CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208799Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208799 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: AirDuo RespiClick Established/Proper Name: Fluticasone Propionate and Salmeterol Xinafoate Dosage Form: Inhalation Powder		Applicant: Teva Pharmaceutical Industries Ltd. Agent for Applicant (if applicable): Teva Branded Pharmaceutical Products R&D Inc.
RPM: Laura Musse		Division: Pulmonary, Allergy, and Rheumatology Products

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: January 27, 2017

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is January 28, 2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 4
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☐ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s)
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☒ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Acceptability May 19, 2016 Review: May 7, 2016
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ Janaury 12, 2017 DMEPA: ☒ July 26, 2016 DMPP/PLT (DRISK): ☒ January 13, 2017 OPDP: ☒ January 11, 2017 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☐
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ January 12, 2017
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☒ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC October 19, 2016 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	April 11, 2011, May 13 and 26, 2016, September 23, 2016, October 6, 13, 20, and 27, 2016, November 24, and 30, 2016, January 5, 19, and 23, 2017
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ December 4, 2015
• EOP2 meeting *(indicate date of mtg)*	☒ December 18, 2013 and March 17, 2014
• Mid-cycle Communication *(indicate date of mtg)*	☒ None
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒
Division Director Summary Review *(indicate date for each review)*	☒ January 27, 2017
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ January 17, 2017
PMR/PMC Development Templates *(indicate total number)* 2	☒ Janaury 12, 2017
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	May 27, 2016, October 26, 2016
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Primary Review page 20/Section 3/3.3 October 26, 2016
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ November 4, 2016
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☒ June 3, 2016 December 9, 2016
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ May 18, 2016 and October 28, 2016
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ November 4, 2016 and May 13, 2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☒ December 16, and 8, 2016, October 24, 2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ December 27, 2016
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	December 16, 2016
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable, December 16, 2016 Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

LAURA MUSSE
01/27/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: January 18, 2017

To: Michael J. McGraw, PharmD, MS Senior Director, Global Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R&D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (610) 786-7051	**Fax number:** (301) 796-9728
Phone number: (610) 727-6136	**Phone number:** (240) 402-3720

Subject: NDA 208799- fluticasone propionate/salmeterol Inhalation Powder, Information Request for Labeling

Total no. of pages including cover: 56

Comments: Please confirm document receipt via email: laura.musse@fda.hhs.gov

Document to be emailed to Mike.McGraw@tevapharm.com

Your submission dated March 29, 2016 to NDA 208799, is currently under review. The enclosed label contains the Division's edits to your propose package insert (PI) and carton and container label. The Division's proposed insertions are underlined; deletions are in strike-outs. These comments are not all-inclusive and we may have additional comments as we continue our review. We also have the following comments on the proposed carton, device back label, and draft foil labeling:

The proposed carton and container labeling includes (b) (4)

(b) (4)

(b) (4)

We note competitor carton and container labeling (e.g., Advair Diskus and Breo Ellipta) do not contain this presentation. We recommend deletion of this incomplete and misleading risk information from the AIRDUO carton and container labeling to avoid the implication that this is the full risk disclosure of the drug.

Please provide your response via email to (Laura.Musse@fda.hhs.gov), as soon as possible or no later than COB on Monday January 23, 2017. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Health Project Manager, at 240-402-3720.

Review/History Clearance

Drafted by: L. Musse	Date: January 17, 2017
Clearance: S. Barnes	Date: January 18, 2017
Finalized: L. Musse	Date: January 18, 2017
File Name: Labeling IR	Date: January 18, 2017

53 Page(s) of Draft Labeling have been Wittheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LAURA MUSSE
01/19/2017

NDA 208798-Fluticasone Propionate
NDA 208799- Fluticasone Propionate/Salmeterol
TEVA

NDA 208798-Fluticasone Propionate
NDA 208799- Fluticasone Propionate/Salmeterol
TEVA

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 5, 2017

To: Michael J. McGraw, PharmD, MS Senior Director, Global Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R&D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (610) 786-7051	**Fax number:** (301) 796-9728
Phone number: (610) 727-6136	**Phone number:** (240) 402-3720

Subject: NDA 208798-Fluticasone Propionate and NDA 208799- fluticasone propionate/salmeterol Inhalation Powder, Information Request for Labeling

Total no. of pages including cover:77

Comments: Please confirm document receipt via email: laura.musse@fda.hhs.gov

Document to be mailed: **YES** **X- NO**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 240-402-3720. Thank you.

Your submission dated March 29, 2016 to NDA 208799, is currently under review. The enclosed label contains the Division's edits to your propose package insert (PI) and carton and container label. The Division's proposed insertions are underlined; deletions are in strike-outs. These comments are not all-inclusive and we may have additional comments as we continue our review. We also have the following comments:

At this time, a response to this labeling information request is not expected. The proposed labeling edits will be discussed on Monday, January 9, 2017, during the scheduled labeling teleconference.

Please acknowledge receipt of this facsimile via phone or email. If you have any questions, please contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

75 Page(s) of Draft Labeling have been Wittheld in Full as b4 (CCI/TS) immediately following this page

Review/History Clearance

Drafted by: L. Musse	Date: January 5, 2017
Clearance: S. Barnes	Date: January 5, 2017
Finalized: L. Musse	Date: January 5, 2017
File Name: Labeling IR	Date: January 5, 2017

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/s/

LAURA MUSSE
01/05/2017

NDA 208798-Fluticasone Propionate
NDA 208799- Fluticasone Propionate/Salmeterol
TEVA

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 5, 2017

To: Michael J. McGraw, PharmD, MS Senior Director, Global Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R&D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (610) 786-7051	**Fax number:** (301) 796-9728
Phone number: (610) 727-6136	**Phone number:** (240) 402-3720

Subject: NDA 208798-Fluticasone Propionate and NDA 208799- fluticasone propionate/salmeterol Inhalation Powder, 505(b)(2) Information Requests

Total no. of pages including cover: 3

Comments: Please confirm document receipt via email: laura.musse@fda.hhs.gov

Document to be mailed: **YES** **X- NO**

Your submissions dated March 28 and 29, 2016 to NDA's 208798 and 208799, are currently under review. We have the following requests for information.

(b) (4)

Please provide a response to the requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by Monday, January 9, 2017. Your response must also be submitted formally to both NDA's shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

Review/History Clearance

Drafted by: L. Musse	Date: January 5, 2017
Clearance: S. Barnes	Date: January 5, 2017
Finalized: L. Musse	Date: January 5, 2017
File Name: 505B2 IR	Date: January 5, 2017

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/s/

LAURA MUSSE
01/05/2017

NDA 208798-Fluticasone Propionate
NDA 208799- Fluticasone Propionate/Salmeterol
TEVA

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 5, 2017

To: Michael J. McGraw, PharmD, MS Senior Director, Global Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R&D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (610) 786-7051	**Fax number:** (301) 796-9728
Phone number: (610) 727-6136	**Phone number:** (240) 402-3720

Subject: NDA 208798-Fluticasone Propionate and NDA 208799- fluticasone propionate/salmeterol Inhalation Powder, Information Request for Labeling Information Request for PMR/PMC Commitment.

Total no. of pages including cover: 2

Comments: Document to be faxed.

Your original submissions, dated March 28 and 29, 2016 to NDAs 208798 and 208799, are currently under review. We have the following request for information:

We request written confirmation of your agreement to conduct the following post-marketing studies and to the scheduled milestones listed below:

1. Pharmacokinetic Study:
   (b) (4) Conduct a double-blind (incorporating an open-label comparator), 3-period, crossover study to determine the pharmacokinetic profile and tolerability of single doses of Fp MDPI and FS MDPI compared to Advair Diskus in patients with persistent asthma 4 through 11 years of age.

   Final Report Submission: December 2019

2. Safety Study:
   (b) (4) Conduct a 12-week, randomized, double-blind, placebo-controlled, efficacy and safety study of Fp MDPI compared with FS MDPI in patients with persistent asthma 4 through 11 years of age.

   Trial Completion: May 2019
   Final Report Submission: December 2019

Respond to this information request by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by Friday January 13, 2017. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Health Project Manager, at 240-402-3720.

Review/History Clearance From

Drafted by:	LMusse	Date: January 4, 2017
Revised by:	SBarnes	Date: January 4, 2017
Clearance:	SBarnes	Date: January 4, 2017
	SSeymour	Date: January 5, 2017
Finalized:	LMusse	Date: January 5, 2017
File Name:	PMC/PMR Commitment	Date: January 5, 2017

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/s/

LAURA MUSSE
01/05/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 30, 2016

To: Michael J. McGraw, PharmD, MS Senior Director, Global Regulatory Affairs	From: CDR Sadaf Nabavian Sr. Regulatory Project Manager for Laura Musse
Company: Teva Branded Pharmaceutical Products R&D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 610-786-7051	Fax number: 301-796-9728
Phone number: 610-727-6136	Phone number: 301-796-2300

Subject: NDA 208798 and NDA 208799; FDA Information Request

Total no. of pages including cover: 3

Comments: Please confirm receipt. Thanks.

Document to be mailed: **YES** **xNO**

NDA 208798/Fluticasone Propionate
NDA 208799/Fluticasone Propionate and Salmeterol
Teva Branded Pharmaceutical Products R&D, Inc.

Dear Dr. McGraw:

Your submissions dated March 28, 2016, to NDA 208798, and dated March 29, 2016, to NDA 208799, are currently under review and we have the following comments.

1. Provide the total number of sites and the number of sites that were located in the United States for Studies FPS-201, FPS-202, FSS-AS-301 and FSS-AS-30017.

2. Submit your primary analysis programs that you used to generate Summary Table 15.2.1.1 (Study FpS-AS-201) and Table 15.2.1.1 (Study FpS-AS-202) in your clinical study reports.

Submit your responses to me via telephone facsimile to 301-796-9728 or email at Sadaf.Nabavian@fda.hhs.gov by COB, December 9, 2016. Your responses will subsequently need to be submitted officially to the NDAs. If you have any questions, please contact Sadaf Nabavian, Senior Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/11.30.2016

Cleared by: SBarnes/11.30.2016

Finalized by: SNabavian/11.30.2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SADAF NABAVIAN
11/30/2016

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 24, 2016

To: Michael J. McGraw, PharmD, MS Senior Director, Global Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R&D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (610) 786-7051	**Fax number:** (301) 796-9728
Phone number: (610) 727-6136	**Phone number:** (240) 402-3720

Subject: NDA 208799- fluticasone propionate/salmeterol Inhalation Powder, Information Request for Labeling

Total no. of pages including cover:51

Comments: Please confirm document receipt via email: laura.musse@fda.hhs.gov

Document to be mailed: **YES** **X- NO**

Your submission dated March 29, 2016 to NDA 208799, is currently under review. The enclosed label contains the Division's edits to your propose package insert (PI) and carton and container label. The Division's proposed insertions are underlined; deletions are in strike-outs. These comments are not all-inclusive and we may have additional comments as we continue our review. We also have the following comments:

I. General Comments

We acknowledge that you have used the [redacted] (b) (4) package inserts as a guide for your package insert, however, the package inserts for inhaled corticosteroids/long-acting beta-agonists (ICS/LABA) have evolved since that time. We recently submitted labeling edits for your other NDA (208798) for ArmonAir RespiClick that is currently under review. While we have made some edits to the AirDuo RespiClick package insert, these are not all inclusive. In order to provide information in the most current format, we request that you revise the AirDuo RespiClick label, modeling it after and applying our edits and comments included in the ArmonAir RespiClick package insert. We also refer you to the package insert of Arnuity Ellipta (NDA 205-625) and Breo Ellipta (NDA 204275) as the most recently approved ICS and ICS/LABAs for reference. Additional comments are provided below.

II. Carton and Container Comments:

1. As currently presented, the strength in the colored boxes does not include units. Include the unit of strength in each location where the strength is listed (i.e. 55 mcg/14 mcg vs. 55/14) to mitigate confusion.

2. You are proposing [redacted] (b) (4)

3. To increase readability, we recommend that the strength is presented in one color and the font size is increased to match the font size of the fluticasone strength. Currently, [redacted] (b) (4), and may be overlooked.

4. Clarify the location on the drug product immediate container (MDPI device) label where the drug product lot number and expiry will be printed.

5. The salt equivalent statement you included for salmeterol xinafoate on the pouch label and carton [redacted] (b) (4). Correct it to state as "14 mcg of salmeterol base, equivalent to 20.3 mcg of salmeterol xinafoate".

Please provide a response to the requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by COB on Wednesday, December 7, 2016. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

49 Page(s) of Draft Labeling have been Wittheld in Full as b4 (CCI/TS) immediately following this page

Review/History Clearance

Drafted by: L. Musse	Date: 11/22/16
Clearance: S. Barnes	Date: 11/22/16
Finalized: L. Musse	Date: 11/24/16
File Name: Label IR #1	Date: 11/24/16

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/s/

LAURA MUSSE
11/24/2016

From:	Steven Kinsley
To:	Mike.McGraw@tevapharm.com
Cc:	Laura Musse, Florence Aisida
Subject:	NDA 208798/208799 CMC Information Request 10-27-16
Date:	October 27, 2016

Dear Mike,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Thursday, November 10, 2016.

1. We note that you have included an (b) (4) in the acceptance criteria for the dose content uniformity testing for both NDAs 208798/99. (b) (4)
(b) (4)

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov

Steven Kinsley

Digitally signed by Steven Kinsley
Date: 10/27/2016 03:36:15PM
GUID: 555cc3bc000836e194b17e8bf695ce5f

NDA 208798-fluticasone propionate
NDA 208799- fluticasone propionate/salmeterol
TEVA

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: October 20, 2016

To: Michael J. McGraw, PharmD, MS Senior Director, Global Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R&D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (610) 786-7051	**Fax number:** (301) 796-9728
Phone number: 610) 727-6136	**Phone number:** (240) 402-3720

Subject: NDA 208798-fluticasone propionate and NDA 208799- fluticasone propionate/salmeterol, Inhalation Powder, Information Request

Total no. of pages including cover: 3

Comments: Please confirm document receipt via email: laura.musse@fda.hhs.gov

Document to be mailed: **YES** **X- NO**

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 240-402-3720. Thank you.

NDA 208798-fluticasone propionate
NDA 208799- fluticasone propionate/salmeterol
TEVA

Your submissions, dated March 28 and 29, 2016 to NDA 208798 and 208799, are currently under review. We have the following requests for information:

Provide the month and year of the anticipated study completion and the final report submission for studies FSS-PK-10007 and FSS-AS-30003.

Please provide a response to the requests by email (Sadaf.Navabian@fda.hhs.gov) and cc me or facsimile (301-796-9728), by 12 noon on Thursday, November 3, 2017. Your response must also be submitted formally to both NDA's shortly thereafter. If you have any questions, please contact Sadaf Nabavian, Regulatory Health Project Manager, at 301-796-2777.

Review/History Clearance

Drafted by: L. Musse	Date: 10/20/16
Clearance: S. Barnes	Date: 10/20/16
Finalized: L. Musse	Date: 10/20/16
File Name: Clinical IR	Date: 10/20/16

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/s/

LAURA MUSSE
10/20/2016

From: Mike McGraw
To: Aisida, Bamidele (Florence)
Cc: Musse, Laura; Kinsley, Steven
Subject: RE: NDA 208799 CMC Information Request
Date: Thursday, October 13, 2016 12:13:30 PM
Attachments: image001.png

Dear Florence,

I confirm receipt of your email.

Regards,
Mike

Michael J. McGraw Sr. Director, Global Regulatory Affairs, Respiratory and Oncology
Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

From: Aisida, Bamidele (Florence) [mailto:Bamidele.Aisida@fda.hhs.gov]
Sent: Thursday, October 13, 2016 12:09 PM
To: Mike McGraw
Cc: Musse, Laura; Kinsley, Steven
Subject: NDA 208799 CMC Information Request
Importance: High

Hello Mike,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Thursday, October 27, 2016:

1) Since this drug product is an ultra-low drug loading product, we are concerned that inhaler content uniformity (b) (4) is not adequately ensured (b) (4) Please provide the following to demonstrate that you have mitigated the risk of blend segregation and the resulting variability in unit-to-unit dosing:

(b) (4)

(b) (4)

From: Aisida, Bamidele (Florence)
To: "Mike McGraw"
Cc: Musse, Laura; Kinsley, Steven
Subject: NDA 208798/208799 CMC Information Request
Date: Thursday, October 06, 2016 11:10:39 AM

Hello Mike.

The following deficiencies have been identified while doing the documentation review of application NDA 208798/208799, in reference to applicable 21 CFR 820 regulations and (or) manufacturing of the finished combination product under 21 CFR Part 4:

1. The information provided by your firm has inadequately addressed the requirements of 21CFR 820.30, Design Controls. Specifically, your firm did not describe its design control system which should include requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file. Your firm should also provide a copy or a summary of the plan used to design the combination product. Your firm should explain how it implemented the plan for the combination product project.

2. The information provided by your firm has inadequately addressed the requirements of 21CFR 820.20, Management Responsibility. Specifically, the submission did not include information addressing which firm has ultimate responsibility for the overall combination product. The submission did not include a description of the organizational structure (i.e. organization structure chart) and explain how it controls all levels of the structure (i.e. agreements). Please provide a description of your procedures for Management Controls.

3. The information provided by your firm has inadequately addressed the requirements of 21CFR 820.50, purchasing controls. The submission did not specify the controls applicable to your firm's suppliers. This would include any contract design, service or contract manufacturers for the combination product under review. Please provide a description of your procedures for Purchasing Controls. Please explain how your firm will ensure that changes made by contractors/suppliers will not affect the final combination product.

4. The information provided by your firm has inadequately addressed the requirements of 21CFR 820.100, Corrective and Preventive Action (CAPA) System. Your firm did not provide any details or a summary of its procedure(s) for its Corrective and Preventive Action (CAPA) System. Please provide a description of your CAPA system and explain how it will ensure identification existing and potential cause of nonconforming practices and products; investigation of the cause of nonconformities, identification of actions needed to correct and prevent recurrence of nonconformance; and, verification or validation of the actions. Please explain how the CAPA system will communicate between facilities involved in the manufacturing of the combination product.

5. The information provided by your firm did not describe its production and process controls. Please provide a summary of the procedure(s) for environmental and contamination controls of the facility where the final manufacturing of the finished combination product occurs, and how such conditions could affect the combination product.
You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA

Staff,' (2003). This document may be found at
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

Please respond to the following with a submission to your NDA by Thursday, October 20, 2016.

Please confirm receipt of this email.

-Florence

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality/CDER/FDA. T: 240.402.2691

NDA 208798-Fluticasone Propionate
NDA 208799- Fluticasone Propionate/Salmeterol
TEVA

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: October 6, 2016

To: Michael J. McGraw, PharmD, MS Senior Director, Global Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R&D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (610) 786-7051	**Fax number:** (301) 796-9728
Phone number: 610) 727-6136	**Phone number:** (240) 402-3720

Subject: NDA 208798-Fluticasone Propionate and NDA 208799- Fluticasone Propionate/Salmeterol, Inhalation Powder, Information Request

Total no. of pages including cover: 3

Comments: Please confirm document receipt via email: laura.musse@fda.hhs.gov

Document to be mailed: **YES** **X- NO**

Your submissions, dated March 28 and 29, 2016 to NDA 208798 and 208799, are currently under review. We have the following requests for information:

> We are concerned that possible unblinding may have occurred due to the black strip that was printed on batch number FS2004 Fluticasone/Salmeterol 50/12.5 mcg, 60 doses. Identify and submit the names of the sites that received batch number FS2004 and the total number of subjects at these sites that received the product in all of the clinical studies.

Please provide a response to the requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by 12 noon on Tuesday, October 11, 2016. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

Review/History Clearance

Drafted by: L. Musse	Date: 10/6/16
Clearance: S. Barnes	Date: 10/6/16
Finalized: L. Musse	Date: 10/6/16
File Name: Clinical IR #2	Date: 10/6/16

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/s/

LAURA MUSSE
10/06/2016

From: Mike McGraw
To: Aisida, Bamidele (Florence)
Cc: Musse, Laura; Kinsley, Steven
Subject: RE: NDA 208798/208799 CMC Information Request
Date: Friday, September 23, 2016 5:47:07 PM
Attachments: image001.png

Dear Dr. Aisida,

I confirm receipt of your email.

We will provide our response by October 7, 2016.

Regards,
Mike

Michael J. McGraw Sr. Director, Global Regulatory Affairs, Respiratory and Oncology
Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

From: Aisida, Bamidele (Florence) [mailto:Bamidele.Aisida@fda.hhs.gov]
Sent: Friday, September 23, 2016 5:01 PM
To: Mike McGraw
Cc: Musse, Laura; Kinsley, Steven
Subject: NDA 208798/208799 CMC Information Request
Importance: High

Dear Dr. McGraw,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Friday, October 7, 2016:

(b) (4)

(b) (4) Since your discussion in P.2.4 indicates that these are critical to the performance of the drug product they should be included in Table 18. Please amend this table to include these dimensions.

Please confirm receipt of this email.

Thanks

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager
HHS | FDA | CDER
Office of Pharmaceutical Quality
Office of Program and Regulatory Operations

Bamidele.aisida@fda.hhs.gov | 240.402.2691

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208799

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Teva Pharmaceutical Industries Ltd.
c/o Teva Branded Pharmaceutical Products R&D Inc.
41 Moores Road
Frazer, PA 19355

Attention: Michael J. McGraw, PharmD, MS
Senior Director, Global Regulatory Affairs

Dear Dr. McGraw:

Please refer to your New Drug Application (NDA) dated March 29, 2016, received March 29, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for fluticasone propionate/salmeterol, inhalation power, 55, 113, and 232 mcg combined with a fixed dose of (b) (4) mcg of salmeterol.

We also refer to your amendments dated June 1, 3, and 6, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is May 27, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by January 9, 2017.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. Change the acceptance criteria for the related substances to have the same values at release and stability.

2. If the wider acceptance criteria have been used to calculate the shelf-life, recalculate the shelf life to take into account the acceptance criteria at release.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

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).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Pulmonary, Allergy, and Rheumatology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, contact Laura Musse, Regulatory Health Project Manager, at (240) 402-3720.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BADRUL A CHOWDHURY
06/23/2016

NDA 208798-Fluticasone Propionate
NDA 208799- Fluticasone Propionate/Salmeterol
TEVA

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: May 27, 2016

To: Michael J. McGraw, PharmD, MS Senior Director, Global Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R&D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (610) 786-7051	**Fax number:** (301) 796-9728
Phone number: 610) 727-6136	**Phone number:** (240) 402-3720

Subject: NDA 208798-Fluticasone Propionate and NDA 208799- Fluticasone Propionate/Salmeterol, Inhalation Powder, Information Request

Total no. of pages including cover: 3

Comments: Please confirm document receipt via email: laura.musse@fda.hhs.gov

Document to be mailed: **YES** **X- NO**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 240-402-3720. Thank you.

Your submissions, dated March 28 and 29, 2016 to NDA 208798 and 208799, are currently under review. We have the following requests for information:

1. Provide the total number of investigators provided in Form 3455 for each application.

2. Provide the number of investigators listed in Form 3455 who are sponsor employees, including both full and part-time employees for each application.

If the above information is already included in the submission, clarify the location.

Please provide a response to the requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by 12 noon on Monday, June 9, 2016.Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

Review/History Clearance

Drafted by: L. Musse	Date: 5/27/16
Clearance: S. Barnes	Date: 5/27/16
Finalized: L. Musse	Date: 5/27/16
File Name: Clinical IR	Date: 5/27/16

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/s/

LAURA MUSSE
05/26/2016

From: Steven Kinsley
To: Mike.McGraw@tevapharm.com
Cc: Laura Musse, Florence Aisida
Subject: NDA 208798/208799 CMC Information Request 5-13-16
Date: May 13, 2016

Dear Dr. McGraw

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Friday, June 03, 2016:

1. Please provide a list of differences between the devices used in the proposed products and the device used in the approved product, ProAir® RespiClick.®

2. Provide a list of information that is common in Modules 2 and 3 for NDA 208798 and 2082799.

3. Amend the drug product specifications to have the same acceptance criteria for release and stability.

4. Amorphous content and surface area testing are not assessed for the fluticasone or salmeterol xinafoate drug substances on release or during stability testing. Although justification for the omission of this testing is provided under 3.2.P.2, several issues should be clarified:

    a. Indicate the time points at which the amorphous content and surface area testing were carried out on the reported drug substance batches (3.2.P.2, Table 3 and Table 7).

    b. Provide data (*e.g.*, stability data) demonstrating that the amorphous content and surface area of the drug substance remain constant over the proposed retest period of the drug substances.

    c. The amorphous content observed for the fluticasone drug substance is relatively wide (3.2.P.2, Table 3, (b) (4) %). Explain why this level of amorphous content variability is not expected to impact drug product performance

If you have any questions, contact Florence Aisida. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,

Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA
240-402-2773

Steven Kinsley -A

Digitally signed by Steven Kinsley -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Steven Kinsley -A, 0.9.2342.19200300.100.1.1=2001720189
Date: 2016.05.20 08:50:52 -04'00'

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208799

PROPRIETARY NAME ACKNOWLEDGEMENT

Teva Pharmaceutical Industries Ltd.
c/o Teva Branded Pharmaceutical Products R&D, Inc.
41 Moores Road
Frazer, PA 19355

ATTENTION: Michael J. McGraw, PharmD, MS
Senior Director, Global Regulatory Affairs

Dear Dr. McGraw:

Please refer to your New Drug Application (NDA) dated and received March 29, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder, 55/14 mcg, 113/14 mcg and 232/14 mcg.

We acknowledge receipt of your correspondence, dated and received March 29, 2016, requesting a review of your proposed proprietary name, AirDuo RespiClick.

If the application is filed, the user fee goal date will be June 27, 2016.

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 Laura Musse, Regulatory Project Manager, in the Office of New Drugs at (240) 402-3720.

Sincerely,

{See appended electronic signature page}

Michael Sinks, PharmD
Safety Regulatory Project Manager
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/

MICHAEL A SINKS
04/15/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208799

NDA ACKNOWLEDGMENT

Teva Pharmaceutical Industries Ltd.
c/o Teva Branded Pharmaceutical Products R&D Inc.
41 Moores Road
Frazer, PA 19355

Attention: Michael J. McGraw, PharmD, MS
Senior Director, Global Regulatory Affairs

Dear Dr. McGraw:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Fluticasone Propionate/Salmeterol Inhalation Powder

Date of Application: March 29, 2016

Date of Receipt: March 29, 2016

Our Reference Number: NDA 208799

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 28, 2016, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have any questions, call me at (240) 402-3720.

Sincerely,

{See appended electronic signature page}

Laura Musse, R.N., M.S., C.R.N.P.
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
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/

PHUONG N TON
04/11/2016
Signed for Laura Musse

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108838
IND 072240

MEETING MINUTES

Teva Branded Pharmaceutical Products R&D, Inc.
74 NW 176 Street
Miami, FL 33169

Attention: Sandra Anderson, M.J., RAC
Associate Director, Regulatory Affairs

Dear Ms. Anderson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Propionate Inhalation Powder and Fluticasone Propionate/Salmeterol Xinafoate Inhalation Powder.

We also refer to the telecon between representatives of your firm and the FDA on November 16, 2015. The purpose of the meeting was to discuss the submission of two 505(b)(2) NDAs for the treatment of asthma in patients aged 12 years and older.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Nina Ton, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	November 16, 2015; 12:00 – 1:00 PM EST
Meeting Location:	Teleconference
Application Number:	IND 108838 and 072240
Product Name:	Fluticasone Propionate Inhalation Powder and Fluticasone Propionate/Salmeterol Xinafoate Inhalation Powder
Indication:	Asthma
Sponsor Name:	Teva Branded Pharmaceutical Products R&D, Inc.
Meeting Chair:	Badrul Chowdhury, MD, PhD
Meeting Recorder:	Nina Ton, PharmD

FDA ATTENDEES

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Lydia Gilbert-McClain, MD, Deputy Director, DPARP
Banu Karimi-Shah, MD, Clinical Team Leader, DPARP
Freda Cooner, PhD, Biostatistics Team Leader, Division of Biometrics II, Office of Biostatistics (OB)
Jade (Yu) Wang, PhD, Biostatistics Reviewer, Division of Biometrics II, OB
Julia Pinto, PhD, Branch Chief, Division of New Drug Products II Branch IV, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Craig Bertha, PhD, CMC Lead, Division of New Drug Products II Branch IV, ONDP, OPQ
Nichelle Rashid, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology
Nina Ton, PharmD, Senior Regulatory Project Manager, DPARP

SPONSOR ATTENDEES

Cynthia F. Caracta, MD, FCCP, Sr. Director, Clinical Research, Global Respiratory R&D
Courtney Nugent, MS, Associate Director, Clinical Pharmacology
Mukul Dalvi, PhD, Sr. Director, Global Respiratory product Development
Seah Kee Tee, PhD, MRPharmS, MBA, Associate director, Global Respiratory Product Development
Yu Ru, MBA, MS, PMP, Project Champion, Respiratory Project Management
Stephanie Dunbar, PhD, Sr. Director, Head of Global Statistics
Gloria Yiu, MS, Principal Statistician, Global Biostatistics

Norma Leyva., PhD, Sr. Principal Statistician, Global Nonclinical Statistics
Evelyn Cheng, MBA, Sr. Manager, Global Regulatory Affairs
Sandra Anderson, MJ, RAC, Associate Director, Regulatory Affairs
Herminia A. Taveras, PhD, MPH, Dedicated Consultant via KPS, Clinical Leader
Susan Franks, MS, Sr. Vice President, Global Regulatory Affairs – Brands
Anat Sakov, PhD, Director, Statistics Head of Respiratory and Biosimilars

1. BACKGROUND

Teva submitted a meeting request dated September 24, 2015, to the Division of Pulmonary, Allergy, and Rheumatology Products. The purpose of the meeting is to discuss the submission of two 505(b)(2) NDAs for the treatment of asthma in patients aged 12 years and older. The Division provided preliminary comments to the Sponsor's questions in the briefing package via electronic correspondence dated November 12, 2015. Sandra Anderson, Teva's Associate Director, Regulatory Affairs, communicated to the Division via email dated November 13, 2015, that Teva requested to change the meeting format from a face-to-face to a teleconference and focus the meeting discussion on Questions 2, 5, 6, 7, and 13. Teva also provided written responses to the FDA's preliminary comments which are incorporated under the corresponding FDA response. The Sponsor's questions and responses are in *italics*, FDA's responses are in normal font, and the meeting discussion is in **bold**.

2. DISCUSSION

Question 1
Does the Agency agree with the proposed plan for the submission of stability data of the registration batches for the Fp MDPI and FS MDPI NDAs?

FDA Response
Yes, we agree with your proposed plan for the stability data to support the NDA. However, applications are expected to be complete at the time of submission, and we cannot commit to reviewing stability data that you submit in amendments during the review period. The expiration dating granted will be based on the data reviewed.

Meeting Discussion
This question was not discussed.

Question 2
Does the Agency agree with Teva's proposal for the label claim metered dose for both Fp MDPI and FS MDPI drug products?

FDA Response
Your approaches for estimating the metered doses (label claims) are reasonable; however, for the mid- and high-dose strengths with fluticasone propionate (Fp), we recommend that you make an effort to obtain data with three significant figures, so that the ones digit of the label claim for Fp

is defined. We recommend that you also specifically address (with characterization data) the proportionality across doses both in terms of the emitted dose and the aerodynamic particle size distributions for each drug substance.

Teva Response
Teva seeks clarification from the Agency regarding the comment "to obtain data with three significant figures, so that the ones digit of the label claim for Fp is defined" for mid- and high-dose strengths with fluticasone propionate. The mass and bulk density has been measured to the capabilities of the analytical balance (5 significant figures) and the (b) (4) *(3 significant figures). These data have been used as such in the calculation of the metered dose and the calculated metered doses have been averaged and rounded to three significant figures as presented. Does the Agency agree with the proposed metered dose label claims for the mid and high strength products?*

Teva will address the proportionality across doses both in terms of the emitted dose and the aerodynamic particle size distributions for each drug substance in the NDA.

Meeting Discussion
Teva asked to clarify FDA's comment regarding the metered dose. FDA noted that Table 4 in the briefing package shows values for some of the parameters having two significant figures (e.g., bulk density, measured metered mass) even though the metered dose for the middle and higher fluticasone propionate dose products would require 3. FDA advised the Sponsor to calculate the dose the same way as Teva's approved albuterol and without rounding off.

Question 3
Are the proposed ICH stability programs and testing schemes for the change in the iteration of the device from NB7/3 to NB8 acceptable to the Agency?

FDA Response
Refer to the response to Question 6 below. However, we have the following comments for your consideration.

Storage of the NB8 inhalers in the upright orientation only is acceptable assuming that there are no storage orientation effects on the collected data for the NB7/3 version that is to be approved earlier.

To expedite the review and approval of the NB8 variant, it would be helpful if you would provide comparative plotted stability data (parameter-by-parameter) for the NB7/3 (60 actuations) versus the variant NB8 drug products (60 and 28 actuations).

With regard to Table 11, we agree with the parameters that you plan to test; however, if there are stability differences noted (see above) between the approved NB7/3 and the variant NB8 drug product, the limited stability test points (missing 3, 9, and 18 months for test plan B in Table 13),

is your risk and may limit the expiration dating period to something less than what is eventually approved for the NB7/3 drug product.

The testing regime in Table 12 is acceptable; however, you could simplify this for dose content uniformity testing to just test 10 of each type of inhaler at both the beginning and end of inhaler life actuations.

Teva Response
Teva acknowledges the Agency's acceptance of the proposed stability program, test parameters, testing regimes, and the associated risks. Teva will provide comparative plotted stability data for the relevant parameters to facilitate review.

Meeting Discussion
This question was not discussed.

Question 4
Are the proposed in-use stability programs and testing schemes, for the change in the iteration of the device from NB7/3 to NB8, acceptable to the Agency?

FDA Response
Refer to the response to Question 6 below. However, we have the following comments for your consideration.

Assuming that no storage orientation effects are found with the approved NB7/3 drug product, and the planned in-use period is 1 month (we recommend studying a period twice as long as the intended in-use period), the in-use stability plan proposed in Table 14 is generally acceptable. However, we recommend including the release data for the particular batches of NB8 drug product in the in-use study, a time-zero test point when product is unwrapped, and an additional test point (e.g., 6 weeks), the latter in the event that there are stability data differences noted between the proposed 1st and the 2nd month test points (a 1 month in-use period could not be granted if there was not some indication that the product maintains quality for some time afterwards).

With regard to the in-use test parameters in Table 12, we generally recommend that in-use stability testing includes examination of all stability parameters. Thus, it is your risk if you leave out parameters that may be found to change in the absence of the protective packaging for the NB7/3 drug product in the original application. If such changes in stability due to the absence of the protective packaging are found in the data in the original application with the NB7/3 drug product version, and these parameters are not included in the in-use stability studies for the variant NB8 drug product, it would not be possible to assess the in-use period or approve the variant drug product.

It would expedite the review and approval of the NB8 variant if you would provide comparative in-use stability data (parameter-by-parameter) for the NB7/3 versus the variant NB8 drug products.

Teva Response
Teva acknowledges the Agency's acceptance of the proposed in-use stability plan and comments, including the addition of in-use stability from time-zero test point when the product is unwrapped, and an additional test point of 6-week to the in-use stability program.

Meeting Discussion
This question was not discussed

Question 5
Does the Agency agree with the proposed drug product characterization program for the Fp MDPI and FS MDPI trade (60 actuations) and sample products (28 actuations) with the NB8 device iteration?

FDA Response
Refer to the response to Question 6 below. However, we have the following comments for your consideration.

In general, your proposed drug product characterization program is acceptable. However, if dose buildup and flow resistance characterization study results indicate differences between the NB7/3 and NB8 product versions (60 actuations each), we recommend to also include studies characterizing the profile of doses near device exhaustion and the pertinent cleaning instructions, if applicable, for the NB8 variant version.

Also, as there are compositional changes to the device, we recommend that you perform the dropping study for the NB8 variant.

In addition, it would expedite the review and approval of the NB8 variant if you would provide comparative drug product characterization (study-by-study) for the (approved) NB7/3 versus the variant NB8 drug products.

Teva Response
Teva acknowledges the Agency's acceptance of the proposed drug product characterization program and comments. The changes from the NB7/3 to NB8 variant involve changes to the (b) (4) *that are not directly subjected to external mechanical stress. However, Teva will conduct a dropping study for the NB8 variant and proposes to conduct this study on only one batch instead of three batches for both the low- and high strengths of the 60-actuation trade product. Teva will provide comparative characterization data for the relevant studies to facilitate review.*

Meeting Discussion
FDA commented that if Teva has information supporting their statement that the changes to the (b) (4) **are not to parts that have mechanical stress, and as such, a dropping study is not necessary; the information and rationale can be covered in their comparability protocol portion of the NDA.**

Question 6

Does the Agency agree with the proposed evaluation for demonstrating equivalence between NB7/3 and NB8 device iterations, for the Fp MDPI and FS MDPI finished products, and the proposed submission category?

FDA Response

We do not entirely agree. See our responses to your questions above. (b) (4) (b) (4) (b) (4) With regard to the submission category, although the proposal you present is relatively comprehensive and may be appropriate, it is not possible to agree now not having reviewed the data that will be in the original application for the drug product that you used in the phase 3 clinical studies. We recommend that you include your complete proposal within a comparability protocol in the original application.

Teva Response

Teva acknowledges the Agency's comments on the submission category and will provide comparability protocols for the proposed changes in the NDA. Teva seeks clarification whether the Agency accepts (b) (4) *change and device variant change with the filing of comparability protocols in the NDA.*

In addition, Teva would like to seek confirmation from the Agency that the proposed study design for filling on low- and high-dose strength products only, as stated in Table 22, is acceptable. Teva would also like to seek confirmation from the Agency on the acceptance of the proposed study design and data package for NB8 as stated in Table 23.

Meeting Discussion

Teva inquired whether FDA will accept a (b) (4) **change and device variant change.** (b) (4) (b) (4)

Question 7

Is the proposed manufacturing strategy for the sample products (28 actuations) of Fp MDPI and FS MDPI acceptable to the Agency?

FDA Response
See our responses above.

Teva Response
Teva would like to confirm that the Agency is referring only to the response to Question 6 above regarding the need for a comparability protocol. Teva seeks confirmation that the proposed manufacturing strategy regarding the sample products is satisfactory.

Meeting Discussion
FDA confirmed that the proposed manufacturing strategy regarding the sample products is reasonable but this too should be formally submitted as a comparability protocol that can be approved with the application in advance of submitting the supplement for this change.

Question 8
Does the Agency agree to Teva's proposal for the qualification of alternate commercial manufacturing sites for Fp MDPI and FS MDPI products?

FDA Response
Your proposal appears reasonable, but will depend on the approval first, of the supplement for the new device variant (NB8). We recommend that you include this new site addition as a comparability protocol in the application that can be considered once the data for your NB7/3 based drug product is fully evaluated.

Teva Response
Teva acknowledges the Agency's comments, and will submit a comparability protocol in the application.

Meeting Discussion
This question was not discussed.

Question 9
In 2012, the FDA released ADVAIR and other products containing LABAs from the class REMS for LABAs. The requirement for a REMS for all LABAs was released since the REMS assessments results demonstrated that information regarding LABA safety and asthma-related death has been widely distributed to physicians with demonstrated uptake of the information into clinical practice.

A Medication Guide has been required to communicate the potential risks of LABAs (eg, salmeterol). ADVAIR DISKUS (the Reference Listed Drug [RLD] for the FS MDPI NDA) carries an asthma-related safety warning (Boxed Warning) and a Medication Guide, but no formal REMS Timetable for Submission of Assessments, communication plan to health care providers, nor Elements to Ensure Safe Use (ETASU) is currently required by the Agency.

Therefore, Teva is anticipating that a formal REMS would not be required for the FS MDPI combination product. To that end, if FS MDPI has an acceptable safety profile or an improved therapeutic index when compared to other recently approved combination LABA products, Teva proposes to communicate asthma-related risks via product labeling and routine pharmacovigilance as described herein. Does the Agency agree with this approach?

FDA Response
Based on the information currently available, we do not believe that a REMS will be necessary. In 2012, FDA released Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder), Advair HFA (fluticasone propionate and salmeterol xinafoate) Inhalation Aerosol, and Serevent Diskus (salmeterol xinafoate inhalation powder) from the requirement for a REMS (see August 9, 2012, letter, available at Drugs@FDA). Maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1.

Meeting Discussion
This question was not discussed.

Question 10
Does the FDA agree that the 4-month safety update can be waived for this submission, as there will be no studies ongoing or patients exposed to Fp MDPI or to FS MDPI between the proposed data cutoff date for the submission (27 October 2015) and the proposed data cutoff date for the 4-month safety update (15 March 2016)?

FDA Response
As all studies will be completed at the data cutoff date for submission, and there will be no new data, submit a statement that you have no update to provide for the 4-month safety update.

Meeting Discussion
This question was not discussed.

Question 11
Teva will provide the following site level data in the NDAs in accordance with the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning. This data will be provided following the Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning (version 1.2). The proposed study data to be included in the NDAs, as well as details will be provided in the briefing document. Does the Division have any additional advice or requirements beyond that in the Guidance documents?

FDA Response
We recommend that you include the following:

1. A data column for days on treatment in the AE data set

2. The total number of patients with major protocol deviations sorted by study and treatment group
3. A list of major protocol deviations in each study
4. The number of investigators who are Sponsor employees (include both full and part-time)
5. Define the patients in the race subgroup of "black" including study sites for each subject

Teva Response
Teva appreciates the Agency's guidance and acceptance of our proposal to provide the site level data in the NDAs in accordance with the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning. Teva also agrees to provide items 1 through 5, inclusive as recommended.

Meeting Discussion
This question was not discussed.

Question 12
In accordance with 21 CFR 314.50 and Industry standard for reporting, Teva will provide case report forms (CRFs) for any patient who

- *experienced serious adverse events during a clinical study*
- *discontinued from a clinical study due to adverse events, whether believed to be drug-related or not, including subjects receiving placebo*
- *died during a clinical study*

All CRFs will be provided as Portable Document Format (PDF) files, organized by study, site, and patient.

In addition, patient narratives will be provided for any patient who falls into any of the above-listed categories. Does the Division agree?

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

Question 13
The planned submission format and datasets to be included in the NDAs will follow the Study Data Specifications guideline published by FDA in July 2012 (version 2.0). The proposed datasets to be included in the NDAs, as well as details regarding format are detailed in the briefing document. Does the Division agree or have any advice on the plan?

FDA Response
As you stated in section 10.4.1.2 of the briefing document, you will submit both raw and derived datasets. However, you only stated that the data will follow CDISC SDTM standards; we request you also submit derived analysis datasets and make sure they follow CDISC ADaM standards.

Additional comment
We have further comments regarding the statistical analysis plan for phase 3 Studies FSS-AS-301 and FSS-AS-30017 submitted on September 24, 2015:

1. For the pulmonary function tests, continue collecting efficacy assessments from discontinued subjects. We do not think a *de jure* estimand is meaningful in your setting from a regulatory perspective. If you do not intend to retrieve dropouts, we suggest you propose methods that incorporate discontinuation as treatment failure in the primary analysis as it estimates a utility-based estimand.
2. For the analysis of standardized baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ at week 12 data, document clearly if a patient was selected to this subset at the beginning of the study in the derived datasets so any early discontinuation in the serial spirometry subset could be identified for sensitivity analysis of missing data.

Teva Response
Teva acknowledges the Agency's comments, and will submit both raw and derived analysis datasets, as well as, follow both CDISC SDTM standards for the raw datasets and CDISC ADaM standards for the derived analysis datasets.

With regard to additional comment 1:

In communications with the FDA on March 24, 2015 regarding the Phase 3 studies (FSS-AS-301 and FSS-AS-30017), Teva wrote that both studies were near completion, and retrieved dropout data have not been collected (as per protocol). Teva's proposal to analyze the landmark endpoint using a modified baseline observation carried forward approach was proposed to and accepted by the Agency via email correspondence on March 27, 2015. Additional sensitivity analyses (e.g. tipping point) are described in the SAP.

With regard to additional comment 2:

Section 3.5 of the SAP details which patients will be selected for this subset. In the subject level analysis dataset (ADSL), all serial spirometry patients can be identified by serial spirometry subset flag (SSSFL). This flag can also be found in other analysis datasets as well. Discontinued patients from the spirometry subset will be listed.

Meeting Discussion
FDA acknowledged Teva's comments and indicated that this proposal is acceptable.

Question 14
Should there be a need for the Sponsor to request a meeting with the Agency regarding the pivotal Phase 3 data after the unblinding of the Phase 3 Studies FSS-AS-301 and FSS-AS-30017,

Teva proposes to conduct a second Type B meeting with the Agency, or a Type C meeting (if only a written response to questions is needed) in the first quarter of 2016. Does the Agency agree with this proposal?

FDA Response
You may submit a Type C meeting request if further guidance is needed.

Meeting Discussion
This question was not discussed.

Question 15
Reference is made to the FDA's EOP2 multidisciplinary meeting minutes dated 17 March 2014 for INDs 108838 and 72240. Specifically, the FDA's response (see Question 2, Section 11.4) indicating that Teva could rely on the ProAir® RespiClick (albuterol sulfate) Inhalation Powder human factors studies to support Fp MDPI and FS MDPI applications, provided that the data submitted in the ProAir RespiClick (NDA 205636) are adequate. NDA 205636 was approved by the FDA on 31 March 2015.

Teva has conducted a second Human Factors Validation Study and intends to submit the report to the FDA under separate cover for NDA 205636.

To that end, Teva would like to rely on this second human factors study conducted to support "label comprehension" for the upcoming Fp MDPI and FS MDPI NDA submissions. Teva has performed human factors testing in keeping with industry trends and other Teva respiratory product development programs. This program for NDA 205636 followed the risk-based approach recommended by the FDA in the 2011 draft guidance, "Applying Human Factors and Usability Engineering to Optimize Device Design." Teva believes that this testing meets the requirements needed to support the Fp MDPI and FS MDPI applications with no additional assessment required (eg, "label comprehension" study).

Does the Agency agree that the described RespiClick Human Factors Validation study is sufficient to support the upcoming Fp MDPI and FS MDPI NDA submissions, without the need to conduct a separate label comprehension study, provided the data submitted in the ProAir RespiClick NDA 205636 are adequate?

FDA Response
Provided your data is adequate, your approach seems reasonable.

Additional comment
We note the inclusion of AQLQ as a secondary endpoint for the phase 3 studies. As AQLQ is a measure that is clinically meaningful to providers and patients, it will be included in Section14 of the package insert irrespective of the results.

We refer you to the non-clinical comments previously conveyed on March 17, 2014.

Meeting Discussion
This question was not discussed.

3. ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*

4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

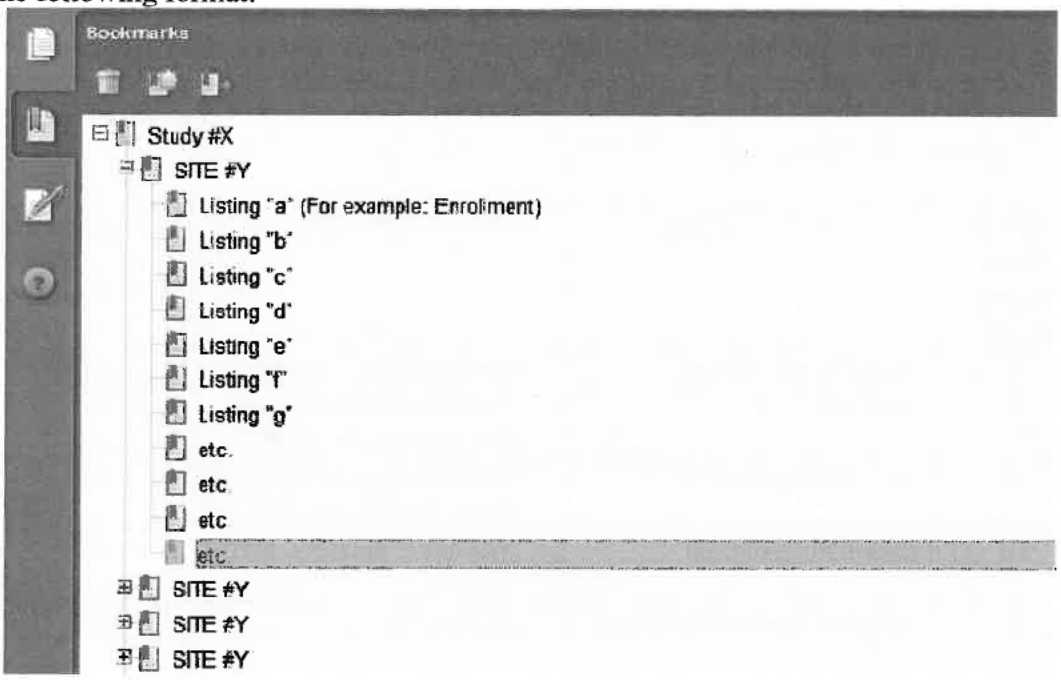
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation

h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

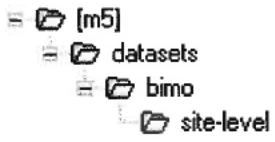
Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4. ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5. ACTION ITEMS

There were no action items.

6. ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PHUONG N TON
12/04/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108838
IND 072240

MEETING MINUTES

Teva Branded Pharmaceutical Products R&D, Inc.
74 NW 176 Street
Miami, FL 33169

Attention: Evelyn Cheng
Senior Manager, Regulatory Affairs

Dear Ms. Cheng:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Propionate Inhalation Powder and Fluticasone Propionate/Salmeterol Xinafoate Inhalation Powder.

We also refer to the telecon between representatives of your firm and the FDA on February 18, 2014. The purpose of the meeting was to discuss the proposed development program to support the filing of the two NDAs.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-796-1648.

Sincerely,

{See appended electronic signature page}

Nina Ton, Pharm.D.
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	February 18, 2014; 2:30 – 3:30 PM ET
Application Number:	IND 108838 and IND 072240
Product Name:	Fluticasone Propionate Inhalation Powder and Fluticasone Propionate/Salmeterol Xinafoate Inhalation Powder
Indication:	Asthma
Sponsor Name:	Teva Branded Pharmaceutical Products R&D, Inc.
Meeting Chair:	Badrul Chowdhury, M.D., Ph.D.
Meeting Recorder:	Nina Ton, Pharm.D.

FDA ATTENDEES

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Lydia Gilbert-McClain, M.D., Deputy Director, DPARP
Banu Karimi-Shah, M.D., Clinical Team Leader, DPARP
Miya Paterniti, M.D. Clinical Reviewer, DPARP
Satjit Brar, Ph.D., Pharm.D., Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Sheetal Agarwal, Ph.D., Clinical Pharmacology Reviewer, DCPII, OCP
Ruthanna Davi, Ph.D., Biostatistics Reviewer, Division of Biometrics II, Office of Biostatistics
Craig Bertha, Ph.D., Acting Team Leader, Division of New Drug Quality Assessment III, Office of New Drug Quality Assessment (ONDQA)
Edwin Jao, Ph.D., CMC Reviewer, Division of New Drug Quality Assessment III, ONDQA
Nina Ton, Pharm.D., Regulatory Project Manager, DPARP

SPONSOR ATTENDEES

Tushar Shah, M.D., Senior Vice President, Global Respiratory Research and Development (R&D)
Christopher O'Brien, M.D., Ph.D., Vice President, Global Respiratory R&D, Clinical Research
Jonathan Steinfeld, M.D., Associate Director, Global Respiratory R&D, Clinical Research
Youyi Shu, Ph.D., Senior Director, Global Biostatistics, Global R&D
Yu Ru, M.S., M.B.A., Director, Project Management, Global Respiratory R&D Project Leader
Mukul Dalvi, Ph.D., Senior Director, Global Respiratory Product Development
Susan Franks, M.S., Vice President, Global Regulatory Affairs, R&D
Steve Viti, Ph.D., M.B.A., Senior Director, Global Regulatory Affairs, Respiratory

Molly E. Shea, Ph.D., Director, Global Regulatory Affairs, Respiratory
Evelyn Cheng, Senior Manager, Global Regulatory Affairs, Respiratory

1. BACKGROUND

Teva submitted an End of Phase 2 meeting request dated December 5, 2013, to the Division of Pulmonary, Allergy, and Rheumatology Products, to discuss the proposed development program to support the filing of the two NDAs. Upon review of the meeting package, the Division provided preliminary comments to GSK's questions via electronic correspondence on February 14, 2014. Evelyn Cheng, Teva's Senior Manager, Regulatory Affairs, communicated to the Division via email dated February 15, 2014 that Teva requested to change the meeting format from a face-to-face meeting to a teleconference. In addition, Teva requested to focus the meeting discussion to Questions 6, 8, 9, and 12, and also provided comments to FDA's responses for these questions. Teva sent one additional question via email dated February 25, 2014 and FDA's response to this question is included in the Post-Meeting Discussion section. Teva's questions and comments to Questions 6, 8, 9, and 12 are in *italics*, FDA's responses are in normal font, and the meeting discussion is in **bold**.

2. DISCUSSION

Question 1
Teva has evaluated the (b) (4) device's dose-counter robustness as part of the ABS program and believes this is relevant and sufficient for the Fp (b) (4) and FS (b) (4) programs. Teva will summarize these data in the Fp (b) (4) and FS (b) (4) submissions. It should be noted that ABS will be submitted for a NDA approximately 1 year before Fp (b) (4) and FS (b) (4) and the devices' dose-counters are similar across all (b) (4) programs.

Does the Agency agree with this approach?

FDA Response
Yes, we agree with your approach as long as the dose counter and device robustness results are found acceptable upon review for the ABS program.

Meeting Discussion
This question was not discussed.

Question 2
Teva has conducted a robust human factors assessment to support the ABS Program and intends to rely on the ABS human factors studies to support the Fp (b) (4) and FS (b) (4) applications. ABS will be submitted for a NDA before Fp (b) (4) and FS (b) (4) and the instructions for use, aside from the number of doses, will be similar across all (b) (4) programs.

Does the Agency agree with this approach?

FDA Response
Provided that the data submitted in the Albuterol (b) (4) program are adequate, your approach is acceptable.

Meeting Discussion
This question was not discussed.

Question 3
Is the proposed pharmacokinetic plan for Fp (b) (4) and FS (b) (4) in patients 12 years of age and older adequate for the NDA submission?

FDA Response
You have proposed to conduct PK studies with your final-to-be-marketed Fp and FS products in adults (18 and older) and in children 4-11 years. In order to be able to extrapolate safety information such as growth effects and HPA axis effects in children aged 4-18 years from reference products to your products, we recommend that you include children aged 12-18 years in your PK studies so that you can establish that systemic exposure of fluticasone and salmeterol in children 4-18 years is lower or similar with your products as compared to the reference products.

Meeting Discussion
This question was not discussed.

Question 4
Is the proposed pharmacokinetic plan for Fp (b) (4) and FS (b) (4) in patients 4 to 11 years of age adequate for a subsequent pediatric supplemental New Drug Application (sNDA) submission?

FDA Response
Your plan seems reasonable; however, we may have comments during the review of your initial Pediatric Study Plan (iPSP) when more PK data is available with your final-to-be-marketed formulations.

Meeting Discussion
This question was not discussed.

Question 5
Teva will provide pharmacokinetic data for Fp (b) (4) and FS (b) (4) in patients 4 to 11 years of age and 18 years of age and older.

Does the Agency agree that these data will provide an adequate pharmacokinetic profile in order to include an indication for patients 12 to 17 years of age in the NDA submission?

FDA Response
See response to Question 3.

Meeting Discussion
This question was not discussed.

Question 6
Teva proposes to study fluticasone propionate doses of 50 mcg, 100 mcg, and 200 mcg both alone as Fp (b) (4) and combined with salmeterol 12.5 mcg in FS (b) (4) The dose-finding studies in Phase 2 demonstrated that these strengths, representing about half the delivered dose corresponding to FLOVENT DISKUS and ADVAIR DISKUS, provide comparable clinical efficacy and safety with lower systemic exposure.

Does the Agency agree with the proposed doses to carry forward into the Phase 3 studies?

FDA Response
Your approach appears reasonable. Due to LABA safety concerns, it is uncertain whether the combination of the lowest dose of Fp (50 mcg) with a LABA will be feasible. See response to Question 9 for further explanation.

Teva's Comment
Teva appreciates the Agency's response. For a comment on the approvability of the Fp 50 mcg dose combined with a LABA please see the Teva comment to FDA's response to Question 9.

Meeting Discussion
See meeting discussion for Question 9.

Question 7
Teva proposes to study the salmeterol xinafoate dose of 12.5 mcg combined with fluticasone propionate in FS (b) (4) The dose-finding study in Phase 2 demonstrated that this strength, representing about one-quarter the delivered dose corresponding to salmeterol in ADVAIR DISKUS, provides comparable clinical efficacy and safety with lower systemic exposure.

Does the Agency agree with the proposed dose to carry forward into the Phase 3 studies?

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

Question 8
Teva proposes to use the two 12-week safety and efficacy Phase 2 studies to serve as the replicates of the planned Fp (b) (4) and FS (b) (4) versus placebo Phase 3 safety and

efficacy studies. The FpS-AS-201 study will support the Fp (b) (4) *50 mcg and 100 mcg doses and the FpS-AS-202 study will support the Fp* (b) (4) *200 mcg dose.*

Does the Agency agree that the Phase 2 studies can serve as replicate studies for the Phase 3 program?

FDA Response

The approach of using Phase 2 studies as replicate evidence of efficacy for the Fp (b) (4) is acceptable.

Teva's Comment

In light of the fact that the Phase 2 study FpS-AS-202 did not demonstrate statistical significance using MMRM (but did, when calculated using LOCF) Teva would like to clarify the need for replication of evidence in two efficacy studies for 505b2 applications. There is precedence in other therapeutic areas where for 505b2 applications a single Phase 3 study (without Phase 2 efficacy data) was adequate for approval where well-known active ingredients were utilized with the same route of administration. Since replication will be established for the two lower dosages with successful completion of the phase 3 program, Teva believes that a single trial at the highest dose with supporting evidence from the phase 2 trial should be adequate for approval of the Fp 200 mcg dose and seeks FDA confirmation.

Meeting Discussion

FDA commented that if the Phase 3 studies show clear efficacy, the Phase 2 studies may be used as replicate evidence of efficacy. The statistical methods used to evaluate the Phase 2 studies would ultimately be a review issue (as described below). The larger issue in the discussion was the proposal for 3 ICS doses. FDA acknowledged Teva's goal of obtaining approval of three ICS doses. In order to do so, however, FDA commented that Teva would need to demonstrate incremental benefit of the higher doses over the lower doses, which has been difficult to do, per review of recent applications. FDA added that establishing clinical benefit of all 3 doses may be difficult and Teva may not be able to show dose separation. For this reason, FDA has recommended adding additional treatment arms in Study 301, in order to provide for a direct comparison of the proposed low- and mid-doses.

(b) (4)

(b) (4) **While FDA acknowledged that Advair has three doses, FDA clarified that Teva's combination product is not** (b) (4) **Advair, and therefore different requirements apply. While the program may not be able to be abbreviated to the degree the Sponsor had initially proposed, several modifications to the program have been deemed acceptable, given the well-known safety profile of the proposed drug product (i.e. only 6 months of safety data will be required instead of 1 year, and absence of full characterization of single ingredients). Teva noted that its product shows benefit at a lower dose than Advair. FDA noted that Teva's lower dose would be another reason to separate its product from Advair.**

Teva asked FDA if there is a recommended statistical method to use for the efficacy analyses to account for the differential dropout rates in Study 202. FDA noted that the Sponsor reported varying statistical results for the treatment effect on the primary efficacy endpoint depending upon the methods used to address missing data. FDA commented that the statistical team would need to thoroughly review the efficacy data to reach a conclusion regarding the adequacy of the demonstration of a treatment effect in this study. Assessing the impact of the missing data would be a review issue. FDA advised the Sponsor that the Agency does not recommend nor endorse a single statistical method for missing data. However, FDA advised Teva that they should provide all pre-specified analyses (primary and sensitivity) as well as at the Sponsor's discretion, other sensitivity analyses that the Sponsor feels are appropriate. FDA indicated that the Sponsor should provide justification for the analysis methods used including description of the estimand associated with each analysis. FDA advised Teva that a baseline-observation-carried-forward approach to missing data may be a useful sensitivity analysis for these data. In addition, FDA recommended that for future studies, Teva should continue to collect efficacy data even if patients discontinue treatment to allow for an assessment of the treatment effect in the entire study population regardless of patients' adherence to treatment.

Question 9

Teva proposes Phase 3 studies with Fp (b) (4) FS (b) (4) and placebo (b) (4) treatment groups in order to demonstrate the efficacy and safety of Fp (b) (4) compared to placebo, and FS (b) (4) compared to placebo. In these studies, the efficacy of FS (b) (4) will also be compared to Fp (b) (4) to demonstrate the added benefit of the salmeterol component.

Does the Agency agree that the proposed program will satisfy the requirements for registering both the monocomponent ICS and the ICS/LABA combination?

FDA Response

Based on the design of your proposed Phase 3 studies, we note that you do not have replication of any of your combination (FpS) treatment arms. Typically, we require replication of efficacy over placebo of the lowest dose strength, with demonstration of an incremental benefit of the higher doses over the lower doses. Therefore, we recommend adding Fp 100 mcg and FpS 100/12.5 mcg treatment arms to Study 301. This will allow for replication of the FpS 100/12.5 mcg, as well as provide a direct comparison of the Fp 50 and 100 mcg doses. Should you be able to establish efficacy of all three steroid doses, conceptually, approval of the lowest dose strength combination (FpS 50/12.5) may not be feasible, given the concerns with LABA safety and combination of LABA with low-dose ICS.

We acknowledge that this advice constitutes a change in our previous position; however, such change is often necessary based on the evolution of drug development and acquisition of new efficacy and safety information.

Teva's Comment

Teva requests clarification on the need for replication at a combination dose that an ICS and LABA is superior to ICS alone when it was not required of the innovator product Advair or like products developed for the United States (Symbicort pMDI) and the overwhelming evidence supports the superiority of ICS and LABA combination as compared to ICS alone. It is not clear why a combination dose needs replication versus replication in two separate studies that the combination of FpS MDPI is superior to Fp MDPI as is planned and was done in the Advair Diskus and Symbicort development programs. With regards to replication of the Fp dose, Teva conducted a dose ranging study (FpS-AS-201 study) where incremental improvements on FEV_1 were observed between 12.5, 25, 50 and 100 mcg twice daily of Fp MDPI. Based on these results, Teva proposes 50 mc twice daily as the lowest dose and does not see the need to include the Fp 100 mcg mono arm as replication of dose in the planned phase 3 clinical trial.

Teva also seeks clarification about FDA's comment that the 50/12.5 mcg Fp/salmeterol dose may not be approvable due to concerns about LABA safety. In vitro results demonstrate that Fp and FS MDPI have (b) (4) *relative to the corresponding Diskus products (Flovent and Advair). The phase 2 results support that similar efficacy can be achieved with Fp and FS MDPI versus higher doses of the Diskus products with similar to lower systemic exposure. Based on the phase 2 results, Teva's 50 mcg product is considered comparable to the innovator 100 mcg dose. Additionally, since the salmeterol dose is reduced four-fold relative to the dose in Advair Diskus, the ratio of Fp to salmeterol for FS 50/12.5 MDPI is four-fold whereas it is only two-fold for the lowest approved dose of Advair Diskus (100/50). Therefore, the FS 50/12.5 mcg dose provides a much higher ICS to LABA ratio than Advair Diskus and should provide a greater margin of safety and should be approvable based on completion of the successful phase 3 program.*

Meeting Discussion

FDA reiterated our recommendation of adding Fp 100 mcg and FpS 100/12.5 mcg treatment arms to Study 301 to show the clinical benefit of adding a LABA to Fp, and also to provide a direct comparison between Fp 50 mcg and 100 mcg doses. Teva proposed adding a low ICS dose to Study 30017 as this would provide a means to show separation between all dose strengths. FDA commented that adding a low ICS dose to Study 30017 may not be the best approach, as the population studied in the Study 30017 may not be appropriate for a low dose ICS.

FDA raised concern with the low dose ICS/LABA combination, as asthma guidelines recommend that LABA should be started with mid-dose ICS. FDA added that whether Fp 50 mcg dose in combination with LABA is appropriate would be determined during the review cycle. However, the 50 mcg dose may be reasonable for the pediatric population. Teva asked if the proposed Fp 25 mcg, Fp 50 mcg, and FpS 50/12.5 mcg would be appropriate doses for the pediatric program. FDA responded that Teva's proposal is generally acceptable and reminded the Sponsor that further comments may be provided when we formally review the initial pediatric study plan (iPSP), which is due in 60 days.

Question 10

Teva proposes two clinical studies to provide important information for prescribers on the relationship of 2 proposed FS (b) (4) strengths with currently marketed fluticasone propionate/salmeterol xinafoate combinations. The clinical endpoints, inclusion criteria, study design, and study conduct are based on the new guidance from the Agency for the development of a generic DPI containing fluticasone propionate and salmeterol xinafoate. (b) (4)

(b) (4)

Does the Agency agree that this information is appropriate for inclusion in the prescribing information?

FDA Response

No, we do not agree. (b) (4)

(b) (4)

Meeting Discussion

This question was not discussed.

Question 11

(b) (4)

(b) (4)

FDA Response

See response to Question 10.

Meeting Discussion

This question was not discussed.

Question 12

(b) (4)

FDA Response

No, we do not agree. (b) (4)

(b) (4)

(b) (4)

Teva's Comment

For the required 6 months safety data, does the Agency request that Teva study each strength or can Teva study only the mid and high strengths, of each of the two products, as they are more likely to demonstrate a safety signal than the low strengths?

Meeting Discussion

Teva stated that their preference is to conduct a separate safety study in parallel with the Phase 3 program, instead of the recommended open-label extension of the Phase 3 studies. Teva proposed to conduct a 6-month, open label, safety study with Fp and FpS using 100 mcg, 200 mcg, 100/12.5 mcg, and 200/12.5 mcg, respectively, compared to Advair, randomized 4 to 1. Each Fp and FpS treatment arm would have 100 subjects. FDA commented that a 6-month safety study with medium and high doses of the single ingredient ICS and LABA/ICS combination conducted in parallel with the Phase 3 program is acceptable; the decision to compare the Teva products against Advair is at Teva's discretion. Teva was reminded to collect devices (both those that were noted to be working properly and those that were identified as having problems) for *in vitro* testing at the end of the study.

Question 13

Does the Agency agree that the proposed overall safety evaluations for FS (b) (4) *included in the proposed Phase 3 program are sufficient to support the proposed 505(b)(2) submission and approval for FS* (b) (4)

FDA Response

No, we do not agree. See response to Question 12.

Meeting Discussion

This question was not discussed.

Question 14

Given these formulations in Teva's novel device (b) (4) *Teva believes this constitutes a new dosage form and therefore the Pediatric Research Equity Act (PREA) is applicable to Fp* (b) (4) *and FS* (b) (4)

Does the Agency agree?

FDA Response

We agree that PREA is applicable to the currently proposed (b) (4) program.

Meeting Discussion

This question was not discussed.

Question 15

Teva proposes a Phase 3 study with Fp (b) (4) FS (b) (4) and placebo (b) (4) in order to demonstrate the efficacy and safety of Fp (b) (4) compared to placebo and FS (b) (4) compared to placebo in patients 4 to 11 years of age. In this study, the efficacy of FS (b) (4) will also be compared to Fp (b) (4) to demonstrate the added benefit of the salmeterol component.

Does the Agency agree that the proposed program will satisfy the requirements for registering both the mono-component ICS and the ICS/LABA combination for use in patients (b) (4) (b) (4)

FDA Response

The proposed Phase 3 study is reasonable; however, approvability will be a review issue.

In addition, we request that you provide the following data when you submit your application for children (b) (4) 12 years of age. Since the appearance of the proposed device for the albuterol DPI looks very much like a metered dose inhaler (MDI), parents may try to use it with a spacer. Therefore, we recommend that you provide data with regard to what happens to the delivered dose if a spacer is used with the proposed device. Although we conceptually agree that no spacer should be used with a DPI, it would be helpful to have *in vitro* data to support whether a labeling warning may be needed regarding such use. Include a plan to acquire this information in your iPSP.

Further comments may be provided after review of the iPSP.

Meeting Discussion

This question was not discussed.

Question 16

In each NDA, Teva will request a waiver for Fp (b) (4) and FS (b) (4) respectively, in patients less than 4 years of age. (b) (4) (b) (4)

Does the agency agree with this approach?

FDA Response

While final decisions regarding pediatric waivers and deferrals are made once the pediatric study plans are submitted and reviewed, your proposal is reasonable. When you submit the NDA for this drug product, submit information about the minimum flow rate required to appropriately use the proposed device, along with the expected flow rates for all pediatric age groups, including the age groups for which you are seeking a waiver. To substantiate your reasoning for your request for waiver in children less than 4 years of age, either submit this data or submit a plan to obtain this data in your iPSP.

Meeting Discussion
This question was not discussed.

Question 17
In the Fp[redacted](b) (4) and FS[redacted](b) (4) NDAs, Teva will request deferrals to initiate Phase 3 in patients 4 to 11 years of age. These studies will begin after the completion of the adult Phase 3 efficacy studies.
Does the agency agree with this approach?

FDA Response
See response to Question 16.

Meeting Discussion
This question was not discussed.

Question 18
Teva intends to study the 12.5 mcg salmeterol dose in the FS[redacted](b) (4) pediatric program. Results from the adolescent and adult salmeterol dose-finding study demonstrated that the 12.5 mcg dose of salmeterol in FS[redacted](b) (4) had similar clinical efficacy as 50 mcg of salmeterol in ADVAIR DISKUS, the approved pediatric dose, but with lower systemic exposure.

Does the agency agree that 12.5 mcg of salmeterol is the optimal dose to carry forward into the FS[redacted](b) (4) pediatric program?

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

Question 19
Does the Agency agree that the change from[redacted](b) (4) equipment can be made[redacted](b) (4)

FDA Response
[redacted](b) (4) is acceptable only if the two[redacted](b) (4) machines have similar design and operation principles.[redacted](b) (4)

Meeting Discussion
This question was not discussed.

Question 20

Does the Agency agree that the change of the (b) (4) *can be made as* (b) (4) (b) (4)

FDA Response

(b) (4) is acceptable for (b) (4) change of NB7/3 only. (b) (4) changes in any formulation contact components should be submitted in a prior approval supplement. Clarify the purpose of providing Population Bioequivalence (PBE) results for device changes that do not impact formulation contact materials.

Meeting Discussion

This question was not discussed.

Question 21

Does the Agency agree that the change of device from NB7/3 to NB8 can be made as a Prior Approval supplement based on the tests, equivalence criteria and data package listed in Table 23?

FDA Response

Yes, we agree. We also recommend that you conduct PBE study on drug product performance of NB7/3 and NB8 devices at release as well as at the 6 month time point of the stability study.

Meeting Discussion

This question was not discussed.

Additional Comments

Nonclinical

- Provide structures of any impurities and degradants of the drug substance and drug product in your submission. Monitor impurities and degradation products of all active ingredients and refer to ICH Guidance [ICH Q3A(R2) and ICH Q3B(R2)] for possible qualification requirements. Impurities or degradants of active ingredients that are identified as structural alerts should be at or below acceptable qualification thresholds to support an IND or NDA as described in the ICH M7 Draft Consensus Guideline, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (Step 2 Version dated February 6, 2013).

- Provide a safety assessment of extractables and leachables with an NDA.

Chemistry, Manufacturing, and Controls (CMC)

- During the development of your oral inhalation combination drug product, provide data to demonstrate that there is pharmaceutical equivalence between the single ingredients as

delivered in the combination and the corresponding monotherapy drug products, for the duration of the clinical studies. In order to demonstrate pharmaceutical equivalence, the following requirements apply:

1) The monotherapy and combination drug products should be delivered via the same device;

2) The formulations should be quantitatively comparable (with the exception of adjustment of excipient levels to compensate for the absent drugs);

3) The monotherapy and combination drug products should provide comparable *in vitro* dose delivery and aerodynamic particle size distribution by cascade impaction (CI). Provide full Aerodynamic Particle Size Distribution (APSD) profile data by CI both graphically and in a tabular fashion on a stage-by-stage basis for the single ingredients as delivered in the combination product and each monotherapy product.

- Although demonstrating pharmaceutical equivalence is not required to support the CMC aspects of your NDA for the combination drug product, it is necessary that pharmaceutical equivalence be demonstrated during development under the IND. Demonstration of pharmaceutical equivalence is required to provide assurance that the resulting clinical/clinical pharmacology data is interpretable and appropriate to assess whether the combination drug product has substantial activity and provides greater than additive activity, or a more durable response, compared to the individual monotherapy drug products alone.

Post-Meeting Discussion

Teva sent a clarification question via email dated February 25, 2014. Teva's question and FDA's response are below.

Question

The Fp MDPI and FS MDPI combined EOP2 briefing document proposed two 12-week safety and efficacy studies (FSS-AS-301 and FSS-AS-30017) for Phase 3. As there was no long term safety study included in the proposed plan, these two studies contained 24-hour urine cortisol and safety labs before and at the end of treatment. Based on feedback before and during the EOP2 meeting, Teva agreed to add a 6 month safety study (FSS-AS-305) to the Phase 3 plan. This study will have 24-hour urine cortisol and safety labs on all patients – approximately 250 patients randomized to Fp MDPI and 250 patients randomized to FS MDPI.

With the addition of the data collected in the safety study, Teva plans to remove the 24-hour urine cortisol and safety labs from the FSS-AS-301 and FSS-AS-30017 efficacy studies. Fluticasone propionate and salmeterol xinafoate are well tolerated medications that did not demonstrate significant changes in safety laboratory studies in the development of FLOVENT and ADVAIR. Teva Fp and FS MDPI demonstrated lower systemic exposure to fluticasone propionate and salmeterol xinafoate than therapeutically comparable FLOVENT and ADVAIR and therefore would be expected to have even less effect on laboratory values than the marketed

products. In addition, data already collected from the Phase 2b studies did not demonstrate significant changes in 24-hour urine cortisol or safety labs after 12 weeks of Fp MDPI. Leaving the safety labs in the 2 efficacy studies would lead to unnecessary patient inconvenience and discomfort.

Does the Agency agree with the removal of 24-hour urine cortisol and safety labs from the 2 efficacy studies?

FDA Response
Yes, we agree.

3. PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

4. DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized

format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

5. LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests.

6. 505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that

21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

7. ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

8. ACTION ITEMS

There were no action items.

9. ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PHUONG N TON
03/17/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 72240 and 108838

MEETING MINUTES

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Evelyn Cheng
Senior Manager, Regulatory Affairs
74 NW 176th St.
Miami, FL 33169

Dear Ms. Cheng:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fluticasone Propionate Inhalation Powder (IND 108838) and Fluticasone Propionate/Salmeterol Xinafoate Inhalation Powder (IND 72240).

We also refer to your September 9, 2013 correspondence requesting a Type-B End-of-Phase 2 CMC meeting to discuss the quality package for the registration of these products and to obtain FDA feedback on the proposed quality program to support the filing of the two NDAs. The Meeting Package was received on October 18, 2013.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

{See appended electronic signature page}

Eric P. Duffy, Ph.D.
Division Director
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B, End Of Phase 2 CMC Only
Meeting Category:	IND
Meeting Date and Time:	November 18, 2013, 1:00 PM to 2:30 PM (ET)
Meeting Location:	Tele Conference
Application Number:	IND 72240 and 108838
Product Name:	Fluticasone Propionate Inhalation Powder and Fluticasone Propionate/Salmeterol Xinafoate Inhalation Powder
Indication:	Asthma
Sponsor/Applicant Name:	Teva Branded Pharmaceutical Products R&D, Inc. (Teva)
Meeting Chair:	Eric P. Duffy
Meeting Recorder:	Youbang Liu

FDA ATTENDEES

Eric P. Duffy, Division Director, Division III, ONDQA
Prasad Peri, Branch Chief, Branch VIII, ONDQA
Craig Bertha, Acting CMC Lead, ONDQA
Edwin Jao, Senior CMC Reviewer, ONDQA
Youbang Liu, Regulatory Project Manager, ONDQA
Miya Paterniti, Medical Officer, DPARP
Banu Karimi-Shah, Medical Officer, Team Lead, DPARP

TEVA ATTENDEES

Mukul Dalvi, Senior Director, Global Respiratory Product Development
Seah Kee Tee, Associate Director, Respiratory R&D, DPI Development
John Simons, Director, Pharmaceutical Development
Yu Ru, Director, Project Management, Global Respiratory R&D
Christopher O'Brien, Vice President, Respiratory R&D
Jonathan Steinfeld, Associate Director, Clinical Research
Steve Viti, Senior Director, Global Regulatory Affairs, Respiratory
Molly E. Shea, Director, Global Regulatory Affairs, Respiratory
Evelyn Cheng, Senior Manager, Global Regulatory Affairs, Respiratory

1.0 BACKGROUND

Teva Global Respiratory Research (part of Teva Branded Pharmaceutical Products R&D, Inc.) is developing Fluticasone propionate (Fp) mono-therapy and Fluticasone propionate/Salmeterol xinafoate (FS) combination therapy in Teva's proprietary (b) (4) device. Three Phase 2b dose ranging studies, covering either fluticasone or salmeterol, have been conducted. The doses selected from these studies will be further evaluated, for safety and efficacy, in the Phase 3 clinical program, for both the FP monotherapy and the FS combination therapy. This combined Phase 3 program will be initiated in Q1 2014.

The purpose of this meeting is to discuss and obtain FDA feedback on the proposed quality program to support the filing of the two NDAs.

2.0 DISCUSSION

The FDA Meeting Preliminary Comments (see Attachment-I) were sent to Teva before the meeting. Teva requested to reduce the Face-to-Face meeting to a teleconference after reviewed the FDA preliminary comments. FDA accepted this request. Teva also sent FDA clarifications via email on November 15, 2013 (see Attachment-II). The meeting discussions were primarily concentrated on the following questions that need clarification or further discussion.

Question 11

Is the proposed (b) (4)
(Figure 5) acceptable?

Agency's Response

No, we do not agree. (b) (4)

(b) (4)

Teva's Clarification (November 15, 2013 Communication)

(b) (4)

(b) (4)

Question 12

Does the Agency agree that the tests proposed for the release of the Fp (b) (4) *and FS* (b) (4) *finished products are adequate for control of the finished products for a NDA submission?*

Agency's Response

The identification test in the current drug product specification is non-specific. As per the recommendations of ICH Q6A, revise the specification to either include a specific test or another nonspecific yet complementary test with acceptance criterion, to assure the identity of both actives.

The drug product specification lists the color of the formulation as "white (b) (4) If there is any color associated with the formulation (either present initially or from degradative processes occurring during shelf life), then we recommend that you develop a method and apply a quantitative acceptance criterion for the color of the drug product formulation.

The testing attributes proposed for the release of Fp (b) (4) nd FS (b) (4) finished products are adequate for control of finished products for an NDA submission; however, the appropriateness and adequacy of the controls for individual related substance as well as of all testing methods and acceptance criteria are review issues to be addressed once the NDA is submitted.

We recommend you to conduct one test using 10 inhalers each at the beginning and end of inhaler life for inter- and intra-inhaler DCU testing.

Teva's Clarification (November 15, 2013 Communication)

The proposed specification for identification lists two methods that are to be used to identify each API in the product: Identification by UPLC and Identification by TLC. As these two methods are complementary, they meet the requirements of ICH Q6A. Does the agency concur that these two methods are complementary and can be used together for identification testing.

Meeting Discussion:

FDA stated that the two chromatography methods should have different principles of separation (e.g., one normal phase vs. one reverse phase) in order to meet ICH Q6A requirements.

[Post-meeting comment: Teva confirmed that its TLC method is a normal phase method and the UPLC is a reverse phase method].

Question 14

Teva proposes to conduct the inter-inhaler dose content uniformity on 10 inhalers at the beginning of inhaler life. Teva will also conduct intra-inhaler dose content uniformity through inhaler life on 3 inhalers and measure Dose 1, Dose 30, and Dose 60 which corresponds to the label claim number of doses. Both these tests will be conducted per the recommendation in the FDA Draft Guidance on MDI and DPI Drug Products (1998). Does the Agency agree with this proposal?

Agency's Response

Your approach is acceptable. However, our current recommendations are that you conduct a single test using 10 inhalers each at the beginning and end of inhaler life for both the inter- and intra-inhalers DCU testing.

Teva's Clarification (November 15, 2013 Communication)

Teva appreciates the Agency's recommendation to conduct a single test using 10 inhalers at the beginning and end of inhaler life, however, if our original proposed approach is acceptable to the Agency we would like to implement our original proposal as indicated in Teva Question 14.

Meeting Discussion:

FDA agreed with Teva's response.

Question 17

Does the Agency agree that the proposed label claim for the finished product can be based on the (b) (4)*?*

Agency's Response

No, we do not agree. For DPIs, the label claim is based on the metered dose (b) (4) (b) (4)

Teva's Clarification (November 15, 2013 Communication)

Teva accepts that the label claim will be based on the metered dose. The metered dose can only be determined using a mathematical calculation because the drug formulation metered into the dose cup cannot be directly measured since the dose cup cannot be removed without destruction of the LCA sub-assembly. Please confirm this approach is acceptable to the Agency.

Meeting Discussion:

FDA agreed with Teva's response.

Question 18

Teva proposes to use the delivered dose of fluticasone propionate to demonstrate dose proportionality for Fp (b) (4) *The product will be considered dose proportional if the mean delivered doses are within ±* (b) (4)*% of the label claim emitted dose of the respective strengths. APSD data including individual stages and stage groupings will also be provided for reference. Is this proposal acceptable to the Agency?*

Agency's Response

Yes, it is acceptable. See comment above on the labeled dose which should correspond to the metered dose (b) (4)

Teva's Clarification (November 15, 2013 Communication)

Teva acknowledges that the label dose on the package should correspond to the metered dose [redacted] in accordance to the Agency's response to Question 17. However, Teva would like to clarify that the dose proportionality for Fp [redacted] can be based on the label claim emitted dose of the respective strengths, rather than the label claim metered dose. Is this in line with the Agency's recommendation?

Meeting Discussion:

FDA agreed with Teva's response.

Question 20

Teva proposes to conduct the Phase 3 clinical trials using the NB7/3 iteration of the [redacted] device, filled using the [redacted] equipment. Teva will submit 18 months stability data on 1 batch, and 12 months stability data on 2 batches of each Fp [redacted] product strength, in the NDA, as supportive data. Teva proposes to commercialize the product using the NB8 iteration of the device, filled using the same [redacted] equipment and will submit 6 months stability data, on 3 batches of each Fp [redacted] product strength in this device iteration, stored at both 40°C/75%RH and 25°C/60%RH, in the NDA, as primary data for the approval of the NB8 device. Teva will also demonstrate similarity in the performance of the products, in the 2 device iterations. Is this proposal acceptable to the Agency?

Agency's Response

Your proposed testing protocol is acceptable to demonstrate similarity between the drug products FS filled at TPI and TPJ sites, respectively. However, the shelf life of the drug product that will be granted depends on the quality and poolabilty of the entire data.

Teva's Clarification (November 15, 2013 Communication)

Teva acknowledges the Agency's acceptance of the testing protocol and accepts that the shelflife of the drug product that will be granted depends on the quality and poolability of the entire dataset. However, it appears that the Agency misunderstood that FS [redacted] drug products will be filled at TPI and TPJ sites. FS [redacted] will only be manufactured at the TPJ site. Teva clarified that Fp [redacted] will be manufactured at TPI for the Phase 3 and commercial supply. Therefore, only similarity of performance for Fp [redacted] in the 2 device iterations filled at TPI will be demonstrated?

Meeting Discussion:

FDA acknowledged Teva's clarification response.

3.0 OTHER DISCUSSION

Devices in Clinical Studies

FDA indicated in preliminary comments "We note that you are planning to use multiple versions of the (b) (4) devices in the phase 3 clinical trials. We strongly recommend that you use device NB/8 for the planned phase 3 clinical trial."

Teva provided more data and clarifications related to the above FDA comment and comments to Teva's Question 19 and 20 in the communication on November 15, 2013 (see Attachement-II).

FDA acknowledged the different devices in the program and strongly recommended that Teva use the final device in all the Phase 3 clinical studies. FDA stated our reservations about the mix and match of devices Teva has used and is planning to use in their program. Use of the final device in Teva's pivotal studies would provide confidence regarding the robustness of the commercial product and avoid the potential need for bridging studies. FDA informed Teva that a (b) (4) change could impact (b) (4) (b) (4) and as a result could confound results in the clinic. FDA clarified that if clinical studies were initiated with one device, and then continued with another, the interpretability of the clinical data may be limited.

Teva explained that the NB8 device will not be available until the 4th quarter of 2014, and waiting for the device may result in a significant delay in the program. Therefore, Teva is proposing to bridge the devices using sensitive in-vitro methods that they predict will show no difference in device performance and therefore, no impact on the clinical data. FDA stated that in vitro comparisons alone are rarely sufficient to support the proposed device changes, and that differences found in in vitro studies are often difficult to interpret.

In summary, FDA stated that data derived from the proposed to-be-marketed product is the Agency's primary interest. To avoid issues with (b) (4) change or any other changes, Teva should use the final device in the pivotal clinical studies. FDA suggested an alternative plan would be for Teva to use the currently available NB7/3 device for Phase 3 clinical studies and submit the NDA based on these data, with the intent to market the NB7/3 device. (b) (4)
(b) (4)

Teva requested to discuss this issue further at a multi-disciplinary End-of-Phase 2 meeting planned in early 2014. FDA acknowledged.

On Teva's proposed NDA stability package using the NB8 device, FDA stated that at least 12 months stability data is needed for the NDA and less stability data may result in refuse-to-file of the NDA. FDA requires an ICH stability package with a minimum of 12 months data.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
None		

5.0 ATTACHMENTS AND HANDOUTS

Attachment-I. Meeting Preliminary Comments for IND 72240 and 108838.

Attachment-II. Teva's response and clarifications via email on November 15, 2013.

Attachment-I. Meeting Preliminary Comments for IND 72240 and 108838.

IND 72240 and 108838

MEETING PRELIMINARY COMMENTS

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Evelyn Cheng
Senior Manager, Regulatory Affairs
74 NW 176th St.
Miami, FL 33169

Dear Ms. Cheng:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fluticasone Propionate Inhalation Powder (IND 108838) and Fluticasone Propionate/Salmeterol Xinafoate Inhalation Powder (IND 72240).

We also refer to your September 9, 2013 correspondence requesting a Type-B End-of-Phase 2 CMC meeting to discuss the quality package for the registration of these products and to obtain FDA feedback on the proposed quality program to support the filing of the two NDAs. The Meeting Package was received on October 18, 2013.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me, at (301) 796-1926.

Sincerely,

{See appended electronic signature page}

Youbang Liu
Regulatory Project Manager
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B, End Of Phase 2 CMC Only
Meeting Category:	IND
Meeting Date and Time:	November 18, 2013, 1:00 PM to 2:30 PM (ET)
Meeting Location:	CDER WO Bldg 22, Room 1421
Application Number:	IND 72240 and 108838
Product Name:	Fluticasone Propionate Inhalation Powder and Fluticasone Propionate/Salmeterol Xinafoate Inhalation Powder
Indication:	Asthma
Sponsor/Applicant Name:	Teva Branded Pharmaceutical Products R&D, Inc. (TEVA)

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 18, 2013, in CDER WO Bldg 22, Room 1421 between TEVA and FDA (U.S. Food and Drug Administration). We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like FDA feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

3.0 BACKGROUND

Teva Global Respiratory Research (part of Teva Branded Pharmaceutical Products R&D, Inc.) is developing Fluticasone propionate (Fp) mono-therapy and Fluticasone propionate/Salmeterol xinafoate (FS) combination therapy in Teva's proprietary (b) (4) device. Three Phase 2b dose ranging studies, covering either fluticasone or salmeterol, have been conducted. The doses selected from these studies will be further evaluated, for safety and efficacy, in the Phase 3

clinical program, for both the Fp monotherapy and the FS combination therapy. This combined Phase 3 program will be initiated in Q1 2014.

The purpose of this meeting is to discuss and gain agreement on the proposed Quality (CMC) program to support Teva's Phase 3 development program, and the NDA exhibit batches, to support an NDA for both the Fp (b) (4) mono and the FS (b) (4) combination products.

4.0 DISCUSSION

Introductory comments

- **We note that you are planning to use multiple versions of the (b) (4) devices in the phase 3 clinical trials. We strongly recommend that you use device NB/8 for the planned phase 3 clinical trial.**
- **For all device versions (NB7/3 and NB8), please provide in vitro performance data (Delivered Dose and APSD) to demonstrate that the mono component product (FP (b) (4) and the dual component product (FS (b) (4) are comparable prior to them being used in the phase 3 studies, to minimize the collection of confounding data from the clinical trials.**
- **We also advise you to make reference to previous chemistry, manufacturing, and controls related advice we have provided for this and other (b) (4) drug products.**

Question 1

Does the Agency agree that the tests proposed for the release of fluticasone propionate are adequate for control of the material for an NDA submission?

Agency's Response

The testing attributes proposed for the release of fluticasone propionate are adequate for control of the material for an NDA submission; however, the appropriateness and adequacy of the controls for individual related substance and (b) (4) as well as of all testing methods and acceptance criteria are review issues to be addressed once the NDA is submitted.

Question 2

Is it acceptable to remove the amorphous content test from the release specification for salmeterol xinafoate?

Agency's Response

We cannot evaluate your proposal in the absence of the associated data. Provide data supported justifications in the NDA.

Question 3

Does the Agency agree that the tests proposed for the release of salmeterol xinafoate are adequate for control of the material for an NDA submission?

Agency's Response

The test attributes proposed for the release of salmeterol xinafoate are adequate for control of the material for an NDA submission; however, the appropriateness and adequacy of the controls for individual related substance and (b) (4) *as well as of all testing methods and acceptance criteria are review issues to be addressed once the NDA is submitted.*

Question 4

Does the Agency agree that the tests proposed for release of lactose monohydrate are adequate for control of the material for an NDA submission?

Agency's Response

The proposed testing attributes are adequate; however, the appropriateness and adequacy of the all testing methods and acceptance criteria are review issues to be addressed once the NDA is submitted.

Question 5

Teva proposes to conduct the flow resistance test of the (b) (4) on a fully assembled device. Does the Agency agree with this approach?

Agency's Response

Yes, we agree.

Question 6

Teva proposes to conduct dose cup width measurement as a test to control and verify the dimension of the dose cup size of the (b) (4) Does the Agency agree with this approach?

Agency's Response

Yes, we agree

Question 7

Does the Agency agree that the verification tests proposed in Table 14, Table 15, Table 16 and Table 17 for the release of (b) (4) device sub-assemblies are adequate for control of the material for an NDA submission?

Agency's Response

The proposed testing attributes are adequate; however, the appropriateness and adequacy of all testing methods and acceptance criteria are review issues to be addressed once the NDA is submitted.

Question 8

Does the Agency agree that the proposal for the routine control of extractables, from the device components in the NB8 iteration (b) (4) is adequate for control of the device component materials for an NDA submission?

Agency's Response

Yes, we agree.

Question 9

Does the Agency agree that the proposed one-time leachables study of (b) (4) formulation contact components in the NB8 iteration (b) (4), using the formulation with the lowest concentration, to demonstrate correlation between the component extractables and the finished product leachables, will allow for control of the device component materials for an NDA submission, via extractables only, without further routine leachables testing if a correlation is demonstrated between extractables and leachables?

Agency's Response

Yes, we agree.

Question 10

The analytical methods for testing the drug product have been validated using samples from the lowest and highest possible drug product compositions, selected based on the drug product strengths being evaluated in the Phase 2b dose ranging studies. The strengths used in the validation, bracket the proposed clinical strengths, however, they do not include the specific strengths that will be evaluated in the Phase 3 clinical studies and the registration stability program. Is this bracketing approach for method validation acceptable to the Agency?

Agency's Response

Yes, we agree.

Question 11

Is the proposed [redacted] (b) (4) (Figure 5) acceptable?

Agency's Response

No, we do not agree. [redacted] (b) (4) (b) (4)

Question 12

Does the Agency agree that the tests proposed for the release of the Fp [redacted] (b) (4) and FS [redacted] (b) (4) finished products are adequate for control of the finished products for a NDA submission?

Agency's Response

The identification test in the current drug product specification is non-specific. As per the recommendations of ICH Q6A, revise the specification to either include a specific test or another nonspecific yet complementary test with acceptance criterion, to assure the identity of both actives.

The drug product specification lists the color of the formulation as "white [redacted] (b) (4) *If there is any color associated with the formulation (either present initially or from degradative processes occurring during shelf life), then we recommend that you develop a method and apply a quantitative acceptance criterion for the color of the drug product formulation.*

The testing attributes proposed for the release of Fp [redacted] (b) (4) *and FS* [redacted] (b) (4) *finished products are adequate for control of finished products for an NDA submission; however, the appropriateness and adequacy of the controls for individual related substance as well as of all testing methods and acceptance criteria are review issues to be addressed once the NDA is submitted.*

We recommend you to conduct one test using 10 inhalers each at the beginning and end of inhaler life for inter- and intra-inhaler DCU testing.

Question 13

Does the Agency agree that the tests proposed for the stability of the Fp and FS [redacted] (b) (4) finished products are adequate for control of the finished products for a NDA submission?

Agency's Response

The testing attributes proposed for the stability of Fp (b) (4) and FS (b) (4) finished products are adequate for control of finished products for an NDA submission; however, the appropriateness and adequacy of the controls for individual related substance as well as of all testing methods and acceptance criteria are review issues to be addressed once the NDA is submitted.

We recommend you to conduct one test using 10 inhalers each at the beginning and end of inhaler life for inter- and intra-inhalers DCU testing.

Question 14

Teva proposes to conduct the inter-inhaler dose content uniformity on 10 inhalers at the beginning of inhaler life. Teva will also conduct intra-inhaler dose content uniformity through inhaler life on 3 inhalers and measure Dose 1, Dose 30, and Dose 60 which corresponds to the label claim number of doses. Both these tests will be conducted per the recommendation in the FDA Draft Guidance on MDI and DPI Drug Products (1998). Does the Agency agree with this proposal?

Agency's Response

Your approach is acceptable. However, our current recommendations are that you conduct a single test using 10 inhalers each at the beginning and end of inhaler life for both the inter- and intra-inhalers DCU testing.

Question 15

Does the Agency agree that the tests proposed for monitoring the stability of the Fp and FS (b) (4) finished products, are sufficient for evaluating the stability and assigning a shelf-life to the products for a NDA submission?

Agency's Response

Yes, we agree.

Question 16

Does the Agency agree that the proposed in-use stability program, for the registration batches, for the Fp and FS (b) (4) products, is adequate to support the NDA submission?

Agency's Response

Yes, we agree.

Question 17

Does the Agency agree that the proposed label claim for the finished product can be based on the (b) (4)

Agency's Response

No, we do not agree. For DPIs, the label claim is based on the metered dose (b) (4) (b) (4)

Question 18

Teva proposes to use the delivered dose of fluticasone propionate to demonstrate dose proportionality for Fp (b) (4) The product will be considered dose proportional if the mean delivered doses are within ± (b) (4)% of the label claim emitted dose of the respective strengths. APSD data including individual stages and stage groupings will also be provided for reference. Is this proposal acceptable to the Agency?

Agency's Response

Yes, it is acceptable. See comment above on the labeled dose which should correspond to the metered dose (b) (4)

Question 19

Teva proposes to conduct the Phase 3 clinical trials using the NB7/3 iteration of the (b) (4) device, filled using the (b) (4) equipment. Teva will submit 18 months stability data on 1 batch, and 12M stability data on 2 batches of each FS (b) (4) product strength, in the NDA, as supportive data. Teva proposes to commercialize the product using the NB8 iteration of the device, filled using (b) (4) equipment, and will submit 6 months stability data, on 3 batches of each FS (b) (4) product strength, in this device iteration, stored at both 40°C/75%RH and 25°C/60%RH, in the NDA, as primary data for the approval of the NB8 device. Teva will also demonstrate similarity in the performance of the products, in the 2 device iterations. Is this proposal acceptable to the Agency?

Agency's Response

Your proposed testing protocol is acceptable to demonstrate similarity between the drug products using NB7/3 iteration device and NB8 iteration device, respectively. *However, the shelf life of the drug product that will be granted will depend on the quality and poolabilty of the data from all versions of the* (b) (4) *devices.*

Question 20

Teva proposes to conduct the Phase 3 clinical trials using the NB7/3 iteration of the (b) (4) device, filled using the (b) (4) equipment. Teva will submit 18 months stability data on 1 batch, and 12 months stability data on 2 batches of each Fp (b) (4) product strength, in the NDA, as supportive data. Teva proposes to commercialize the product using the

NB8 iteration of the device, filled using the same (b) (4) equipment and will submit 6 months stability data, on 3 batches of each Fp (b) (4) product strength in this device iteration, stored at both 40°C/75%RH and 25°C/60%RH, in the NDA, as primary data for the approval of the NB8 device. Teva will also demonstrate similarity in the performance of the products, in the 2 device iterations. Is this proposal acceptable to the Agency?

Agency's Response

Your proposed testing protocol is acceptable to demonstrate similarity between the drug products FS filled at TPI and TPJ sites, respectively. However, the shelf life of the drug product that will be granted depends on the quality and poolabilty of the entire data.

Question 21

Is the proposal for investigating the effect of varying flow rates acceptable?

Agency's Response

Yes, we agree.

Question 22

Is the proposal for investigating the effect of storage on the particle size distribution acceptable?

Agency's Response

Yes, we agree.

Question 23

Is the approach to investigating dose build-up and flow resistance acceptable?

Agency's Response

Yes, we agree.

Question 24

Is the proposal for investigating the effect of metering and dosing orientation acceptable?

Agency's Response

Yes, we agree.

Question 25

Is it acceptable to the Agency for Teva to use the initial stability time-point data to demonstrate in vitro dose proportionality for Fp (b) (4) and FS (b) (4) products?

Agency's Response

Yes, we agree.

Question 26

Is the proposal for investigating the effect of patient use acceptable?

Agency's Response

Yes, we agree.

Question 27

Is the proposal for testing the returned normally functioning clinical samples from the clinical batches used in the Phase 3 clinical studies acceptable?

Agency's Response

Yes, we agree.

Question 28

Is the proposal for investigating the effect of moisture acceptable?

Agency's Response

Yes, we agree.

Question 29

Is the proposal for profiling of doses near device exhaustion acceptable?

Agency's Response

Yes, we agree.

Question 30

Is the proposal for establishing the appropriateness of the minimum and optimum fill weight acceptable?

Agency's Response

Yes, we agree.

Question 31

Is the proposal for developing cleaning instruction acceptable?

Agency's Response

Yes, we agree.

Question 32

Does the Agency agree that the proposal for product ruggedness studies to establish dose performance after handling, transportation and misuse scenario acceptable?

Agency's Response

Yes, we agree. However, the ruggedness of the dose counter under misuse conditions in terms of accuracy/functionality should also be evaluated.

Question 33

Is the proposed temperature excursion study acceptable?

Agency's Response

Yes, we agree.

Question 34

Is the proposed program for the characterization of the drug product, adequate for the NDA submission?

Agency's Response

Yes, we agree.

Question 35

The (b) (4) device has been developed with three potential metering volumes. (b) (4) (b) (4) (b) (4) Teva has used this formulation strategy, when the manufacturing process was scaled up from the Phase 2b process

to the proposed commercial process. Therefore, the formulation compositions used in the Phase 2b dose ranging clinical studies are different than the compositions that Teva will use in the Phase 3 clinical studies. The formulation compositions used in the Phase 3 clinical studies will be identical to the future commercial product. Is this formulation strategy acceptable to the Agency?

Agency's Response

Yes, we agree.

Attachment-II. Teva's response and clarifications via email on November 15, 2013.

Liu, Youbang

From: Evelyn Cheng <Evelyn.Cheng@tevapharm.com>
Sent: Friday, November 15, 2013 2:26 PM
To: Liu, Youbang
Subject: Fp (b) (4) IND 108838 / FSS (b) (4) IND 72240 End-of-Phase 2 Meeting Scheduled for Nov 18, 2013 - Discussion Points

Hi Youbang,

The purpose of this communication is to indicate which of the FDA comments we seek to clarify during our teleconference on Monday. All FDA comments are in italics. Clarification is requested on:

Agency Introductory Comments (bullets)

- *We note that you are planning to use multiple versions of the (b) (4) devices in the phase 3 clinical trials. We strongly recommend that you use device NB8 for the planned phase 3 clinical trial.*

Teva's Comment:

Regarding this bulleted comment and Comments 19 and 20, please refer to Tables 1, 2 and Table 20 (reproduced from Briefing Document) below.

Please confirm that the NB8 with (b) (4) (see Table 20) device iteration can be approved if the NDA contains:

- Clinical Studies conducted with the device iterations outlined in Table 1 below. Note that Device iteration NB8 will be used in one Phase 3 Clinical Study. Device iteration NB8 with (b) (4) will not be used in a Phase 3 Clinical Study
- Stability Data as outlined in Table 2 below:
- An in vitro comparison demonstrating equivalence between NB7/3, NB8 and NB8 with (b) (4)

Table 1: Device Use in Clinical Studies*

		Device Iteration			
Clinical Study Protocol Number	Phase	NB7/2	NB7/3	NB8	NB8 + (b) (4) (b) (4)
FpS-AS-101 (Complete)	1	X	-	-	-
FpS-AS-102 (Complete)	1	X	-	-	-
Phase 1 PK High strength	1		X		
Phase 1 PK Low strength	1		X		
FpS-AS-201 (Complete)	2	X	X	-	-

		Device Iteration			
Clinical Study Protocol Number	Phase	NB7/2	NB7/3	NB8	NB8 + (b) (4) (b) (4)
FpS-AS-202 (Complete)	2	X	X	-	-
FSS-AS-201 (Complete)	2	X	-	-	-
FSS-AS-PIII Low strength study	3	-	-	X	-
FSS-other PIII studies	3	-	X	-	-
Commercial					X

*Overall clinical program still to be discussed with FDA at End-of-Phase 2 Clinical meeting to be held in 1Q2014.

X indicates which device version has/will be used in each clinical study or is intended for Commercial use.

Table 2: Stability Data on Potential Strengths to be included in NDA submission

Strength*	NB7.2**	NB7/3	NB8	NB8 + (b) (4) (b) (4)
Fp (b) (4)				
50 mcg	1 batch: 6M ACC, 24 M CRT	3 batches: 6M ACC, 12M CRT	None	3 batches: 6M ACC, 6M CRT
100 mcg	1 batch: 6M ACC, 24M CRT	3 batches: 6M ACC, 12M CRT	None	3 batches: 6M ACC, 6M CRT
200 mcg	1 batch: 6M ACC, 24M CRT	3 batches: 6M ACC, 12M CRT	None	3 batches: 6M ACC, 6M CRT
(b) (4)				
FS (b) (4)				
50 mcg/12.5 mcg		3 batches: 6M ACC,12M CRT	None	3 batches: 6M ACC 6M CRT

2

Strength*	(b) (4)	NB8	NB8 – (b) (4)
100 mcg/12.5 mcg	3 batches: 6M ACC 12M CRT	None	3 batches: 6M ACC 6M CRT
200 mcg/12.5 mcg	3 batches: 6M ACC 12M CRT	None	3 batches: 6M ACC 6M CRT
(b) (4)			

*Strengths to be submitted are still to be confirmed.

**These batches are at pilot scale. All other batches are at commercial scale.

ACC: Accelerated condition (40°C/75%RH); CRT: Controlled room temperature (25°C/60%RH)

Table 20: Modification to the (b) (4) device iteration NB7/2to NB8 with (b) (4)

(b) (4)

- *For all device versions (NB7/3 and NB8), please provide in vitro performance data (Delivered Dose and APSD) to demonstrate that the mono component product (FP (b) (4) and the dual component product (FS (b) (4) are comparable prior to them being used in the phase 3 studies, to minimize the collection of confounding data from the clinical trials.*

Teva's Comment:

Teva would like clarification on whether the Agency is requesting that in vitro performance data (Delivered Dose and APSD) for Fp and FS (b) (4) be submitted to the IND prior to the start of Phase 3 studies. or is the Agency requesting the in vitro performance data be submitted in the NDA.

Question 11

Is the proposed (b) (4) (Figure 5) acceptable?

Agency's Response:

3

No, we do not agree. (b) (4)

(b) (4)

Teva's Comment:

(b) (4)

Does the Agency agree this approach is also acceptable for these two products?

Question 12

Does the Agency agree that the tests proposed for the release of the Fp (b) (4) **and FS** (b) (4) **finished products are adequate for control of the finished products for a NDA submission?**

Agency's Response:

The identification test in the current drug product specification is non-specific. As per the recommendations of ICH Q6A, revise the specification to either include a specific test or another nonspecific yet complementary test with acceptance criterion to criterion, to assure the identity of both actives.

Teva's comment:

The proposed specification for identification lists two methods that are to be used to identify each API in the product: Identification by UPLC and Identification by TLC. As these two methods are complimentary, they meet the requirements of ICH Q6A. Does the agency concur that these two methods are complimentary and can be used together for identification testing?

Question 14

Teva proposes to conduct the inter-inhaler dose content uniformity on 10 inhalers at the beginning of inhaler life. Teva will also conduct intra-inhaler dose content uniformity through inhaler life on 3 inhalers and measure Dose 1, Dose 30, and Dose 60 which corresponds to the label claim number of doses. Both of these tests will be conducted per the recommendation in the FDA draft Guidance on MDI and DPI Drug Products (1998). Does the Agency agree with this proposal?

Agency's Response:

Your approach is acceptable. However, our current recommendations are that you conduct a single test using 10 inhalers each at the beginning and end of inhaler life for both the inter- and intra-Inhalers DCU testing.

Teva's Comment:

Teva appreciates the Agency's recommendation to conduct a single test using 10 inhalers at the beginning and end of inhaler life, however, if our original proposed approach is acceptable to the Agency we would like to implement our original proposal as indicated in Teva Question 14.

Question 17

Does the Agency agree that the proposed label claim for the finished product can be based on the (b) (4) (b) (4),

Agency's Response:

No, we do not agree. For DPIs, the label claim is based on the metered dose (b) (4)

Teva's Comment:

Teva accepts that the label claim will be based on the metered dose. The metered dose can only be determined using a mathematical calculation because the drug formulation metered into the dose cup cannot be directly measured since the dose cup cannot be removed without destruction of the LCA sub-assembly. Please confirm this approach is acceptable to the Agency?

Question 18

Teva proposes to use the delivered dose of fluticasone propionate to demonstrate dose proportionality for Fp (b) (4) The product will be considered dose proportional if the mean delivered doses are within ± (b) (4)% of the label claim emitted dose of the respective strengths. APSD data including individual stages and stage groupings will also be provided for reference. Is this proposal acceptable to the Agency?

Agency's Response

Yes, it is acceptable. See comment above on the labeled dose which should correspond to the metered dose and (b) (4)

Teva's Comment:

Teva acknowledges that the label dose on the package should correspond to the metered dose and not the (b) (4) in accordance to the Agency's response to Question 17. However, Teva would like to clarify that the dose proportionality for Fp Spiromax can be based on the label claim emitted dose of the respective strengths, rather than the label claim metered dose. Is this in line with the Agency's recommendation?

Question 20

Teva proposes to conduct the Phase 3 clinical trials using the NB7/3 iteration of the (b) (4) device, filled using the (b) (4) equipment. Teva will submit 18 months stability data on 1 batch, and 12 months stability data on 2 batches of each Fp (b) (4) product strength, in the NDA, as supportive data. Teva proposes to commercialize the product using the NB8 iteration of the device, filled using the same (b) (4) (b) (4) equipment and will submit 6 months stability data, on 3 batches of each Fp (b) (4) product strength in this device iteration, stored at both 40°/75%RH and 25°C/60%RH, in the NDA, as primary data for the approval of the NB8 device. Teva will also demonstrate similarity in the performance of the products, in the 2 device iterations. Is this proposal acceptable to the Agency?

Agency's Response:

5

Your proposed testing protocol is acceptable to demonstrate similarity between the drug products FS filled at TPI and TPJ sites, respectively. However, the shelf life of the drug product that will be granted depends on the quality and poolability of the entire data.

Teva's Comment:

Teva acknowledges the Agency's acceptance of the testing protocol and accepts that the shelf-life of the drug product that will be granted depends on the quality and poolability of the entire dataset. However, it appears that the Agency misunderstood that FS (b) (4) drug products will be filled at TPI and TPJ sites. FS (b) (4) will only be manufactured at the TPJ site.

Teva would like to clarify that Fp (b) (4) will be manufactured at TPI for the Phase 3 and commercial supply. Therefore, only similarity of performance for Fp (b) (4) in the 2 device iterations filled at TPI will be demonstrated.

We look forward to the End-of-Phase 2 meeting on Monday at 1pm.

Best regards,
Evelyn

Evelyn Cheng Sr Mgr, Regulatory Affairs
Tel: 305-575-8329 Fax: 305-575-8339
Evelyn.Cheng@tevapharm.com www.tevapharm.com

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YOUBANG LIU
12/18/2013

PRASAD PERI
12/18/2013
Signed for Dr. Eric P. Duffy