Date of Acceptable Clinical Review 1/29/2019 Date of Acceptable Dissolution N/A Date of Acceptable REMS N/A
Date of Acceptable Bioequivalence 1/29/2019 - Date of BE Guidance (if any) 9/2013 Date of Acceptable Labeling 1/29/2019 - Date of last RLD labeling update 1/7/2019 Date of Acceptable Quality 1/30/2019 - DMF No(s). (b) (4) Date(s) Acceptable 8/20/18 & 5/11/18 - No outstanding DMF review amendments ☒ - Date of Acceptable Overall Manufacturing Inspection 7/18/2018	If applicable: Date of Acceptable Microbiology N/A Date of Acceptable Clinical Review 1/29/2019 Date of Acceptable Dissolution N/A Date of Acceptable REMS N/A			
☒	☐	MMA: All amendments submitted to the Agency on or after December 5, 2016 contain (1) a patent certification or section viii statement, (2) a recertification, or (3) a verification statement per 21 CFR 314.96(d).		
☐	☒	Are consults pending for any discipline?		
☒	☐	OSIS Clinical Endpoint and Bioequivalence Site Inspections are acceptable		
☒	☐	Is there a pending legal or regulatory issue (refer to Policy Alert Tracker)? If YES → OGD Policy Lead confirmed ANDA may proceed ☒ ; Memo uploaded (if applicable) ☒		
☐	☒	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES → Verify a second filing review was completed (if applicable) and that all disciplines completed new reviews ☐		
☒	☐	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff or Division liaison 30 to 60 days prior to approval, Date emailed 8/16/2018		

Review Discipline/Division and RPM TL Endorsements

Applicable review discipline/division endorsements completed
 RPM Team Leader endorsement completed

Additional Notes (if applicable)

Originating Office: ORO

Effective Date: 24Jan2018

Page 1 of 7

Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 60225	Version: 03
Document Status: Effective		
Title: Approval Routing Summary Form	Author: Kevin Denny	

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 1/29/2019

Name: IM

Patent/Exclusivity Certification: ☐ PI ☒ PII ☐ PIII ☐ PIV ☐ section viii If Paragraph IV Certification- did applicant: Notify patent holder/NDA holder: Yes ☐ No ☐ Was applicant sued w/in 45 days: Yes ☐ No ☐ Has case been settled: Yes ☐ No ☐ Applicant addressed all listed exclusivities Yes ☐ No ☐ Do the patent and exclusivity certifications align? Yes ☐ No ☐ Have there been any revisions to the use code since the original submission? Yes ☐ No ☐	RLD = <u>Advair Diskus</u> NDA# <u>21077</u> ☒ RX or ☐ OTC Date Checked in Orange Book#: <u>1/29/2019</u> Type of Letter: ☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) LETTER RECOMMENDED FOR DRUGS@FDA Yes ☒ No ☐
Forfeiture Information Is a forfeiture memo needed for the first applicant: Yes ☐ No ☐ If yes, the date forfeiture memo was completed Date _____ ANDA # _____	180 Day Exclusivity Information Is applicant eligible for 180 day exclusivity Yes ☐ No ☒ ☐ Sole ☐ Shared ANDA Exclusivity for each strength: Yes ☐ No ☐ Which strength(s) eligible _____
Comments: BOS = Advair Diskus (NDA 21077) Application submission 12/29/2015 with a PIII certification to the '360 patent. Acknowledgment letter signed 2/19/2016. Amendment 3/2/2016 Mylan revised their certification to the '360 patent from PIII to PII as the patent expired 2/23/2016 with an associated pediatric exclusivity expiring 8/23/2016. Amendment 2/26/2018 with an updated exclusivity statement to the M-214 (exp. 12/20/2020) (b) (4) (b) (4)	
Labeling review 1/11/2019 found the proposed ANDA labeling Adequate. There remains no unexpired patents and no additional unexpired exclusivities listed in the OB to the NDA. There is a pending CP involving Advair and other MDI products, 2009-P-0597, that requests FDA to not approve any ANDA referencing inhalation products containing fluticasone propionate and/or salmeterol xinafoate unless conforms to the RLD: in patient instructions for use and handling, Q1/Q2 BE, successful clinical testing in pediatric and adults as part of BE, and successfully clinically tested in asthma and COPD patients. Andrea B., the CP lead, states a response to the CP will be issued at the same time ANDA 208891 is approved and therefore a memo to the ANDA program will not be necessary.	
Mylan's ANDA is eligible for Full Approval.	
180 Day Exclusivity Status/Landscape: N/A Citizen Petitions Impact: Does not prevent the approval of this ANDA and CP response will be issued along with this ANDA approval First Legally Approvable Date: upon the expiration of the pediatric exclusivity period associated with the '360 patent, 8/23/2016 If Tentative Approval, anticipated full approval date: N/A	

Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 60225	Version: 03
Document Status: Effective		
Title: Approval Routing Summary Form	Author: Kevin Denny	

2. Final Decision

Date: 1/30/2019

Name: sgk

ANDA received on 12/29/2015 for the 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg/50 mcg strengths

RTR'd? Yes No If yes, RTR'd on Enter date

Priority Status? Yes No If yes, prioritization factor is First Generic

Basis of Submission (RLD)

Drug Name Advair Diskus
 NDA # 021077
 Applicant Name GlaxoSmithKline

Verified the following:

1. Completion of the following endorsement tasks, if applicable:
 - a. Division of Legal and Regulatory Support Endorsement
 - b. Paragraph IV Evaluation
 - c. REMS Endorsement
 - d. Quality Endorsement
 - e. Bioequivalence Endorsement
 - f. Clinical-Bioequivalence Endorsement
 - g. Labeling Endorsement
 - h. RPM Team Leader Endorsement
2. All applicable endorsement tasks are completed in the platform within 30 days of potential approval.
3. No updates to patents and/or exclusivities in Orange Book since the Division of Legal and Regulatory Support Endorsement
4. No Reference Listed Drug updates at Drugs@FDA since the Labeling Endorsement
5. No issues listed on the current version of the Policy alert list since the RPM Team Leader Endorsement
6. No new alerts in the Submission Facility Status View since the Quality Endorsement
7. Overall Inspection Recommendation of Approve of the current project (see screenshot below)
8. No new DMF amendments since Quality Endorsement
9. No amendments received since the RPM Team Leader Endorsement

This ANDA is ready for **FULL APPROVAL**.

*****INCLUDE SNIP OF SUBMISSION FACILITY STATUS VIEW AT THE TIME OF APPROVAL*****

Originating Office: ORO	Effective Date: 24Jan2018	Page 3 of 7

Please ensure you are using the most current version of this Form. It is available at:
 OGD Approved Controlled Documents SharePoint
<http://ogd.fda.gov/QDoc/Library/Index>

Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 60225	Version: 03
Document Status: Effective		
Title: Approval Routing Summary Form	Author: Kevin Denny	

REFERENCES / ASSOCIATED DOCUMENTS

4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Version	Effective date	Name	Role	Summary of changes
01	10/1/2014	Heather Strandberg	Author	New Form
02	10/03/2017	Kevin Denny	Reviser	• Update form to reflect revisions to SOP 4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA, Version 04 • Remove content adequately captured in the platform • Update information captured in the Division of Legal and Regulatory Support Endorsement section • Other minor administrative corrections to format and content
03	1/24/18	Kevin Denny	Reviser	• Update Final Decision section

Originating Office: ORO	Effective Date: 24Jan2018	Page 7 of 7

Memorandum

FROM: Sarah Yim, M.D.
Division Director
Division of Clinical Review (DCR), Office of Bioequivalence, Office of Generic Drugs (OGD)

Sarah K. Yim -S
Digitally signed by Sarah K. Yim -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, cn=Sarah K. Yim -S,
0.9.2342.19200300.100.1.1=1300379643
Date: 2019.01.29 13:54:26 -05'00'

THROUGH: Andre Raw, Ph.D.
Acting Senior Science and Policy Advisor
Office of Life Cycle Drug Products (OLDP), Office of Pharmaceutical Quality (OPQ)

Andre S. Raw -S
Digitally signed by Andre S. Raw -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Andre S. Raw -S,
0.9.2342.19200300.100.1.1=1300154978
Date: 2019.01.29 13:04:35 -05'00'

Mishale Mistry, PharmD, MPH
Associate Director
Division of Medication Error Prevention and Analysis (DMEPA), Office of Medication Error Prevention and Risk Management, Office of Surveillance and Epidemiology (OSE)

Mishale Mistry -S
Digitally signed by Mishale Mistry -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Mishale Mistry -S,
0.9.2342.19200300.100.1.1=1300434420
Date: 2019.01.29 15:18:20 -05'00'

TO: Abbreviated New Drug Application 208891, Mylan Pharmaceuticals Inc., for fluticasone propionate and salmeterol inhalation powder for oral inhalation, 100mcg/50mcg, 250mcg/50mcg, 500mcg/50mcg

SUBJECT: Evaluation of Device Orientation of ANDA 208891

The purpose of this memo is to document CDER's decision to find that the proposed device orientation for abbreviated new drug application (ANDA) 208891, fluticasone propionate and salmeterol inhalation powder for oral inhalation, submitted by Mylan Pharmaceuticals Inc. (Mylan), is acceptable. This memorandum has been prepared in consultation with relevant Agency components. The signatories on the through line have reviewed and concur with the content relevant to their subject matter expertise.

I. Background

The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (the Hatch-Waxman Amendments) created, among other things, section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Under section 505(j), an ANDA applicant can rely on FDA's previous finding that the reference listed drug (RLD) is safe and effective so long as the ANDA applicant demonstrates that the proposed drug product and the RLD are the same with respect to active ingredient(s), dosage form, route of administration, strength, and, with certain exceptions, labeling. An ANDA must also include sufficient information to demonstrate that the proposed product is bioequivalent to the RLD and that the ANDA meets the approval requirements relating to chemistry, manufacturing, and controls (CMC) (i.e., the methods used in, or facilities and controls used for, the manufacture, processing, and packing are adequate to assure and preserve the identity, strength, quality, and purity).

An ANDA generally is not required to be the same as the listed drug it references in certain respects. For example, a generic drug generally can differ from its RLD in certain respects with regard to the device. Drug

Advair Diskus, Mylan submitted, among other things, (1) a device orientation study, (2) an assessment of orientation of use on uniformity of emitted dose and aerodynamic particle size distribution, and (3) an assessment of the impact of potential powder buildup on device functionality.

Mylan's device orientation study is a non-dosing study user handling assessment.¹ CDER reviewed the study to support the robustness of the performance of the proposed delivery device given the design differences identified between the proposed product and Advair Diskus and to confirm the therapeutic equivalence of the products.² The study was designed to demonstrate that, regardless of the orientation of the inhaler, users who used the device in the incorrect orientation would be able to inhale with a sufficient inhalation profile to receive the required dose. The study measured peak inhaled flow rates (PIFR) by connecting the proposed product delivery device to the inhalation profiling system which assessed the participant's inhalation profile. The participant's mean PIFR and mean total inhaled volume (TIV) were recorded over three inhalations and assessed against the assessment criteria. If the participant achieved a PIFR of >30 L/min and TIV >1 L, it could be expected that the participant would have received a full dose. If the mean data from the 3 inhalations were <30 L/min PIFR and <1L TIV, respectively, then the participant was asked to demonstrate one further inhalation vertically to enable an assessment of whether the root cause was device related.

The results of the device orientation study demonstrate that of the 110 subjects, 12 used the proposed product in the horizontal orientation (rather than the vertical orientation) at any point during the study, although the inhalation profile of these subjects suggests that 11 of the 12 received the target dose nonetheless. Eleven of these subjects were previous Advair Diskus users and one was a naïve user. The study showed that participants could generate an inhalation flow rate sufficient to ensure that the participant would receive a full dose regardless of orientation of the proposed product. The study, among others, provided adequate assurance of the performance of the device when used in either the horizontal or vertical orientation, supporting the conclusion that the proposed product would be expected to consistently and reproducibly perform the same as the Advair. The study was designed to simulate actual use of the device at the point of substitution without any provision of additional training or health care provider intervention.

In addition, the assessment of orientation of use on uniformity of dose and aerodynamic particle size distribution demonstrate that device functionality and pharmaceutical performance attributes (i.e., uniformity of emitted dose and aerodynamic particle size distribution) are maintained such that the target dose is delivered when the device is used either vertically or horizontally. The assessment of the impact of potential powder buildup from doses that were intentionally not evacuated confirmed the robustness of the device constituent part in that the device functionality was maintained.

¹ See ANDA 208891, Module 3.2.P.7.2.6.1, Device Orientation Study for further details regarding study design.

² Mylan includes certain statements in its submission indicating that the intent of the device orientation study was to "confirm that intended users could use the device safely and effectively" using the proposed product and instructions for use. To clarify, this study was not a clinical investigation to demonstrate safety and effectiveness of the proposed product. The study is not a "clinical investigation" within the meaning of FDA regulations (21 CFR 312.3) because no drug was administered or dispensed. Further, no clinical endpoints were measured to assess the safety and effectiveness of the product because no drug or placebo was administered. Rather, as discussed above, CDER's review focused on the performance of the proposed delivery device and whether it could emit the full dose regardless of orientation. Although the device orientation study was not requested by CDER and is not specifically included in the battery of testing recommended in FDA's draft guidance on "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products – Quality Considerations," (Quality Draft Guidance) the effect of orientation of the device on delivered dose is a typical quality characterization study expectation for a DPI; as is the effect of varying flow rate on DPI performance (Quality Draft Guidance, Table 2). Mylan's device orientation study supports the robustness of the delivery device and the potential for orientation to impact product performance. FDA has the authority to review this information pursuant to the statute (e.g., provisions for ANDAs regarding the methods used in, or facilities and controls used for, the manufacture, processing, and packing are adequate to assure and preserve the identity, strength, quality, and purity). We also note that the proposed product is a combination product (as defined in 21 CFR 3.2(e)), and the approval is consistent with applicable authorities.

products that are approved in ANDAs are generally considered by FDA to be therapeutically equivalent to their RLD. Products classified as therapeutically equivalent can be substituted with the full expectation that the generic product will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling.

These general principles apply to products submitted in ANDAs, including drug-device combination products. A generic combination product classified as therapeutically equivalent to the RLD can be expected to produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling. This does not mean, however, that the proposed generic combination product and its RLD need to be identical in all respects. FDA recognizes that an identical design may not always be feasible and, in certain instances, differences in the design of the user interface for a generic combination product as compared to the RLD may exist without precluding approval of the generic combination product under an ANDA. In some instances in which differences exist, certain additional information and/or data relating to the user interface of the proposed generic combination product may be appropriate to support approval of the proposed generic combination product in an ANDA. The extent to which differences between the proposed product and the RLD affect the approvability of the proposed ANDA product will be evaluated on a case-by-case basis.

FDA issued draft guidance setting forth an approach consisting of threshold analyses for analyzing differences between the user interface of the proposed generic combination product and the user interface of its RLD and one type of study (comparative use human factors study), when warranted, that could inform whether such differences would be acceptable to support approval in an ANDA. See FDA's draft guidance "Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA" (CUHF ANDA Draft Guidance). The comparative use human factors studies described in the CUHF ANDA Draft Guidance are intended to confirm that the differences in device and labeling between the generic combination product and RLD are acceptable and that the proposed generic combination product can be substituted with the full expectation that the generic combination product will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling. The CUHF ANDA Draft Guidance states that FDA intends to consider whether the generic combination product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the generic combination product.

II. Discussion

As a preliminary matter, OGD has concluded that Mylan's proposed product has the same active ingredient, route of administration, dosage form, strength, and is bioequivalent to the RLD, Advair Diskus. Mylan's proposed product is intended to be used vertically, whereas the RLD, Advair Diskus, is intended to be used horizontally. Consistent with the CUHF ANDA Draft Guidance, Mylan submitted in support of its ANDA the recommended threshold analyses of its proposed product and Advair Diskus consisting of a labeling comparison, comparative task analysis, and physical comparison of the delivery device. OGD/DCR and OSE/DMEPA concluded that the difference in device orientation between the proposed product and Advair Diskus is an "other than minor difference", which is defined as a difference that may impact an external critical design attribute based on the principles set forth in the CUHF ANDA Draft Guidance. In such instances, the CUHF ANDA Draft Guidance recommends, as one approach, the submission of additional data, such as a comparative use human factors study, to assess whether differences that may not be minor would preclude approval of the proposed product under an ANDA. The objective of such a study is to demonstrate that the use of error rate, associated with a difference in an external critical design attribute for the proposed user interface does not preclude approval of the proposed product in an ANDA.

As with all guidance, applicants may use an alternative approach if it satisfies the requirements of the applicable statutory provisions and regulations. To support the differences in device between its proposed product and

III. Conclusion

Together, the data described above provide sufficient information to support a conclusion that differences in device orientation between Mylan's proposed product and the RLD, Advair Diskus, are acceptable and that the proposed product can be substituted with the full expectation that the proposed product will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling. Further, the data (in particular the device orientation study) are sufficient for CDER to conclude that the proposed product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the proposed product.³ Finally, CDER concludes that a comparative use human factors study is unnecessary for this ANDA because even if the study identified a difference in error rate with respect to device orientation, the data provided by Mylan are sufficient to show that the device performance is of sufficient robustness that any difference in orientation would not result in sub-therapeutic doses being delivered to patients or undermine a finding of therapeutic equivalence. In sum, the data provided in ANDA 208891 support the acceptability of the difference in device orientation for the proposed product, the statutory and regulatory requirements for approval, and the conclusion that the proposed product is therapeutically equivalent to the RLD.

³ As a result of the above-described conclusions, differences in labeling that flow from the difference in device orientation between the proposed product and the RLD are also acceptable.

OGD Memorandum

Date: January 29, 2019

FROM: Kimberly Witzmann, MD
Team Lead
Division of Therapeutic Performance
Office of Research and Standards, Office of Generic Drugs

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THROUGH: Banu Karimi-Shah, MD
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Date: 2019.01.29 12:53:57 -05'00'

TO: Abbreviated New Drug Application (ANDA) 208891, Fluticasone Propionate and Salmeterol Inhalation Powder, 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg/50 mcg

This memorandum describes FDA's current thinking on several issues related to demonstrating bioequivalence (BE) for ANDA 208891, Fluticasone Propionate and Salmeterol Inhalation Powder, 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg/50 mcg, relative to issues that were raised in two citizen petitions submitted to the Agency. FDA's Office of Generic Drugs has drafted this memo in consultation with the Division of Pulmonary, Allergy, and Rheumatology Products in FDA's Office of New Drugs.

I. BACKGROUND

A. Advair Diskus (NDA 021077)

On August 24, 2000, FDA approved New Drug Application (NDA) 021077, for Advair Diskus, submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act (FD&C Act). There are three approved strengths (100/50, 250/50 and 500/50 mcg) of Advair Diskus. Product formulations are doses of 72.5 mcg micronized salmeterol xinafoate (SX) (equivalent to 50 mcg salmeterol) with 100, 250 or 500 mcg of micronized fluticasone propionate (FP), blended with sufficient lactose to a total weight of 12.5 mg, respectively. Each dose is contained in an individual foil blister, which is part of a blister-strip linking 60 blisters.

Advair Diskus is indicated for the following:¹

- Treatment of asthma in patients aged 4 years and older.
- Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD).

The Advair Diskus labeling makes the following recommendations for ‘dosage and administration’:²

- Treatment of asthma in patients aged 12 years and older: 1 inhalation of Advair Diskus 100/50, Advair Diskus 250/50, or Advair Diskus 500/50 twice daily. Starting dosage is based on asthma severity.
- Treatment of asthma in patients aged 4 to 11 years: 1 inhalation of Advair Diskus 100/50 twice daily.
- Maintenance treatment of COPD: 1 inhalation of Advair Diskus 250/50 twice daily.

B. Citizen Petition Docket No. FDA-2016-P-3356

On October 13, 2016, Sandoz Inc. (Sandoz) submitted a citizen petition requesting that the Agency refrain from approving any ANDA that references NDA 21077, Advair Diskus 100/50 (fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder) as the reference listed drug (RLD) unless the Agency ensured the following:³

- Type I error rate is adequately controlled in pharmacokinetic (PK) BE testing, including accounting for Type I error rate inflation caused by batch-to-batch variability of the RLD;
- The dose used in PK BE testing retains the necessary sensitivity to product differences existing at the marketed single inhalation dose of the RLD; and
- The sampling schedule used in PK BE testing is robust and centered around the actual time to maximum plasma concentration of both active ingredients at the marketed dose of the RLD.

The following two publications, which describe the findings of two PK studies conducted by Sandoz for Advair Diskus 100/50, are cited in the Sandoz Petition:

- Getz, EB, Carroll, KJ, Jones, B, Benet, LJ, Batch-to-batch Pharmacokinetic Variability Confounds Current Bioequivalence Regulations: A Dry Powder Inhaler Randomized Clinical Trial; *Clin Pharmacol Ther.* 2016 Sep;100(3):223-31.⁴
- Getz, EB, Carroll, KJ, Mielke, J, Benet, LJ, Between-Batch Pharmacokinetic Variability Inflates Type I Error Rate in Conventional Bioequivalence Trials: A Randomized Advair Diskus® Clinical Trial, *Clin Pharmacol Ther.* 2017 Mar; 101(3):331-340.⁵

On March 10, 2017, FDA denied the Sandoz Petition without comment on whether the Agency would take the actions requested.

C. Citizen Petition Docket No. FDA-2017-P-6750

On December 5, 2017, Mylan Inc. (Mylan) submitted a citizen petition requesting that the Agency refrain from approving any ANDA for Advair Diskus that relies on multiple-batch PK BE study designs unless, after conducting an appropriately rigorous review under established standards for establishing BE, generally, and for this product

¹ Advair Diskus Labeling (Reference ID 3924273, initial approval: 2000, last updated: January 7, 2019) https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021077s061lbl.pdf (last accessed on January 9, 2019).

² Id.

³ Sandoz Inc., Citizen Petition Docket No. FDA-2016-P-3356, received October 13, 2016 (Sandoz Petition), at 2.

⁴ Sandoz Petition, at 6, n.23 [hereinafter referred to as Publication 1].

⁵ Sandoz Petition, at 7, n.24 [hereinafter referred to as Publication 2].

specifically, FDA concludes that such a study design is valid and will ensure patients receive a robust and reliable therapeutically equivalent product.⁶ Mylan also requested that the Agency refrain from approving any ANDA unless it contains the results of a PK BE study that reflects sound development work and clearly demonstrates equivalent rigor to the well-established single-batch test versus reference study design that Mylan states is outlined in FDA's Draft Guidance on Fluticasone Propionate and Salmeterol Xinafoate (recommended September 2013) (Draft FP/SX PSG)⁷ and used broadly by FDA.⁸

On May 6, 2018, FDA denied the Mylan Petition without comment on whether the Agency would take the actions requested.

II. STATUTORY AND REGULATORY BACKGROUND

A. 505(b)(1) NDAs – General

Section 505(b)(1) of the FD&C Act sets forth the requirements for submitting a “stand-alone” NDA. Such an application must contain the following:

- full reports of investigations to show that the drug is safe and effective;
- a list of articles used as components of the drug;
- a statement of the drug's composition;
- a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug;
- samples of the drug as necessary;
- proposed labeling for the drug; and
- pediatric assessments.⁹

505(b)(1) NDA applicants submit data demonstrating that the proposed product is of adequate quality and stability for approval. FDA approves an NDA if the information and data provided by the applicant demonstrate that the drug product is safe and effective for the conditions prescribed, recommended, or suggested in the proposed labeling.

B. ANDAs - General

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the FD&C Act which established the ANDA approval pathway for generic drugs.¹⁰ To obtain approval, an ANDA applicant is not required to conduct independent clinical studies to demonstrate the safety and effectiveness of the proposed generic drug product. Instead, the application relies on FDA's previous finding that the RLD is safe and effective. The ANDA applicant must identify the listed drug on which it seeks to rely, and, with limited exceptions, a drug product described in an ANDA must contain the same active ingredient(s), route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD.¹¹ An ANDA must also include sufficient information to demonstrate that the proposed

⁶ Mylan Inc., Citizen Petition Docket No. FDA-2017-P-6750, received December 5, 2017 (Mylan Petition), at 1.

⁷ Draft FP/SX PSG, available at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081320.htm>.

⁸ Mylan Petition, at 2.

⁹ See also 21 CFR 314.50 for a description of the NDA approval requirements.

¹⁰ For the purpose of this response, the term *generic drug* refers to a new drug product for which approval is sought in an ANDA submitted under section 505(j) of the FD&C Act.

¹¹ Sections 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act; see also 21 CFR 314.94(a) and 21 CFR 314.127.

product is bioequivalent to the RLD.¹² FDA will not approve the ANDA if there is insufficient evidence of the foregoing or there is inadequate information to ensure the identity, strength, quality, and purity of the drug.¹³

The statute does not require the ANDA applicant to demonstrate that the generic drug is the same as the RLD in all respects. For example, a generic drug does not need to be identical to and can differ from the RLD with respect to the delivery device, provided that such differences are determined to be acceptable in an ANDA.

Therapeutic equivalents are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.^{14,15}

C. Bioequivalence

1. General Framework

An ANDA applicant must demonstrate that its proposed generic drug is bioequivalent to the RLD.¹⁶ Section 505(j)(8)(B)(i) of the FD&C Act states that a generic drug is bioequivalent to the listed drug if:

[T]he rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses. . . .¹⁷

Further, section 505(j)(8)(C) of the FD&C Act provides:

For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

The bioequivalence testing methods may include comparative *in vivo* data (data from a study on human subjects) or *in vitro* data (data from laboratory studies), or both.¹⁸ FDA regulations describe these types of evidence that may be used to establish bioequivalence:

¹² See e.g., sections 505(j)(2)(A)(iv), 505(j)(4)(F), and 505(j)(8) of the FD&C Act.

¹³ See e.g., sections 505(j)(2)(A) and (j)(4) of the FD&C Act; see also 21 CFR 314.94 and 21 CFR 314.127.

¹⁴ See e.g., 21 CFR 314.3 (defining therapeutic equivalents, pharmaceutical equivalents, and bioequivalence).

¹⁵ See also FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (Orange Book), preface to the 38th edition, at page vii. (The Orange Book Preface notes that FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable *in vitro* standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; and (5) they are manufactured in compliance with Current Good Manufacturing Practice (CGMP) regulations.)

¹⁶ See, e.g., sections 505(j)(2)(A)(iv) of the FD&C Act (requiring "information to show that the new drug is bioequivalent to the listed drug") and 505(j)(4)(F) of the FD&C Act (providing that FDA must approve an ANDA unless, among other things, the "information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug"); 21 CFR 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the RLD); 21 CFR 314.127(a)(6)(i) (providing that FDA will refuse to approve an ANDA if information submitted in the ANDA is insufficient to show that the drug product is bioequivalent to the RLD referred to in the ANDA). RLDs are identified in the Orange Book, available on FDA's website at <https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>.

¹⁷ See also 21 CFR 314.3(b), 320.1 and 320.23(b).

¹⁸ 21 CFR 320.24(a).

FDA may require in vivo or in vitro testing, or both, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products The selection of the method used to meet an in vivo or in vitro testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section. The method used must be capable of measuring bioavailability or establishing bioequivalence, as appropriate, for the product being tested.¹⁹

Section 320.24(b) (21 CFR 320.24(b)) of FDA's regulations describes preferred bioequivalence methods in general descending order of accuracy, sensitivity, and reproducibility. The bioequivalence methods include: (1) in vivo pharmacokinetic studies in whole blood, plasma, serum, or other appropriate biological fluid, or an in vitro test that has been correlated with and is predictive of in vivo bioavailability data; (2) in vivo studies in which urinary excretion of the active moiety and, when appropriate, its active metabolite(s) are measured; (3) in vivo pharmacodynamic effect studies; (4) comparative clinical endpoint studies; and (5) other in vitro studies acceptable to FDA that ensure human in vivo bioavailability.²⁰ In addition, consistent with section 505(j)(8)(C) of the FD&C Act, section 320.24(b)(6) of the regulations state that FDA may accept "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence." The statute, regulations, and case law give FDA considerable flexibility in determining how the bioequivalence requirement is met.²¹

2. FDA's Draft Product-Specific Guidance on Fluticasone Propionate and Salmeterol Xinafoate

FDA's Draft FP/SX PSG recommends in vitro studies (for all the strengths to establish equivalent in vitro performance) and in vivo studies (PK studies to establish equivalent systemic exposure (for all the strengths) and a comparative clinical endpoint bioequivalence study to further support equivalent local delivery (for the 100/50 strength)) to support a demonstration of bioequivalence (as well as formulation and device considerations) for a generic product. This approach to bioequivalence is sometimes referred to as a "weight-of-evidence" approach. The Draft FP/SX PSG's recommendations regarding the PK BE studies are as follows:

- a single-dose two-way crossover fasting PK BE study in normal healthy males and non-pregnant females from the general population (because healthy volunteers would generally be most sensitive to potential product variations);
- the use of the minimum number of inhalations that is sufficient to characterize a PK profile by using a sensitive analytical method;
- that subjects should adhere to labeling as follows: "Rinse your mouth with water after breathing in the medicine. Spit the water out. Do not swallow."; and

¹⁹ 21 CFR 320.24(a). In the preamble to the final rule setting forth FDA's regulations for ANDAs, the Agency explained that, depending upon the drug, it would determine the appropriate bioequivalence methodology on a case-by-case basis:

Bioequivalence can be established by pharmacodynamic measurement as well as by in vitro techniques and bioequivalence studies with clinical endpoints. The preferred method for establishment of bioequivalence . . . is *determined on a case-by-case basis*, depending on the drug under study ("Abbreviated New Drug Application Regulations" final rule, 57 FR 17950 at 17972 (April 28, 1992) (emphasis added)).

²⁰ 21 CFR 320.24. Whereas a pharmacokinetic study measures the rate and the extent to which the drug is delivered to biological fluids (generally the bloodstream), a pharmacodynamic study measures effects associated with the delivery of the active ingredient to the site of action.

²¹ See e.g., *Schering Corp. v. FDA*, 51 F.3d 390, 398 (3d Cir. 1995) (noting that the FD&C Act "vests the FDA with the discretion to determine whether in vitro or in vivo bioequivalence studies, or both, will be required for the approval of generic drugs under the abbreviated application process").

- that PK equivalence should be based on area under the curve (“AUC”) and maximum concentration (“Cmax”) for fluticasone propionate and salmeterol in plasma. The 90% confidence intervals (“CIs”) for the geometric mean test/reference (“T/R”) ratios (also referred to as “GMR”) of AUC and Cmax should fall within the limits of 80.00-125.00%.

A description of the Draft FS/SX PSG recommendations regarding *in vitro* studies (all strengths), and a comparative clinical endpoint study (for 100/50 strength) is as follows:

- Single actuation content (SAC) test: The SAC test is an *in vitro* test recommended to ensure equivalence of a Test dry-powder inhaler (DPI) to the corresponding Reference DPI with respect to the amount of aerosolized drug delivered per single actuation, based on a sensitive, drug-specific chemical/chromatographic assay. The delivered mass of drug substance is expressed both as an actual of the label claim and as a percentage of the label claim. Because DPIs are used over a range of inspiratory flow rates (due to variations in the inspiratory effort across the patient population), SAC may vary with the inspiratory flow rate. Therefore, we recommend that the SAC should be determined at a minimum of three flow rates which are expected to reasonably cover the range of flow rates generated by the relevant patient population. These recommended flow rates for Advair Diskus are 30, 60 and 90 L/min. In addition, we believe that possible differences in device material and formulation between the Test and Reference products may influence the DPI performance over different stages of the product life. Therefore, for each flow rate, it is also important to demonstrate equivalence in SAC at multiple stages of the product life, including the beginning (i.e., the 1st labeled actuation), the middle (i.e., the 50% of the labeled number of actuations), and the end (i.e., the last labeled actuation) lifestages, and for emitted dose (ED). This way, 9 SAC matrices are compared to ensure that dose delivery from both the Test and Reference products after single inhalation delivery is indeed the same throughout the product life. We recommend that SAC equivalence of the Test and Reference product data be based on the population bioequivalence method (PBE). This PBE test is designed in such a way that it would penalize the generic applicant if their product were more variable than the RLD, or if it were to deliver different amounts of drug after single inhalation as compared to the RLD. Moreover, for each of these matrices, we recommend the SAC tests include three batches each of the Test and Reference products, with a minimum of 10 units tested from each batch.
- Aerodynamic particle size distribution (APSD): We also recommend that the generic applicant demonstrate equivalence of aerodynamic particle size distribution (APSD) at 30, 60 and 90 L/min (beginning and end life stages). This APSD *in vitro* test further assures the equivalence of drug delivery between the Test and Reference products.
- Comparative clinical endpoint BE study for the 100/50 strength: We recommend a 4-week study in which patients administer a single inhalation twice daily of the 100/50 strength product. It is the Agency’s position that comparative clinical endpoint study helps provide additional assurance of equivalence of local (to the site of action in the lungs) drug delivery of the labeled dose for this drug product, given the state of science at this time.

III. DISCUSSION

As described above, the Sandoz and Mylan citizen petitions have requested certain actions with respect to the recommended PK BE study for an ANDA that cites Advair Diskus as its RLD. The Sandoz petition cites certain data purporting to demonstrate batch-to-batch variability for the Advair Diskus 100/50 strength. Specifically, Sandoz argues that this batch-to-batch variability increases the likelihood of what Sandoz refers to as a “Type I error” in finding a generic product bioequivalent to its RLD in a PK BE study, when it is in fact not bioequivalent and states that FDA should require PK BE studies to utilize a “multiple-batch design” to control for the possibility

of this Type I error. Sandoz also states that FDA should require that the PK BE study be conducted using “a single inhalation dosing regimen and an early time point sampling regimen.”²² Mylan in turn argues that the multiple-batch approach is inappropriate and that “PK BE can be demonstrated using the straightforward method described in the Draft FP/SX PSG.”²³ In particular, Mylan argues that PK BE studies should be performed using representative batches of each strength of the RLD and test product.²⁴ Mylan’s CP does not address the single inhalation dosing regimen and PK sampling regimen discussed in Sandoz’s petition.

FDA’s approval of ANDA 208891, sponsored by Mylan, is consistent with the actions requested in Mylan’s CP. As explained below, however, Sandoz asserts that a PK BE study for Advair Diskus 100/50 strength should have certain characteristics that differ from the PK BE study for the 100/50 strength Mylan submitted in support of its application. This memorandum therefore focuses on Sandoz’s requested actions and its various supporting arguments. The Sandoz and Mylan ANDAs contain data consistent with the actions requested in their respective petitions. FDA may accept different approaches to demonstrating BE, so long as the requirements for approval are met.

A. Batch-to-Batch Variability of Advair Diskus 100/50

Sandoz asserts that its research shows that due to the batch-to-batch variability of the RLD (Advair Diskus 100/50), there is batch-to-batch PK variability for the RLD²⁵ and that the batch-to-batch PK variability of this RLD is “(i) larger than is consistent with FDA’s definition of bioequivalence, (ii) reproducible, and (iii) not isolated to the occasional outlying batch.”²⁶

The NDA reviews for Advair Diskus show that FDA was aware of the batch-to-batch variability for Advair Diskus 100/50. For example, the following table includes specification acceptance criteria for fluticasone propionate and salmeterol approved in Supplement-001 for Advair Diskus:

²² Sandoz Petition, at 12.

²³ Mylan Petition, at 2.

²⁴ Mylan Petition, at 5.

²⁵ Sandoz Petition, at 5-8.

²⁶ *Id.* at 8.

(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4) This issue would be evaluated by OGD during the normal course of ANDA review.

OGD Memorandum

Date: January 28, 2019

FROM: Chi-Ann Wu, PharmD.
Director, Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

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THROUGH: Sally Seymour, M.D.
Director (Acting)
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TO: Abbreviated New Drug Application (ANDA) 208891, Fluticasone
Propionate and Salmeterol Inhalation Powder, 100 mcg/50 mcg, 250
mcg/50 mcg and 500 mcg/50 mcg

This memo was prepared in consultation with OND.

The RLD sponsor conducted two postmarketing safety trials with Advair Diskus (SAS 115358 and SAS 115359) and submitted the related study data to the Agency under NDA 21077 (Advair Diskus)/S-056 and S-057. These supplements were part of a group of supplements submitted for the inhaled corticosteroid/long-acting beta agonist (ICS/LABA) products held by different sponsors (Advair Diskus, Symbicort, Dulera, Advair HFA, Breo Ellipta, AirDuo) to update the labeling of the products with the results of completed large safety trials and a meta-analysis of the combined trials. In addition to the Advair Diskus studies, the sponsors of two other ICS/LABA products (Symbicort and Dulera) also conducted postmarketing safety studies. The four postmarketing safety studies with ICS/LABA products were conducted in response to postmarketing requirements (PMRs) under section 505(o)(3) imposed on the Advair Diskus, Symbicort, and Dulera NDAs. As a result of these ICS/LABA safety trials and supplements, class labeling changes were made to all ICS/LABA products, including the removal of the Boxed Warning for asthma-related death and the revision of section 5.1 with class Warning language. For those products which were the subject of the ICS/LABA safety trials (Advair Diskus,

Sybmicort, and Dulera), the Clinical Studies section (14) was also updated with the results of the individual ICS/LABA safety trial(s).

FDA approved S-056 and S-057 for NDA 21077 on December 20, 2017 and has determined that the supplements qualified for 3-year exclusivity. In the Orange Book, the 3-year exclusivity for Advair Diskus expires on December 20, 2020 and is denoted with the exclusivity code M-214: “INFORMATION ADDED TO THE CLINICAL TRIALS SECTION OF THE LABELING REGARDING A POSTMARKETING SAFETY AND EFFICACY STUDY EVALUATING THE RISK OF SERIOUS ASTHMA-RELATED EVENTS.”

(b) (4)

(b) (4)

(b) (4) We find this exclusivity carve-out acceptable for the following reasons:

- (b) (4) OND’s December 20, 2017 cross-discipline team leader review for NDA 21077 (Advair Diskus)/S-056 and S-057. With the approval of these supplements, Section 14 (Clinical Studies) of the Advair Diskus prescribing information (PI) was updated with the results of the two individual ICS/LABA safety trials with Advair Diskus, whereas the approved labeling changes to section 5.1 (Warnings and Precautions) of the Advair Diskus PI were consistent with class labeling changes for all ICS/LABA products (see p. 20-21 of the review, describing the “template Warning language” for section 5.1 to be used for all ICS/LABA products). The information included in Section 14 of the Advair Diskus PI related to the two safety trials is protected by 3-year exclusivity. However, the safety class labeling language in section 5.1 for all ICS/LABA products is not within the scope of the 3-year exclusivity for Advair Diskus. See, e.g., 59 Fed. Reg. 50338, 50357 (Oct. 3, 1994). Therefore, the inclusion of section 5.1 in Mylan’s proposed generic drug labeling is appropriate.
- Although not determinative, we note that Mylan’s proposed carve-out is also consistent with the M-214 exclusivity code definition, which expressly notes that the 3-year exclusivity relates to the information added to the clinical trials section of the labeling.
- OND has determined that Mylan’s proposed carve-out of the information from section 14 of the labeling does not render the proposed generic drug product less safe or effective than the RLD for the remaining, non-protected conditions of use.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 28, 2019

FROM: Chi-Ann Wu, PharmD.
Director, Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Chiann Y. Wu -S

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0.9.2342.19200300.100.1.1=1300135338
Date: 2019.01.28 17:09:52 -05'00'

THROUGH: Ashley Boam, M.S.B.E.
Director
Office of Policy for Pharmaceutical Quality
Office for Pharmaceutical Quality
Center for Drug Evaluation and Research

Ashley B.
Boam -S

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cn=Ashley B. Boam -S,
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Date: 2019.01.28 22:42:19 -05'00'

Sarah Yim, M.D.
Director
Division of Clinical Review
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Sarah K. Yim -S

Digitally signed by Sarah K. Yim -S
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ou=FDA, ou=People, cn=Sarah K. Yim -S,
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Date: 2019.01.28 20:39:42 -05'00'

Sally Seymour, M.D.
Director (Acting)
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

Sally M.
Seymour
-S

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222097, cn=Sally M. Seymour -S
Date: 2019.01.29 07:21:30 -05'00'

TO: Abbreviated New Drug Application 208891, Mylan Pharmaceuticals Inc., for
fluticasone propionate and salmeterol inhalation powder for oral inhalation,
100mcg/50mcg,250mcg/50mcg,500mcg/50mcg

SUBJECT: PIF Data in Description Section of Labeling for Mylan ANDA 208891
Referencing Advair Diskus (NDA 021077) as RLD

BACKGROUND

The purpose of this memorandum is to document the decision of the Office of Generic Drugs (OGD) to find that the labeling for abbreviated new drug application (ANDA) 208891, (fluticasone propionate and salmeterol inhalation powder) for oral inhalation, should include the

peak inspiratory flow (PIF) data from the reference listed drug's (RLD) labeling in the Description Section of the labeling for ANDA 208891, with certain permissible differences.

Mylan submitted ANDA 208891 referencing New Drug Application (NDA) 021077 for Advair Diskus. The Description Section (Section 11) of the Prescribing Information for NDA 021077 references PIF data for several of the patient populations the Advair Diskus is intended to treat. PIF is a respiratory parameter of the patient and may vary for asthma, chronic obstructive pulmonary disease (COPD), and other patient populations. PIF is a patient factor that informs the actual amount of drug delivered to the lung. NDA 021077's labeling states:¹

ADVAIR DISKUS is a purple plastic inhaler containing a foil blister strip. Each blister on the strip contains a white powder mix of micronized fluticasone propionate (100, 250, or 500 mcg) and micronized salmeterol xinafoate salt (72.5 mcg, equivalent to 50 mcg of salmeterol base) in 12.5 mg of formulation containing lactose monohydrate (which contains milk proteins). After the inhaler is activated, the powder is dispersed into the airstream created by the patient inhaling through the mouthpiece.



The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

The PIF data for NDA 021077 were generated using patients enrolled in clinical trials for NDA 021077. PIF for patients of differing lung functions were tested using the DISKUS inhaler with Inhalation Profile Recorders without inhalation of study drug.

¹ Drugs@FDA, Labels for NDA 021077, Suppl-61, January 7, 2019.

STATUTORY BACKGROUND

The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (the Hatch-Waxman Amendments) created, among other things, section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Under section 505(j), an ANDA applicant can rely on FDA's previous finding that the RLD is safe and effective so long as the ANDA applicant demonstrates that the proposed drug product and the RLD are the same with respect to active ingredient(s), dosage form, route of administration, strength, and, with certain exceptions, labeling.² An ANDA must also include sufficient information to demonstrate that the proposed product is bioequivalent to the RLD, and that the ANDA meets the approval requirements relating to chemistry, manufacturing, and controls (CMC) (i.e., the methods used in, or facilities and controls used for, the manufacture, processing, and packing are adequate to assure and preserve the identity, strength, quality, and purity).³

ANALYSIS

As a preliminary matter, OGD has concluded that Mylan's proposed product has the same active ingredient, route of administration, dosage form, and strength as the RLD, Advair Diskus. OGD has also determined that Mylan's proposed product is bioequivalent to the RLD through both in vitro and in vivo testing (in addition to having the same formulation), consistent with the recommendations in the draft product specific guidance on *Fluticasone Propionate; Salmeterol Xinafoate* (i.e., single actuation content (SAC) study, aerodynamic particle size distribution (APSD) study, fasting pharmacokinetic studies, and a clinical endpoint study).⁴ As such, we do not expect a difference in: (1) local delivery based on the clinical endpoint study (i.e., the rate or extent to which the active ingredient in Mylan's product reaches the site of drug action in the lungs as compared to the rate and extent the active ingredient in the RLD reaches the site of drug action in the lungs); (2) systemic exposure based on the pharmacokinetic studies; or (3) device performance based on in vitro studies based on SAC and APSD data performed at 30 L/min, 60 L/min and 90 L/min flow rates. (The SAC and APSD data are performed at 30 L/min, 60 L/min and 90 L/min flow rates to assess for equivalent performance of products across the range of potential inhalation flow rates.) In addition, FDA has determined, among other things, that Mylan's proposed device is acceptable from a performance and quality standpoint based on device development and performance testing, including data demonstrating that Mylan's proposed product meets the criteria for Assay and Uniformity of Dosage Units (tests designed to characterize the mass content or drug within individual dosage units (i.e., pre-metered drug-containing blisters within the device component)) within a batch as well as between batches. Mylan's product is therefore expected to perform the same as the RLD, Advair Diskus.

² See sections 505(j)(2)(A) and 505(j)(4) of the FD&C Act.

³ See sections 505(j)(2)(A)(iv), 505(j)(4)(F), 505(j)(2)(A)(vi), and 505(j)(4)(A) of the FD&C Act.

⁴ Draft guidance on Fluticasone Propionate; Salmeterol Xinafoate (Sept. 2013).

Given these conclusions, and after consultation with subject-matter experts in the Office of New Drugs and the Office of Pharmaceutical Quality, OGD has determined that labeling for the Mylan ANDA should contain the PIF data from the Advair Diskus labeling. The PIF data in the Advair Diskus labeling reflects information about use of the product for patients with certain lung function. These same data are relevant to Mylan's product because, given the above-mentioned conclusions regarding bioequivalence and quality, Mylan's product can be expected to perform the same as Advair Diskus including for those patients with the same lung function as described in the Advair Diskus product labeling. Mylan's Wixela Inhub labeling should therefore include the following in the Description Section (Section 11), with certain permissible differences shown below due to the fact that the Mylan product is produced and distributed by a different manufacturer than Advair Diskus:

Wixela™ Inhub™ is a grey colored plastic inhaler containing two foil sealed discs, each disc containing 30 pre-metered doses. Each of the 60 doses contains a white to off white powder mix of micronized fluticasone propionate (100 mcg, 250 mcg, or 500 mcg) and micronized salmeterol xinafoate salt (72.5 mcg, equivalent to 50 mcg of salmeterol base) in 12.5 mg of formulation containing lactose monohydrate (which contains milk proteins). After the inhaler is activated, the powder is dispersed into the airstream created by the patient inhaling through the mouthpiece.



The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.



ANDA 208891

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

ATTENTION: Wayne Talton
Head of Global Regulatory Affairs

Dear Mr. Talton:

Please refer to your Abbreviated New Drug Application (ANDA) dated and received July 13, 2018, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Propionate and Salmeterol Inhalation Powder.

We also refer to your correspondence, dated and received July 19, 2018, requesting review of your proposed proprietary name, Wixela Inhub.

We have completed our review of the proposed proprietary name, Wixela Inhub and have concluded that it is conditionally acceptable.

If your application receives a complete response and six months or more has elapsed between the date you were notified of our decision on your proposed proprietary name and the date you respond to the application deficiencies, please submit a new request for review of your proposed proprietary name when you respond to the application deficiencies. See the Guidance for Industry, Contents of a Complete Submission for the Evaluation of Proprietary Names, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>.

If any of the proposed product characteristics as stated in your above submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Frank Giannandrea, Regulatory Project Manager in the Office of Generic Drugs, at (240) 402-2704.

Sincerely,

{See appended electronic signature page}

Danielle Harris, PharmD, BCPS
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DANIELLE M HARRIS
09/06/2018



ANDA 208891

**POST-CRL MEETING
MEETING MINUTES**

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Wayne Talton
Head of Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2015, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Fluticasone Propionate and Salmeterol Inhalation Powder USP, 100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg.

We also refer to the post-complete response letter (post-CRL) meeting between the applicant and FDA on July 6, 2018. The purpose of the requested post-CRL meeting was to clarify deficiencies noted in the complete response letter issued by this office on June 27, 2018.

A copy of the official minutes of the post-CRL meeting is enclosed for your information. Please notify the Agency in writing via the Electronic Submissions Gateway of any significant differences in understanding regarding the meeting outcomes.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, please contact Frank Giannandrea, Regulatory Project Manager, at (240) 402 - 2704.

Sincerely,

{See appended electronic signature page}

Frank Giannandrea, Pharm.D.
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research



MEMORANDUM OF MEETING MINUTES

Meeting Type: Post-complete response letter meeting

Meeting Date and Time: July 6, 2018; 1:15 p.m. EDT

Application Number: 208891

Product Name: Fluticasone Propionate and Salmeterol Inhalation Powder USP, 100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg

Applicant Name: Mylan Pharmaceuticals Inc.

Meeting Recorder: Frank Giannandrea

FDA ATTENDEES

Frank Giannandrea, CDER/OGD/ORO/DPM
 Yen Anh Bui, CDER/OGD/ORO/DPM
 Elizabeth Katz, CDRH/ODE/DAGID/ RPDB
 Bhagwant Rege, CDER/OPQ/OLDP/DMRP
 Dhaval Gaglani, CDER/OPQ/OLDP/DMRP/MRBIII
 Fang Yuan, CDER/OPQ/OLDP/DMRP/MRBIII
 Candice Cottle-Delisle, OPQ/OPRO/DRBPM/RBPMBII

APPLICANT ATTENDEES

Wayne Talton, Head of Global Regulatory Affairs
 Roisin Wallace, Head of Global Device Development
 Michelle Lee-Bourner, Head Respiratory Regulatory Affairs
 Andrea Miller, Head of Global R&D and Regulatory Affairs
 Arnd Annweiler, Head of Global Biologics, Global Key Brands and Respiratory R&D

A. BACKGROUND

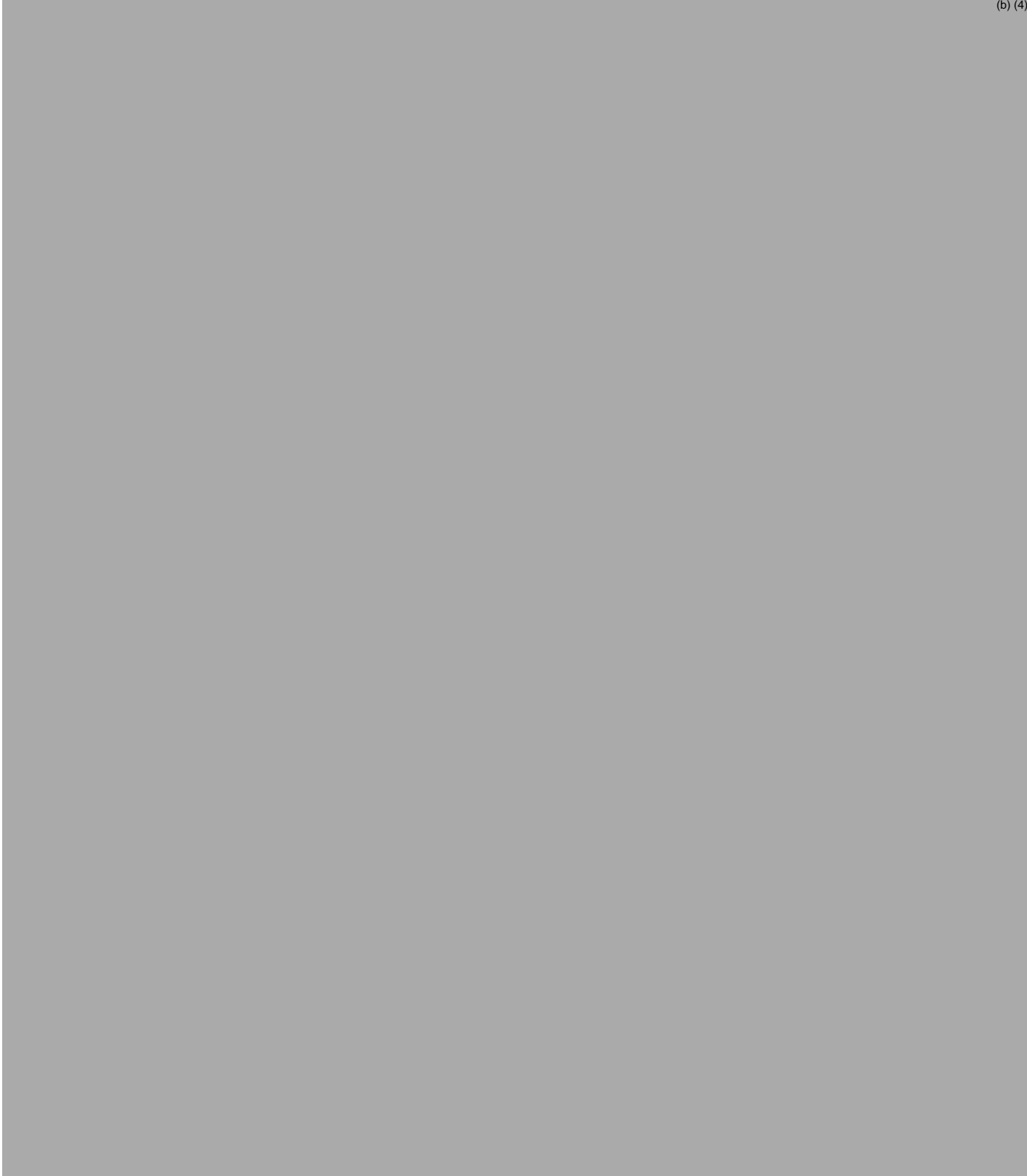
The purpose of the post-complete response letter meeting was to clarify deficiencies noted in the complete response letter dated June 27, 2018.

B. DISCUSSION

Pharmaceutical Quality

Device

- a. Applicant Question to Deficiency 9: Based on the above and the fact in the CRL FDA requested a number of pieces of information related to study execution details and additional clarifications on duration of contact assessment for each device component, Mylan is surprised to subsequently receive in this MINOR CRL a question related to the fundamental categorization of this DPI; therefore, Mylan request clarification from the Agency regarding the comment related to 'external communication'.



- f. Applicant Question to Deficiency 12: Mylan confirms that the requested information was provided in the 1st Major Complete Response Amendment. Clarification is sought from the Agency regarding the need to provide further information.

FDA response:

We acknowledge your comment. No further information is requested.

C. ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

D. ACTION ITEMS

Action Item/Description	Owner	Due Date
Issue Meeting Minutes	FDA	August 5, 2018

E. ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.



Frank
Giannandrea

Digitally signed by Frank Giannandrea

Date: 8/03/2018 03:05:54PM

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ANDA 208891

POST-CRL MEETING REQUEST GRANTED

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Wayne Talton
Head of Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2015, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Fluticasone Propionate and Salmeterol Inhalation Powder USP, 100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg.

We also refer to your correspondence received on June 29, 2018, requesting a post-complete response letter meeting to clarify deficiencies noted in the complete response letter issued by this office on June 27, 2018.

Your request for a post-complete response letter meeting is granted and the teleconference is scheduled as follows:

Date: Friday, July 6, 2018
Time: 1:15 p.m. – 1:45 p.m. EDT (30 minutes)
Phone Arrangements: Local: 1-210-795-0506
Toll free: 1-877-465-7975
Meeting ID: 906 578 732

FDA Participants: Frank Giannandrea, CDER/OGD/ORO/DPM
Yen Anh Bui, CDER/OGD/ORO/DPM
Elizabeth Katz, CDRH/ODE/DAGID/RPDB
Dhaval Gaglani, CDER/OPQ/OLDP/DMRP/MRBIII
Fang Yuan, CDER/OPQ/OLDP/DMRP/MRBIII
Candice Cottle-Delisle, OPQ/OPRO/DRBPM/RBPMBII
Bhagwant Rege, CDER/OPQ/OLDP/DMRP

Discussion points and action items will be summarized at the conclusion of the teleconference and reflected in FDA's meeting minutes.

If you need to reschedule or cancel the post-complete response letter meeting, please notify the Agency in writing via the Electronic Submissions Gateway.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

ANDA 208891

If you have any questions, please contact Frank Giannandrea, Regulatory Project Manager, at (240) 402-2704.

Sincerely,

{See appended electronic signature page}

Frank Giannandrea, Pharm.D.
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research



Frank
Giannandrea

Digitally signed by Frank Giannandrea
Date: 7/03/2018 12:19:45PM
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Memorandum

DATE: June 26, 2018

FROM: Sarah Yim, M.D.
Division Director, Division of Clinical Review
Office of Generic Drugs

TO: Abbreviated New Drug Application (ANDA) 208891, Fluticasone Propionate and Salmeterol Xinafoate, 100/50µg, 250/50µg, and 500/50µg

SUBJECT: Reserve Samples for Clinical Endpoint Study MGR001-3001 for ANDA 208891

The purpose of this memorandum is to document the decision of the Office of Generic Drugs (OGD) that the sponsor of ANDA 208891 complied with the relevant requirements to retain reserve samples for clinical endpoint study MGR001-3001 for ANDA 208891, Fluticasone Propionate and Salmeterol Xinafoate, 100/50µg, 250/50µg, and 500/50µg.

I. Background

On December 29, 2015, Mylan Pharmaceuticals Inc. (Mylan) submitted ANDA 208891 for Fluticasone Propionate and Salmeterol Xinafoate, 100/50µg, 250/50µg, and 500/50µg. To demonstrate that Mylan's test product was bioequivalent to the reference listed drug (RLD), New Drug Application (NDA) 021077, Advair Diskus, 100/50µg, 250/50µg, and 500/50µg, Mylan submitted, in part, clinical endpoint study MGR001-3001. During the review of the ANDA, FDA inspected 16 clinical sites for clinical endpoint study MGR001-3001 and found that 6 of the clinical sites did not retain reserve samples of test and reference drug products from all shipments (i.e., first shipment and subsequent shipments) during the study.¹ FDA's Office of Study Integrity and Surveillance (OSIS) reviewed the inspectional findings for clinical endpoint study MGR001-3001 and concluded that the reserve samples from the inspected clinical sites were not considered representative of the study products based on the applicant's selection of reserve samples only from the first shipment.² OSIS further concluded that because Mylan did not retain reserve samples from subsequent shipments, the reliability of the clinical data from clinical endpoint study MGR001-3001 could not be determined.³ OSIS deferred the issue to OGD for further evaluation.⁴ Among the deficiencies identified in the Complete Response (CR) Letter dated March 28, 2017 for ANDA 208891, OGD requested that Mylan provide (1) the number of shipments of test and reference product received from the study sponsor during the course of clinical endpoint study MGR001-3001 and (2) documentation to support that reserve samples were appropriately retained.⁵

¹ X. Li (Office of Study Integrity and Surveillance (OSIS)) to D. Conner (OGD), *Review of Clinical Site Inspections covering the following application: ANDA 208891, Fluticasone Propionate and Salmeterol Inhalation Powder, sponsored by Mylan Pharma UK Ltd.* (October 25, 2016), at 1-2.

² *Id.*, at 3.

³ *Id.*

⁴ *Id.*

⁵ ANDA 208891, Complete Response Letter (March 28, 2017), at 33-34.

Mylan provided responses to the Agency's clinical endpoint study deficiencies described above in a CR Response dated August 28, 2017.⁶ Mylan also provided additional information regarding clinical endpoint study MGR001-3001 in an Information Request (IR) Response dated March 22, 2018.⁷ OGD consulted OSIS to review Mylan's responses. OSIS concluded that the information submitted by Mylan confirmed that, for clinical endpoint study MGR001-3001, Mylan did not retain reserve samples of test and reference drug products from subsequent shipments used during the study. OSIS recommended that OGD assess the potential impact of the lack of reserve samples for each subsequent shipment from all clinical sites.

II. Legal and Regulatory Background

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), which established the current ANDA approval process. To obtain approval, an ANDA applicant is not required to submit independent evidence of the safety and effectiveness of the proposed generic drug product. Instead, the applicant relies on FDA's previous finding that the RLD is safe and effective. The ANDA applicant must identify the listed drug on which it seeks to rely and, with limited exceptions, a drug product described in an ANDA must contain the same active ingredient, conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the listed drug it references.⁸

An ANDA applicant must also demonstrate that its proposed generic drug is bioequivalent to the RLD.⁹ The bioequivalence testing methods may include *in vivo* data (data from a study on human subjects) or *in vitro* data (data from laboratory studies), or a combination of *in vivo* and *in vitro* data.¹⁰ 21 CFR 320.38 provides that if bioavailability testing was performed under contract, the contract research organization "shall retain an appropriately identified reserve sample of the drug product for which the applicant is seeking approval (test article) and of the reference standard used to perform an *in vivo* bioavailability study . . . that is representative of each sample of the test article and reference standard provided by the applicant for the testing." FDA's recommendations regarding the information needed to meet this regulatory requirement is contained in a guidance document entitled FDA's guidance for industry on *Handling and Retention of BA and BE Testing Samples* (May 2004) (Retention Sample BE Guidance). This guidance contains the following recommendation for retention of samples for multiple studies and shipments:¹¹

[I]f additional supplies of the test article and reference standard will be used by a testing facility to perform the same study or additional studies, the testing facility should retain a sufficient quantity of reserve samples from the subsequent shipment. . . . These approaches are to ensure that the reserve samples are in fact representative of the batch provided by the study sponsor and/or drug manufacturer to the testing facility.

⁶ ANDA 208891, Sequence 0021, CR Response (August 28, 2017).

⁷ ANDA 208891, Sequence 0032, IR Response (March 22, 2018).

⁸ Section 505(j)(2)(A) and (j)(4) of the FD&C Act. See also 21 CFR 314.94(a).

⁹ See, e.g., section 505(j)(2)(A)(iv) of the FD&C Act (requiring "information to show that the new drug is bioequivalent to the listed drug"); 21 CFR 314.94(a)(7) (requiring that an ANDA contain information to show that the drug product is bioequivalent to the RLD); and 21 CFR 314.127(a)(6)(i) (stating that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the RLD referred to in the ANDA).

¹⁰ See section 505(j)(7)(A)(i)(III) of the FD&C Act; see also *Schering Corp. v. FDA*, 51 F.3d 390, 398 (3d Cir. 1995) (noting that this provision "vests the FDA with the discretion to determine whether *in vivo* or *in vitro* bioequivalence studies, or both, will be required for the approval of generic drugs under the abbreviated approval processes").

¹¹ Retention Sample BE Guidance, at 4.

Applicants can choose to use an approach other than those set forth in a guidance document provided that the alternative approach satisfies the relevant statutory and regulatory requirements.¹²

III. Discussion

Based on internal discussion with OSIS, OGD’s Office of Bioequivalence (OB), OGD’s Office of Research and Standards (ORS), and the Office of Generic Drug Policy (OGDP), OGD’s Division of Clinical Review (DCR) sent three additional IRs to Mylan seeking clarifying information regarding Mylan’s process for retaining reserve samples for clinical endpoint study MGR001-3001.¹³ In IR Responses dated April 26, 2018, May 25, 2018 and June 7, 2018, Mylan provided the following additional information:¹⁴

- There were five separate batches of clinical supplies (investigational product) made by the manufacturers. The five batches consisted of two separate batches of test product, one batch of reference product, one batch of placebo (in test device), and one batch of placebo (in reference device). Each of the five batches were shipped in their entirety to the Clinical Supplies CRO, Catalent Pharma Services (Catalent), by their respective manufacturers in separate individual shipments.¹⁵

Table 1: MGR001-3001 IP Bulk Shipments to, and Pack / Label Run at, Catalent

Investigational Product	Batch Number	Shipped from:	Receipt/ Tracking No.	Catalent Pharma Solutions			
				Quantity received	Date received	Quantity packed	Date Packed
MGR001 Placebo	605-039						(b) (4)
Placebo Diskus	E113247-0003I001						
Advair 100/50 Diskus	4ZP4083						
MGR001 100/50 (batch A)	631-001						
MGR001 100/50 (batch B)	631-002						

- All the investigational products were packaged and assigned blinded kit numbers prior to study start and prior to shipment to individual clinical sites.
 - The five batches of investigational product received by Catalent were packaged into blinded “kits”¹⁶ under a single Packaging Reference (PR0008) with each batch of investigational product packaged and labeled in a single run by Catalent.¹⁷

¹² 21 CFR 10.115(d)(2). See also Retention Sample BE Guidance, at 1.

¹³ ANDA 208891, Information Request (April 20, 2018); ANDA 208891, Information Request (May 24, 2018); ANDA 208891, Information Request (June 4, 2018).

¹⁴ ANDA 208891, Sequence 0036, IR Response (April 26, 2018) (April 26, 2018 IR Response); ANDA 208891, Sequence 0038 (May 25, 2018) (May 25, 2018 IR Response); ANDA 208891, Sequence 0039 (June 7, 2018) (June 7, 2018 IR Response).

¹⁵ May 25, 2018 IR Response.

¹⁶ Mylan uses the term “kit” to refer to a single unit of product.

¹⁷ April 26, 2018 IR Response.

Table 2: MGR001-3001 IP Pack / Label Summary (Packaging Reference PR0008)

Investigational Product	Batch Number	Catalent Packaged Batch Number	Qty Packaged	Rec_Num (Sequence #) ¹ Range Packaged	Lowest Kit_Num (ID) – Highest Kit_Num (ID) in Range ²
MGR001 Placebo	605-039	CLR-9011162-001	5200		
Placebo Diskus	E113247-0003I001	CLR-9011162-002	2400		
Advair 100/50 Diskus	4ZP4083	CLR-9011162-003	2200		
MGR001 100/50 (batch A)	631-001	CLR-9011162-004	2375		
MGR001 100/50 (batch B)	631-002	CLR-9011162-005	2375		

¹ Each Rec_Num (Sequence #) corresponds to a random Kit_Num (ID) as shown in the Material Schedule.

² The Kit_Num (ID) range is recorded in the Certificate of Compliance for each packaging run.



(b) (4)

¹⁸ May 25, 2018 IR Response.

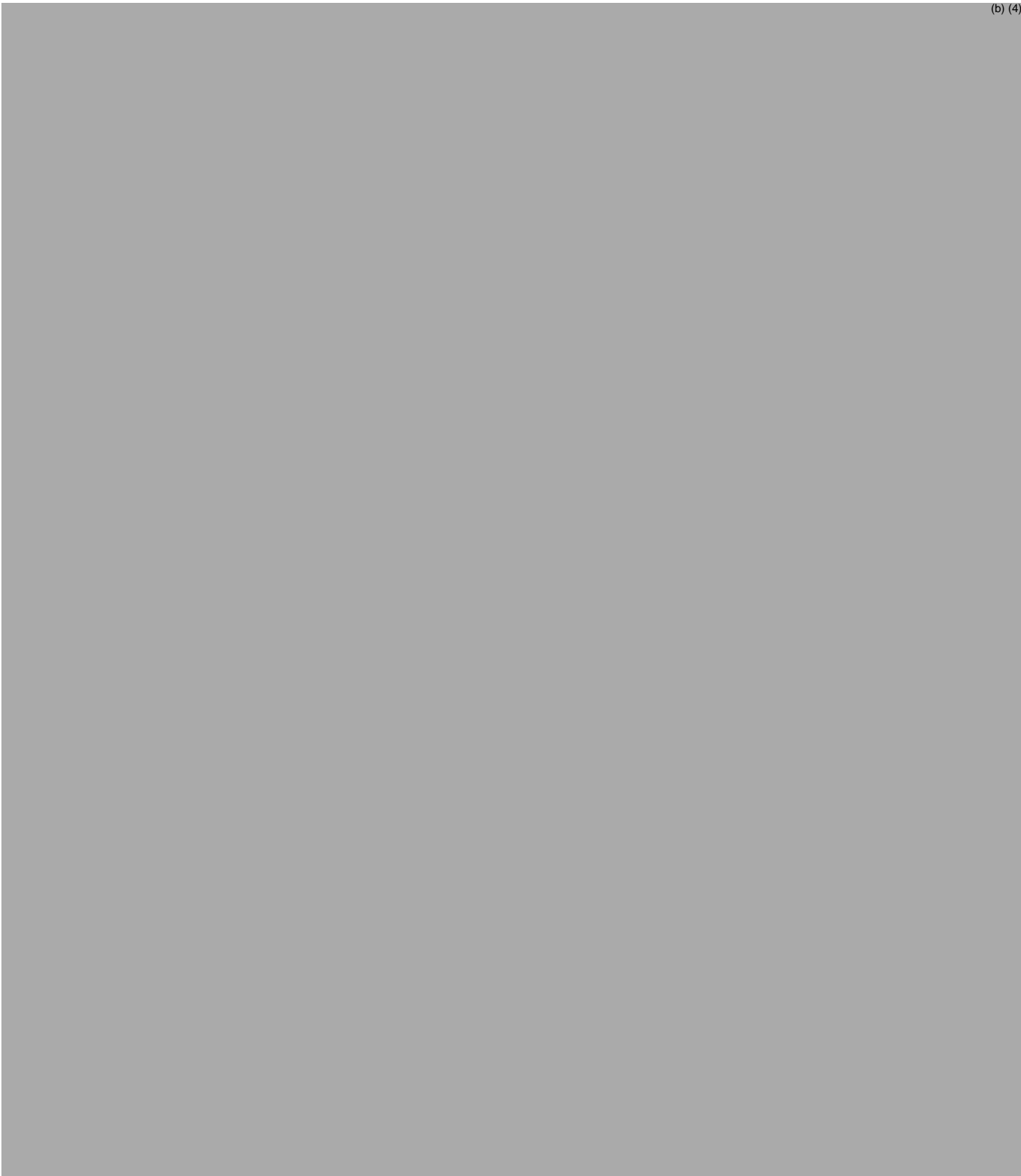
¹⁹ Id.

²⁰ Id.

²¹ Id.

²² Id.

²³ June 7, 2018 IR Response.



²⁴ Id.

²⁵ Id.

²⁶ OSIS Review dated October 25, 2016, at 3 (available at <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f880df431c>).

²⁷ April 26, 2018 IR Response.

IV. Conclusion

As described above, each of the five batches of investigational product were manufactured and shipped in its entirety to Catalent, and the five batches of investigational product were then packaged and labeled by Catalent under a single Packaging Reference (PR0008) with each batch of investigational product packaged and labeled in a single run. Therefore, as such, the investigational product in all kits as shipped by Catalent to each clinical site participating in clinical endpoint study MGR001-3001, whether as part of a first shipment or subsequent shipment, must have originated from any part of each of the five batches of investigational product initially received by Catalent. Accordingly, although reserve samples of investigational product from subsequent shipments were not retained by each clinical site as described in FDA's Retention Sample BE Guidance, we conclude that Mylan's approach to retaining reserve samples for this clinical endpoint study is acceptable because the reserve samples retained from the first shipment at each clinical site are representative of the investigational products used in the clinical endpoint study as contemplated by 21 CFR 320.38. To the extent Mylan's approach to retaining reserve samples is not consistent with the Retention Sample BE Guidance, a departure from the guidance is appropriate because Mylan has demonstrated that its approach satisfied the applicable statutory and regulatory standards. Accordingly, the clinical endpoint study is acceptable for review.



Sarah
Yim

Digitally signed by Sarah Yim

Date: 6/27/2018 08:18:48AM

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MEMORANDUM

DEVICE ORIENTATION STUDY REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: June 25, 2018

Requesting Office or Division: Office of Bioequivalence

Application Type and Number: ANDA 208891

Product Name and Strength: Wixela Inhub (fluticasone propionate and salmeterol xinafoate) Inhalation Powder
100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg

Applicant/Sponsor Name: Mylan Pharmaceuticals Inc.

FDA Received Date: August 28, 2017

OSE RCM #: 2018-121

DMEPA Associate Director: Mishale Mistry, PharmD, MPH

**DMEPA Acting Director,
OMEPRM Deputy Director:** Lubna Merchant. M.S., PharmD

1 REASON FOR REVIEW

This review responds to a consult request from the Division of Clinical Review (DCR) within the Office of Generic Drugs (OGD). DCR requested that DMEPA review the additional information submitted by Mylan, as part of their response to a Complete Response (CR), to determine whether the information submitted by Mylan, addressed the bioequivalence Deficiency comment 47 and is sufficient to support the device orientation study and if the proposed product can be substituted for the RLD with the full expectation that the proposed product will produce the same clinical effect and safety profile under the conditions specified in labeling.

2 REGULATORY HISTORY

ANDA 208891 Wixela Inhub (fluticasone propionate and salmeterol xinafoate) inhalation powder was received for review by OGD on December 29, 2015. On February 16, 2016, Mylan

Pharmaceuticals Inc. submitted the results of a device orientation study. DMEPA completed a review of the study on March 16, 2017.^{a,b}

On March 28, 2017, OGD issued a complete response (CR Letter) which included deficiencies related to the device orientation study, specifically recommending that Mylan provide the results of the three threshold analyses (e.g., comparative labeling analysis, comparative task analyses, physical comparison in the design of the delivery device constituent), as well as their overall assessment of the identified differences for the proposed product when compared to the RLD. The CR Letter referred to FDA's current thinking set forth in FDA's Draft Guidance on "Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA" (CUHF ANDA Draft Guidance) (January 2017). The CR Letter stated that "the Agency may view the design differences for [the] proposed presentation as not being minor if these analyses suggest that differences in the user interface between the proposed product as compared to that of the RLD may impact the clinical effect or safety profile of [the] proposed product as compared to the RLD when the proposed product is substituted for the RLD. In such cases, additional information and/or data, such as data from comparative human factors studies, may be warranted." The CR Letter also provided the opportunity for the applicant to use an alternative approach to address the issue. On August 28, 2017, Mylan Pharmaceuticals Inc. submitted additional comparative data and threshold analyses, as part of their response to a Complete Response (CR) received on March 28, 2017.

3 ANALYSIS AND DISCUSSION

Mylan provided the results of the threshold analyses consistent with the Draft Guidance. Based on their analyses, Mylan concluded that there is no difference between the proposed product and the RLD that has the potential to impact the clinical effect or safety profile of the use of the product in the intended use environment in the absence of healthcare provider (HCP) intervention or training, such that the end-user will achieve the required therapeutic dose. Mylan noted that this outcome is additionally underwritten through the device orientation study, which considered all critical tasks with a specific focus on orientation of use and the through-life testing of the proposed product demonstrating that device functionality and Uniformity of Emitted Dose are maintained regardless of orientation. Mylan asserts that the

^a Owens, L. Device Orientation Study Review for Wixela Inhub (ANDA 208891). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAR 16. RCM No.: 2016-1503.

^b In our previous review of the Device Orientation Study dated March 16, 2017, it was stated that "of the 110 participants, which consisted of Advair users and Advair/DPI naïve users, 10 participants used the device horizontally at some point over the three tasks. Of the 10 participants, nine (n=9) were Advair users and one (n=1) was a DPI naïve user (see Appendix C, Table 2). However, per their inhalation profile, nine of these 10 participants received the target delivered dose." Per the Applicant's response dated June 19, 2018 to an Information Request sent on June 18, 2018, 12 subjects inhaled from the inhaler in the horizontal position at some point across Tasks 1 to 3. Inhalation profile measurements were taken for all 12 participants who inhaled in the horizontal orientation during any of the three tasks. Eleven of the 12 participants met the inhalation profile success criteria of PIFR >30 L/min and TIV >1 L. As stated in our previous review, "One participant reported a low PIFR and TIV, which could potentially indicate an underdose, but this participant experienced challenges with the lung function test and did not achieve the required volumes when using the device correctly with a vertical orientation". See Appendix B.

outcome of the device development program is such that the proposed product has been demonstrated to be substitutable for the RLD.

Although we agree with the overall conclusion regarding therapeutic equivalence, we disagree with Mylan's conclusion that there are no "other than minor" differences between the proposed product and the RLD delivery device based on the threshold analyses. We conclude based on the threshold analyses that the difference in orientation between the proposed product and the RLD is an "other than minor" difference in external critical design attribute. Our previous review also identified the proposed orientation of use as a key difference between the proposed product and the RLD. Specifically, the proposed product is intended to be held vertically during administration whereas the RLD is intended to be held horizontally during administration. In addition, the second step in using the devices is different due to the difference in orientation. The RLD instructs patients to slide the lever until you hear a click whereas the proposed product instructs patients to "push the yellow lever down to the end of the purple arrows (you may hear a click)."^c

When such differences in design are identified between an ANDA product and RLD, our current thinking in the CUHF ANDA Draft Guidance is to recommend that the Applicant provide additional data, such as data from a comparative use human factors study to address whether the proposed product can be substituted for the RLD with the full expectation that it will produce the same clinical and safety profile as the RLD under the conditions specified in the labeling.^d

Although Mylan has not submitted this type of study, it has adopted an acceptable alternative approach to support approval of its proposed product. We have carefully considered this approach and have concluded that the device orientation study conducted by Mylan prior to issuance of the CUHF ANDA Draft Guidance - together with other studies, data, and information submitted by Mylan - support approval of the product in an ANDA and a finding that the proposed product can be substituted for the RLD with the full expectation that it will produce the same clinical and safety profile as the RLD under the conditions specified in the labeling.^e

^c The difference in lever is considered a minor difference. We note that there other minor differences between the proposed product and the RLD, but they are not the focus of this review.

^d For example, FDA recommends that sponsors consider designing a comparative use human factors study to provide sufficient data to confirm that the use error rate, for the critical task(s) as impacted by the differing external critical design attribute of the delivery device constituent part for the proposed generic combination product, is not worse than the corresponding use error rate for the RLD when used by patients and caregivers in representative use scenarios and use environments consistent with the labeled conditions of use. See CUHF ANDA Draft Guidance (available at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm536959.pdf>).

^e Our previous review noted that the device orientation study was not a comparative use human factors study and therefore generally does not provide sufficient data and information to evaluate the acceptability in an ANDA of the differences in the proposed product's device as compared to the RLD. This statement warrants clarification. The objective of a comparative human use study is to demonstrate that the use of error rate, associated with a difference in an external critical design attribute for the proposed user interface does not preclude approval of the proposed product in an ANDA. (See CUHF ANDA Guidance). Although imprecise, the language in the previous review was intended to convey that Mylan's device orientation study did not assess user error rate consistent with the draft guidance and we could not assess the acceptability of the differences in delivery device on this basis. However, upon further consideration, we have concluded that a comparative use human factors study is

In addition to the threshold analyses, Mylan conducted a non-dosing device orientation study.^f The difference in orientation noted in the reviewed study is associated with the external critical design and is considered an “other than minor difference.”. We requested supporting data to further evaluate this other than minor difference. In their response, Mylan noted that they have considered the orientation of the device, both from a design perspective and patient use throughout development; and that they have conducted studies to confirm that the orientation of the device does not impact the function and performance of the device or product performance. Mylan has demonstrated that the majority of patients use the device in the vertical orientation; nevertheless, the device was designed such that each dose has an individual airway that is not impacted by orientation. Mylan’s data demonstrate that in cases where the patients potentially use the device in the horizontal orientation, there is no impact on emitted dose. In addition, the in vitro data showed that, regardless of the device orientation, powder is isolated within the device, minimizing potential powder build up and impact on subsequent doses. The Office of Pharmaceutical Quality (OPQ) reviewed the information and data that Mylan provided for their Assessment of Orientation of Use on Uniformity of Emitted dose to support their conclusion that uniformity of emitted dose is maintained regardless of the orientation of the device during use. In their consult response, dated February 27, 2018, OPQ concluded that that the study design included substantial scenarios (i.e., combination of orientation of actuation and evacuation), representing the potential “orientation of use” and appropriate number of dose pockets per scenario for evaluation; and that the Uniformity of Emitted Dose data generated under each scenario met the Quality Control specification. Hence, the Quality Reviewer concludes that the data support the Applicant’s claim that Uniformity of Emitted Dose is maintained regardless of orientations of device during use^g. With this additional information, Mylan has provided data to support that the difference in orientation of use demonstrated in the non-dosing device orientation study for the proposed product would not result in sub therapeutic doses being delivered to patients or undermine a finding of therapeutic equivalence.

With regards to the difference in the lever, Mylan argues that the key perceptual, intellectual and manual activities are the same for users interacting with both inhalers for use of the lever. Mylan states that a minor difference exists due to a difference in the additional cues provided

unnecessary for this ANDA because even if the study identified a difference in error rate with respect to device orientation, the data provided by Mylan are sufficient to show that the device performance is of sufficient robustness that any difference in orientation would not result in sub therapeutic doses being delivered to patients or undermine a finding of therapeutic equivalence.

^f We note that no drug or placebo was administered or dispensed and no clinical endpoints were measured. Rather, the study was designed to evaluate whether participants who used the proposed product in the wrong orientation could generate an inhalation flow rate sufficient to ensure that the participant would receive a full dose, regardless of orientation of the proposed product. The study was designed to simulate actual use of the device at the point of substitution without any provision of training or health care provider intervention.

^g

<http://panorama.fda.gov/document/preview?versionID=5a959b5f008bf9a507e97d8bb111af63&ID=5a948cb5007ad0f9a3cd0b28b874d30f>

to the user to support use of the lever. The cue for completion of the movement is audible and tactile for the RLD (click and end of lever stroke) whereas for the proposed product the cue is visual and tactile (end of the purple arrows and end of lever stroke). Mylan states the mechanical movements within the proposed product during the movement of the lever may produce an audible click (audible cue). Mylan states that these cues provide the user with additional information which are not essential to enable the user to perform the task. Mylan's view is that the same potential for use error exists with both inhalers, i.e., at worst case the user cannot or does not push the lever therefore not making a dose available for inhalation. We agree with Mylan that in order to activate the dose, the lever must be pushed fully before inhaling the medication. This sequential order is identical between the proposed product and the RLD and both delivery devices have tactile cues. The fact that the additional cue for completion for Mylan's product is visual whereas for the RLD it is audible is not significant, in particular because this product is used in a chronic use setting where a potential delay in dose is not critical. Therefore, we conclude that there is no difference between the proposed product and the RLD in clinical effect or safety profile to the user with regard to the lever.

4 CONCLUSION

Based on the comprehensive data, studies, and information submitted by Mylan and our evaluation of that information, we conclude that the proposed product can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in labeling,^h and we have no additional recommendations. We defer to OGD to make a final determination regarding approval of the ANDA.

^h The Orange Book and regulations include a definition of therapeutic equivalence. We have concluded that the data we reviewed that were submitted by Mylan support this finding.

APPENDIX A. ADDITIONAL INFORMATION RECEIVED ON AUGUST 28, 2017



Cover Letter -
0021 - Addendu...

APPENDIX B. ADDITIONAL INFORMATION RECEIVED ON JUNE 19, 2018

Table 2 – Study MGR000-1004 Use Errors Relating to Orientation of Inhalation – Breakdown of Observations, Participant Demographics and Inhalation Profile Measurements.

Participant Number	Task Number	Orientation of Inhalation	Mean PFIR (LPM) ¹	Mean TIV (L) ¹	User Group	Age Group	Dominant Hand	Gender	Advair® Dose	Time Using Advair® Diskus® (Years)	Other Inhaler(s) used by participant
(b) (6)	1	Horizontal	67.97	2.19	Advair® Diskus®	18 to 64	Right	Male	100/50	7	ProAir® HFA, Qvar™
	2	Horizontal									
	3	Horizontal									
	1	Horizontal	38.25	1.75	Advair® Diskus®	18 to 64	Right	Female	250/50	7	ProAir® HFA
	2	Horizontal									
	3	Horizontal									
	1	Horizontal	51.18	2.17	Advair® Diskus®	18 to 64	Right	Female	250/50	14	ProAir® HFA
	2	Horizontal									
	3	Horizontal									
	1	Vertical	61.11	2.27	Advair® Diskus®	12 to 17	Right	Male	250/50	3.5	Proventil® HFA
	2	Vertical									
	3	Horizontal									
	1	Horizontal	41.51	1.25	Advair® Diskus®	18 to 64	Left	Female	500/50	2.5	Flovent®
	2	Horizontal									
	3	Horizontal									
	1	Horizontal	41.81	1.33	DPI Naïve	18 to 64	Right	Female	n/a	n/a	ProAir® HFA
	2	Horizontal									
	3	Horizontal									
	1	Horizontal	34.61	1.10	Advair® Diskus®	65+	Right	Male	100/50	4	Spiriva®
	2	Horizontal									
	3	Horizontal									
	1	Horizontal	14.40	0.48	Advair® Diskus®	65+	Right	Female	100/50	0.5	Symbicort®
	2	Horizontal									
	3	Horizontal									
	1	Horizontal	45.73	2.08	Advair® Diskus®	65+	Right	Female	250/50	1	n/a
	2	Horizontal									
	3	Horizontal									
	1	Horizontal	51.35	1.69	Advair® Diskus®	18 to 64	Right	Female	250/50	1	ProAir® HFA, Ventolin® HFA
	2	Horizontal									
	3	Vertical									
1	Horizontal	39.21	1.41	Advair® Diskus®	65+	Right	Female	250/50	5	ProAir® HFA	
2	Vertical										
3	Vertical										
1	Horizontal	73.52	2.42	Advair® Diskus®	12 to 17	Right	Male	250/50	5	Ventolin® HFA	
2	Horizontal										
3	Horizontal										

¹ – Mean Peak Inhaled Flow Rate (PIFR) and mean Total Inhaled Volume (TIV) measurements taken with the device in the horizontal position using an Inhalation Profile System (IPS).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MISHALE P MISTRY
06/25/2018

IRENE Z CHAN on behalf of LUBNA A MERCHANT
06/26/2018

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: April 5, 2018

TO: Sarah Yim, MD
Division of Clinical Review
Office of Bioequivalence
Office of Generic Drugs

FROM: Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Acting Deputy Director
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Evaluation of Mylan's Response to CR Deficiency
Comments in Response to OSIS EIR Findings on Clinical
Endpoint Study MRG001-3001 for ANDA 208891

Background:

On December 8, 2017, the Office of Bioequivalence in OGD sent OSIS a Request for Consultation to ask for OSIS' assessment of Mylan's response to the Complete Response letter, which was sent to Mylan on March 28, 2017. The letter included deficiency comments to be addressed by Mylan, including BE deficiencies #48 (reserve samples) and #49 (blinding codes) that resulted from OSIS' inspection of clinical endpoint study MRG001-3001 for ANDA 208891.

In the Consultation, OGD posed the following question to OSIS: "Does the information provided by the Applicant in their responses to Deficiencies 48 and 49 under Bioequivalence Section of the CR letter adequately address your concerns and support that the data from the clinical endpoint study MRG001-3001 are acceptable for further agency review? If not, please provide justification and rationale."

BE Deficiency 48:

FDA's inspections of the clinical sites for this study found that reserve samples were retained from only the first shipment to each site.

On March 15, 2018, OGD/DCR followed up on the reserve sample issue by sending an IR that requested the sponsor to clarify if any used or unused drug products from subsequent shipments to other clinical sites were currently available or have been destroyed. If available, they might serve as substitutes for reserve samples. In their response dated March 22, 2018, Mylan stated that none of the clinical sites had leftover drug products, as all unused drug products were destroyed.

This OSIS reviewer concludes that the information submitted in the applicant's CR response dated on August 28, 2017 and the IR response dated on March 22, 2018 are consistent with OSIS's original understanding on reserve samples, as documented with inspectional findings. This OSIS reviewer recommends that DCR/OGD assess the potential impact of the lack of reserve samples for each subsequent shipment from all clinical sites. I believe that study sites retained reserves only from the first shipment of drug products to each site.

BE Deficiency 49:

The dates of study conduct for Study MGR001-3001 were 10/22/2014 to 7/10/2015. Based on the clinical amendment submitted to OGD on 3/15/2018, the randomization schedule was generated on 4/1/2014, and the Material Schedule (blinding codes) was generated on 4/8/2014.

To the reviewer's knowledge, the materials schedule contains the blinding codes for all materials (reserve samples and subject dosing materials). The material schedule SAS data set has an accompanying SAS log file indicating the SAS System program execution date/time as 4/8/2014 for generating the materials schedule. That date is 6 months before the study started. This reviewer randomly selected subjects from submitted CRFs to verify their receipt of the intended products.

Documents referenced:

Mylan provided the following information on August 28, 2017 in response to the CR letter. The following four documents are referenced:

- 1) MGR001-3001 IRT Transaction Log
<\\cdsesub1\evsprod\anda208891\0021\m5\53-clin-stud-rep\535-rep-effic-safety-stud\asthma-and-copd\5351-stud-rep-contr\mgr001-3001\mgr001-3001-batch-1.pdf>
- 2) MGR001-3001 Unblinded Catalent Shipments
<\\cdsesub1\evsprod\anda208891\0021\m5\53-clin-stud-rep\535-rep-effic-safety-stud\asthma-and-copd\5351-stud-rep-contr\mgr001-3001\mgr001-3001-batch-2.pdf>
- 3) Appendix 16.1.7-1.1 (contained in eCTD from ANDA 208891)
- 4) MGR001-3001 Actual Randomisation number to treatment
<\\cdsesub1\evsprod\anda208891\0021\m5\53-clin-stud-rep\535-rep-effic-safety-stud\asthma-and-copd\5351-stud-rep-contr\mgr001-3001\mgr001-3001-random.pdf>

In Mylan's clinical amendment after the F2F meeting on 3/1/2018 (submitted to OGD on 3/15/2018), the following three documents are referenced:

- 1) The original material schedule created on 4/8/2014, provided as a SAS data set. These constitute the blinding codes.
- 2) The original randomization schedule created on 4/1/2014, provided as a SAS data set. This list shows the products intended to be dosed with blind-coded kits.
- 3) An Excel file of subject dispensing visit IRT log. This list shows the blind-coded kits dispensed to subjects.

Conclusion:

This OSIS reviewer is satisfied that the documents show that subjects were dose with the products as reported.

Xingfang Li -S

Digitally signed by Xingfang Li -S
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ou=People, cn=Xingfang Li -S,
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Date: 2018.04.05 12:49:55 -04'00'

Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
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Date: 2018.04.05 12:26:34 -04'00'

Michael F. Skelly, Ph.D.
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John A. Kadavil -S

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Date: 2018.04.05 14:43:38 -04'00'

John A. Kadavil, Ph.D.
Acting Deputy Director
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cc:

OSIS/Kassim/Choe/Taylor/Haidar/Mitchell/CDER-OSIS-
BEQ@fda.hhs.gov

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas

OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/Li

Draft: XFL 4/4/2018

Edit: MFS 4/4/2018; JAK 4/5/2018



ANDA 208891

DISCIPLINE REVIEW LETTER

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
Morgantown, WV 26504-4310
Attention: Wayne Talton

Dear Wayne Talton:

This communication is in reference to your abbreviated new drug application (ANDA) dated August 28, 2017, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Propionate and Salmeterol Inhalation Powder USP, 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg/50 mcg .

We have completed the Labeling review of this ANDA and have the following preliminary thoughts on possible deficiencies:

Labeling Deficiencies determined as of 2/5/2018 based on your submission dated 8/28/2017:

1. GENERAL COMMENTS

- a. We note that on December 16, 2009, Ropes & Gray, LLP, on behalf of GlaxoSmithKline, submitted a citizen petition to FDA (Docket No. FDA-2009-P-0597) regarding abbreviated new drug applications (ANDAs) that reference generic copies of oral inhalation products containing fluticasone propionate and/or salmeterol xinafoate. On December 5, 2017, Mylan Inc. submitted a citizen petition to FDA (Docket No. FDA-2017-P-6750) regarding ANDAs for fluticasone propionate and salmeterol xinafoate inhalation powder that rely on Advair Diskus as the reference listed drug (RLD). The issues raised by the above-referenced citizen petitions are under review by the Agency, and FDA has not made a final decision on these issues. The deficiency comments included in this communication do not represent a final decision by the Agency on the issues raised in the pending citizen petitions.
- b. We note that the Medication Guide (MG) has been replaced with Patient Information in the most recently approved reference listed drug (RLD) labeling, Advair Diskus®, NDA 021077/S-056 and 057, approved 12/20/2017. Please replace references to “Medication Guide” (MG) with “Patient Information” in your labels/labeling where applicable (i.e., “Read the accompanying Medication Guide...”)
- c. The Orange Book has updated exclusivity (M-214) for the RLD. Address the new exclusivity and revise the insert labeling and Patient Information accordingly.

2. CONTAINER LABEL (Inhaler label)

- a. Relocate the expression of strength to appear directly below the established name.
- b. Replace “30 days” with “1 month” to be consistent with RLD.
- c. The RLD container label (back panel) includes “Do not exhale into the mouthpiece or tip downward when in use.” Revise to include this statement to better align with RLD. Please provide rationale for any changes to the statement if needed.
- d. Revise to include a placement for lot number expiration date.

3. FOIL POUCH LABEL

Refer to comments 2.a and 2.b.

4. CARTON LABELING

- a. Refer to comments 2.a and 2.b.
- b. Delete the Medication Guide statement on the principal display panel.
- c. Side panel:
Change “Follow the 4 steps below each time you take a dose” to “Instructions for using [Product Name]” followed by “Read the Patient Information that comes with...” to be consistent with the RLD Instructions for use: Refer to comment 7.b for instructions for use, and revise accordingly.
- d. Side panel including “Dose Counter” and “Important Information”: RLD includes the following information under the header “Remember:”

Remember:

- Always use the DISKUS in a level, flat position.
- Make sure the lever firmly clicks into place.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. Do not swallow the water.
- **Do not** take an extra dose, even if you did not taste or feel the powder.
- **Do not** take the DISKUS apart.
- **Do not** wash the DISKUS.
- Always keep the DISKUS in a dry place.
- **Do not** use the DISKUS with a spacer device.

Revise to better align with the above information. For example, RLD

includes “Do not use the [inhaler name] with a spacer device” when your product includes “Do not use a spacer.” Please provide rationale for any information you choose to delete or change.

5. PRESCRIBING INFORMATION

Revise your insert labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Advair Diskus[®], NDA 021077/S-056 and 057, approved 12/20/2017.

6. Patient Information (previously Medication Guide)

Refer to comment 5.

7. Instructions for Use (IFU)

a. Refer to comment 5.

b. Although there are some design and operational differences between your product and the RLD, we believe it is possible to revise all sections of the Instructions for Use (IFU) of your proposed product with respect to text, device illustrations, and organization of the tasks within the operating steps for dose administration, to better align with the IFU of the RLD product. For example, the headers in the IFU of your proposed product should be revised to better align with the following headers in the IFU of the RLD product:

Instructions for Use

Title

For oral inhalation

“Read this Instructions for Use before you start using...”

Your [Product Name] inhaler

[High definition photograph of your inhaler]

Important information about your [Product Name] inhaler:

How to use your [Product Name] inhaler

Follow these steps every time you use [Product Name]

Step 1...Step 5

Also, note that the RLD includes 5 steps instead of 4 steps, and uses the word “1 month” instead of “30 days.”: Please revise accordingly.

c. Title: Delete “60 DOSE” appearing next to “for oral inhalation.”

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated

and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these possible deficiencies before the end of this review-cycle, we request a complete written response no later than February 15, 2018. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**DISCIPLINE REVIEW LETTER
LABELING
REFERENCE # 20673622**

If you do not submit a complete written response by February 15, 2018, these possible deficiencies may be incorporated in a complete response letter.

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the GDUFA II Commitment Letter¹, these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review.

If you respond to these issues during this review cycle, depending on the timing of your response, we may not be able to consider your response before taking action on your application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit:

¹ The term "GDUFA II Commitment Letter" refers to the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>).
U.S Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

www.fda.gov/ectd.

If you have any questions, please contact Danielle Russell, Labeling Project Manager,
at Danielle.Russell@fda.hhs.gov.

Sincerely,

Danielle E.
Russell -A



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Russell -A
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=200140
1090, cn=Danielle E. Russell -A
Date: 2018.02.12 15:40:55 -05'00'

Danielle Russell, Pharm.D.
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 11/6/2017

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: ANDA 208891

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

Although the last inspection was classified as a VAI, based on the inspectional outcome and our recommendation to the review division, an inspection is not needed at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	Mylan Pharmaceuticals, Inc.	3711 Collins Ferry Road, Morgantown, WV

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stewart-S

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 11/6/2017

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: [REDACTED] (b) (4)
ANDA 208891
[REDACTED] (b) (4)

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Worldwide Clinical Trials Early Phase Services, LLC.	2455 NE Loop 410, Suite 150, San Antonio, TX
Analytical	[REDACTED] (b) (4)	

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 208891

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

ATTENTION: Joseph J. Sobecki
Vice President, Regulatory Affairs

Dear Mr. Sobecki:

Please refer to your Abbreviated New Drug Application (ANDA) dated and received December 29, 2015 submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Propionate and Salmeterol Dry Powder Inhaler, 100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg.

We also refer to:

- Your February 15, 2016, correspondence, received February 16, 2016, requesting review of your proposed proprietary name, Wixela Inhub
- Your amendments to the Request for Proprietary Name Review, dated and received February 17, 2016 and February 25, 2016.

We have completed our review of the proposed proprietary name, Wixela Inhub and have concluded that it is conditionally acceptable.

If your application receives a complete response and six months or more has elapsed between the date you were notified of our decision on your proposed proprietary name and the date you respond to the application deficiencies, please submit a new request for review of your proposed proprietary name when you respond to the application deficiencies. See the Guidance for Industry, Contents of a Complete Submission for the Evaluation of Proprietary Names, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>

If any of the proposed product characteristics as stated in your February 15, 2016 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact CAPT Aaron Sigler, Deputy Director in the Division of Project Management, Office of Generic Drugs, at (240) 402-8786.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
07/22/2016