CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205382Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205382 SUPPL # HFD # 570

Trade Name Incruse Ellipta

Generic Name umeclidinium bromide

Applicant Name umeclidinium bromide

Approval Date, If Known April 30, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 203975 umeclidinium /vilanterol

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

AC4115408, DB2113373, DB2113359

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☒	NO ☐
Investigation #2	YES ☒	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Although the studies were previously submitted for NDA 203975 (umeclidinium/vilanterol), there are portions of the essential studies (mainly in support of (b) (4) for UMEC) that had not been previously reviewed.

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Although the studies were previously submitted for NDA 203975 (umeclidinium/vilanterol), there are portions of the essential studies (mainly in support of the [redacted] (b) (4) for UMEC) that had not been previous reviewed.

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

AC4115408, DB2113373

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Angela Ramsey
Title: Senior Program Management Officer
Date: April x, 2014

Name of Office/Division Director signing form: Badrul A. Chowdhury, M.D., Ph.D.
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

ANGELA H RAMSEY
04/30/2014

BADRUL A CHOWDHURY
04/30/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 205382 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Incruse Ellipta Established/Proper Name: umeclidinium bromide Dosage Form: 62.5 mcg		Applicant: GlaxoSmithKline Agent for Applicant (if applicable):
RPM: Angela Ramsey		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:

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 April 30, 2014	☒ 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, (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).

swer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA plement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(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

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: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ 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) April x, 2014
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)*	11/21/13; 6/11/13 11/19/13; 6/11/13
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 7/10/13 DMEPA: ☐ None 12/6/13; 11/19/13 DMPP/PLT (DRISK): ☐ None 12/20/13 OPDP: ☐ None 12/24/13 SEALD: ☐ None 3/18/14 CSS: ☐ None Other: ☐ None
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	6/28/13
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	☒ Not a (b)(2)
❖ 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 should be filed with the respective discipline.

• 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 If PeRC review not necessary, explain:	9/18/13; Full waiver granted
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) *(do not include previous action letters, as these are located elsewhere in package)*	3/19/14; ; 3/3/14; 1/29/14; 1/15/14; 1/8/14; 11/21/13; 9/26/13; 7/10/13; 5/13/13
❖ 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)	10/8/13
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 1/18/12
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 10/29/10
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A 10/8/13
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A 2/5/14
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(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)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 3/26/14
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	12/19/13; 6/18/13
• 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)*	12/19/13 pg 19
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ 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 1/6/14
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
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 6/6/13
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)*	☐ None 2/4/14; 6/13/13
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)*	☐ None 12/27/13; 6/18/13
OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
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 1/13/14
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 12/12/13; 6/13/13
❖ 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 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 3/20/14; 5/31/13
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 6/6/13
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None Biopharm:6/14/13 Biometrics: 12/2/13
❖ 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)*	3/20/14; pg 138
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: 3/25/14 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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
❖ 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

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

FACSIMILE TRANSMITTAL SHEET

Date: March 19, 2014

To: Vicki Gunto Director, Global Regulatory Affairs	**From:** **Angela Ramsey** **Senior Program Management Officer**
Company: GSK	**Division of Pulmonary, Allergy, and Rheumatology Drug Products**
Fax number: 919-315-8319	**Fax number: 301-796-9728**
Phone number: 919-483-5894	**Phone number: 301-796-2284**

Subject: **NDA 205382 (umeclidinium) labeling fax #4**

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

NDA 205382

We continue our review of the labeling in your submission dated, April 30, 2013 to NDA 205382 and we have the following requests:

Highlights:

1. Remove "inhaler" after first instance of drug name. Only the drug name should be included in the HL Limitation Statement as follows: "These highlights do not include all the information needed to use the INCRUSE ELLIPTA ~~inhaler~~ safely and effectively. See full prescribing information for INCRUSE ELLIPTA."

2. Insert 4-digit year that the active moiety (umeclidinium) was originally approved (i.e., 2013).

Submit your responses to me via email at angela.ramsey@fda.hhs.gov by Monday, March 24, 2014. Your responses will subsequently need to be submitted officially to the NDA.

These labeling changes are not necessarily the Agency's final recommendations and additional labeling changes may be forthcoming as we continue to review the application. If you have any questions, please contact Angela Ramsey, Senior Program Management Officer, at 301-796-2284.

Drafted by: Ramsey/March 19, 2014
Initialed by: Barnes/March 19, 2014; Limb/March 19, 2014
Finalized: Ramsey/ March 19, 2014

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

/s/

ANGELA H RAMSEY
03/19/2014

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

FACSIMILE TRANSMITTAL SHEET

Date: March 3, 2014

To: Vicki Gunto Director, Global Regulatory Affairs	**From:** **Angela Ramsey** **Senior Program Management Officer**
Company: GSK	**Division of Pulmonary, Allergy, and Rheumatology Drug Products**
Fax number: 919-315-8319	**Fax number: 301-796-9728**
Phone number: 919-483-5894	**Phone number: 301-796-2284**

Subject: **NDA 205382 (umeclidinium) labeling fax #3**

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

NDA 205382

We continue our review of the labeling in your submission dated, February 11, 2014 to NDA 205382 and we have the following request:

> Revise Table 1 and the accompanying text in Section 6 to reflect the results of Trials 1 and 2 (DB2113373 and AC4115408), the same trials described in Section 14.

Submit your responses to me via email at angela.ramsey@fda.hhs.gov by Friday, March 7, 2014. Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Angela Ramsey, Senior Program Management Officer, at 301-796-2284.

Drafted by: Ramsey/February 28, 2014
Initialed by: Jordan-Garner for Barnes/February 28, 2014; Limb/February 28, 2014
Finalized: Ramsey/ March 3, 2014

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

/s/

ANGELA H RAMSEY
03/03/2014

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Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: January 29, 2014

To: Vicki Gunto Director, Global Regulatory Affairs	**From:** **Angela Ramsey** **Senior Program Management Officer**
Company: GSK	**Division of Pulmonary, Allergy, and Rheumatology Drug Products**
Fax number: 919-315-8319	**Fax number: 301-796-9728**
Phone number: 919-483-5894	**Phone number: 301-796-2284**

Subject: **NDA 205382 (umeclidinium) labeling fax #2**

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

NDA 205382

Your NDA 205382 submitted on April 30, 2013 is currently under review. These labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as we continue to review the application. Submit revised labeling incorporating the changes shown in the attached marked up labeling. We also have the following requests regarding labeling:

1. Provide a reference to allow us to confirm the numbers in Table 1.

2. We request clarification on your calculations of SGRQ response probabilities. Both the statistical analysis plan and the Study Report (Table 51) for Study DB2113373 indicate that patients with a missing SGRQ change score and no subsequent non-missing scores are characterized as non-responders. This is a reasonable approach, but it does not appear to have been followed in your analyses. Because the Day 168 visit was the final visit at which SGRQ was assessed, patients with missing SGRQ change scores at Day 168 could not have had subsequent non-missing SGRQ scores. Therefore, all patients with missing SGRQ scores at Day 168, by your stated definition, would be characterized as non-responders. However, your Day 168 calculations in the proposed labeling and in Table 51 of the Study Report are not based on all randomized patients. For example, the SGRQ response probability of 44% on UMEC 62.5 is based on a sample size (denominator) of 388 patients. If all patients with missing SGRQ scores at Day 168 were characterized as non-responders, then all of the 418 randomized patients (except perhaps a few patients with missing baseline data) would be included in the denominator for analyses, and the response rate would instead be around 41%. Please clarify, or correct your computations to match your analysis plan.

3. The following comments pertain to container labels and carton labeling:
    a. All Container Labels
        i. Revise the labels so that the strength is included with the proprietary name and established name on all panels, i.e.,
        Incruse Ellipta
        (Umeclidinium Inhalation Powder)
        62.5 mcg
        ii. Unbold the statement 'Rx Only' and decrease the prominence of the NDC, since as currently presented this statement competes for prominence with the proprietary name

iii. Decrease the prominence of the company name and logo above the proprietary name

iv. As currently presented, it is difficult to read the information presented in the (b) (4) font against the light green background on the container label. Revise the white font color to another color (e.g., black) to provide better contrast against the green background and improve the readability of the labels

b. All Carton Labeling

i. Revise the labels so that the strength is included with the proprietary name and established name on all panels, i.e.,
Incruse Ellipta
(Umeclidinium Inhalation Powder)
62.5 mcg

Submit your responses to me via email at angela.ramsey@fda.hhs.gov by Tuesday, February 5, 2014. Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Angela Ramsey, Senior Program Management Officer, at 301-796-2284.

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

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/s/

ANGELA H RAMSEY
01/29/2014

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

FACSIMILE TRANSMITTAL SHEET

DATE: January 8, 2014

To: Vicki Gunto Global Regulatory Affairs	**From:** Leila P. Hann
Company: Glaxo Group, d/b/a GlaxoSmithKline	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 919-315-0033	**Fax number:** 301-796-9728
Secure Email: vicki.x.gunto@gsk.com	**Phone number:** 301-796-3367

Subject: NDA 205382 (umeclidinium) Labeling Information Request

Total no. of pages including cover: 41

Comments:

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

Your NDA 205382 submitted on April 30, 2013 is currently under review. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as we continue to review the application. Submit revised labeling incorporating the changes shown in the attached marked up labeling. We also have the following comments regarding labeling:

1. Update the label with the new tradename.

2. In Section 6.1 provide a rationale for your selection of terms for events with an incidence of < 1% (lines 99-101).

3. Provide a reference to allow us to confirm the numbers of geriatric patients listed in Section 8.5. The references included in the original annotated label were reviewed, but the source numbers were not readily apparent.

4. In Section 12.3, Absorption subsection, confirm the numbers where indicated. They do not appear to be consistent with the Anoro Ellipta label.

5. Revise Section 14 to include a description of UMEC dose-ranging trials, consistent with the presentation of umeclidinium dose ranging information in the Anoro Ellipta label.

6. In the introductory paragraph of 14.2 include a summary of the demographic and baseline disease characteristics of the population where indicated.

7. Revise Figure 2 (formerly Figure 3) to include results from both Day 1 and 168.

In order to facilitate the review of your NDA submission, provide the requested information no later than noon, January 13, 2014. If you have any questions, please contact Angela Ramsey, Senior Program Management, at 301-796-2284.

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

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/s/

ANGELA H RAMSEY
01/08/2014

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

FACSIMILE TRANSMITTAL SHEET

Date: November 26, 2013

To: Vicki Gunto Director, Global Regulatory Affairs	**From:** **Angela Ramsey** **Senior Program Management Officer**
Company: GSK	**Division of Pulmonary, Allergy, and Rheumatology Drug Products**
Fax number: 919-315-8319	**Fax number: 301-796-9728**
Phone number: 919-483-5894	**Phone number: 301-796-2284**

Subject: **NDA 205382 (umeclidinium) submission dated, April 30, 2013**

Total no. of pages including cover: **3**

Comments:

Document to be mailed: YES XNO

NDA 205382

Your submission dated, April 29, 2013, received April 30, 2013, is currently under review. We have the following requests for information:

1. Provide the following tables:

Table A. Summary of non-fatal AEs, UMEC Development Program

	Placebo	**UMEC 62.5**	**UMEC 125**
	N	N	N
	n (%)	n (%)	n (%)
Primary Efficacy Trials (AC4115408, DB2113361, DB2113373, DB2113374)			
Long-Term Safety Trial (DB21133459)			
Exercise Trials (DB2114417, DB2114418)			
Additional Integrated Trial (AC4113589)			
All Clinical Trials AC4115408, DB2113361, DB213373, DB2113374, DB21133459, DB2114417, DB2114418, AC4113589			
Supportive Trials, not integrated (AC4113073, AC4115321)			
Total (all 10 trials)			

Note: include on-treatment events

Table B. Nonfatal SAE PTS, by SOC and PT, Primary Efficacy Trials*, ITT Population

	Placebo N=555	UMEC 62.5 N=418	UMEC 125 N=629
	n (%)	n (%)	n (%)
Any non-fatal SAE			
SOC			
Any event			
PT			
PT, etc.			
SOC			
Any event			
PT			
PT, etc.			

*AC4115408, DB2113361, DB2113373, DB2113374

Note: include on-treatment events

2. Clarify if the adjudication of non-fatal SAEs presented in Table X and Y of the ISS includes both on-treatment and post-treatment events.

3. Confirm the numbers in the following table, and complete the missing cells:

Table C. Summary of Adverse Events Leading to Dropout, UMEC Clinical Development Program

	Placebo	UMEC 62.5	UMEC 125
	N	N	N
	n (%)	n (%)	n (%)
Primary Efficacy Trials	623	487	698
	26 (4)	32 (7)	44 (6)
Long-Term Safety Trial	109	--	227
	12 (11)	--	20 (9)
Exercise Trials	321	89	91
	17 (5)	2 (2)	3 (3)
Additional Integrated Trial			
All Clinical Trials	1124	576	1087
	55 (5)	34 (6)	68 (6)
Supportive Trials, not integrated			
Total (all 10 Trials)			

Note: Dropout is defined as discontinuation of study treatment or withdrawal from the study

Note: N=Number of patients in the ITT population

Note: n(%) = number (percentage) of AEs leading to Dropout for each trial grouping

Submit your responses to me via email at angela.ramsey@fda.hhs.gov by Friday, December 6, 2013. Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Angela Ramsey, Senior Program Management Officer, at 301-796-2284.

Drafted by: Ramsey/November 26, 2013
Initialed by: Barnes/November 26, 2013; Pippins/November 26, 2013; Limb/November 26, 2013
Finalized: Ramsey/ November 26, 2013

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/s/

ANGELA H RAMSEY
11/26/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205382

INFORMATION REQUEST

Glaxo Group Limited d/b/a GlaxoSmithKline.
Attention: Susan Holmes, M.S.
Director, CMC Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Ms. Holmes:

Please refer to your New Drug Application (NDA) submitted April 29, 2012 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for umeclidinium inhalation powder.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by December 4, 2013 in order to continue our evaluation of your NDA.

(b) (4)

(b) (4)

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

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

CRAIG M BERTHA on behalf of PRASAD PERI
11/21/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205382

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Glaxo Group Limited, England d/b/a GlaxoSmithKline
c/o GlaxoSmithKine
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Vicki Gunto, Ph.D.
Director, Global Regulatory Affairs

Dear Dr. Gunto:

Please refer to your New Drug Application (NDA) dated April 29, 2013, received April 30, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Umeclidinium Powder for Oral Inhalation, 62.5 mcg.

We also refer to your September 6, 2013, correspondence, received September 6, 2013, requesting review of your proposed proprietary name, Incruse Ellipta. We have completed our review of the proposed proprietary name, Incruse Ellipta, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your September 6, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Angela Ramsey, at (301) 796-2284.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
11/21/2013

MEMORANDUM OF TELECONFERENCE

Teleconference Date: October 8, 2013

Application Number: NDA 205382
Product Name: umeclidinium bromide (umec)
Sponsor/Applicant Name: GlaxoSmithKline (GSK)

Subject: Mid-Cycle Communication of the review of umeclidinium bromide

FDA Participants : Susan Limb, MD, Clinical Team Leader
Jennifer Pippins, MD, Clinical Reviewer
Joan Buenconsejo, Ph.D., Statistical Team Leader
Gregory Levin, Ph.D., Statistical Reviewer
Carol Hill, Regulatory Project Manager

Sponsor Participants: Elaine Jones, Vice President, Medicine Development Leader
Alison Church, Director, Clinical Development
Vicki Gunto, Director, Global Regulatory Affairs

BACKGROUND:
The purpose of the teleconference dated October 8, 2013, was to provide an update on the status of the review and highlight review issues for umeclidinium bromide in the treatment of COPD.

DISCUSSION: The Division stated that the review remains ongoing and is in keeping with the projected timeline. To date, the main safety issue identified is the cardiovascular risk profile, and the main efficacy issue is the level of evidence to support (b) (4)

GSK asked if the action date for this application would be moved to coincide with that for NDA 203975 (umeclidinium and vilanterol inhalation powder) since the applications are closely linked. The Division stated no; the goal date for umeclidinium will remain April 30, 2014.

GSK also asked for preliminary feedback on the observational study submitted to NDA 203975 on October 4, 2013, and noted that GSK is considering a similar proposal for the umeclidinium monotherapy application. The Division commented that the proposed observational study will be discussed at the wrap-up meeting for NDA 203975, and feedback will be provided to GSK on this matter.

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/s/

ANGELA H RAMSEY
10/16/2013

PeRC PREA Subcommittee Meeting Minutes
September 18, 2013

PeRC Members Attending:
Lynne Yao
Hari Cheryl Sachs
Karen Davis-Bruno (Did not review Ferric Citrate & Desvanlafaxine)
Patricia Dinndorf
Tom Smith
Julia Pinto (Did not review Ferric Citrate & Desvanlafaxine)
Ethan Hausman
Wiley Chambers
Lily Mulugeta
Daiva Shetty
Martha Nguyen
Dianne Murphy
Gregory Reaman
Jane Inglese
William Rodriguez
George Greeley
Coleen LoCicero
Robert "Skip" Nelson
Rachel Whitten
Maura O'Leary

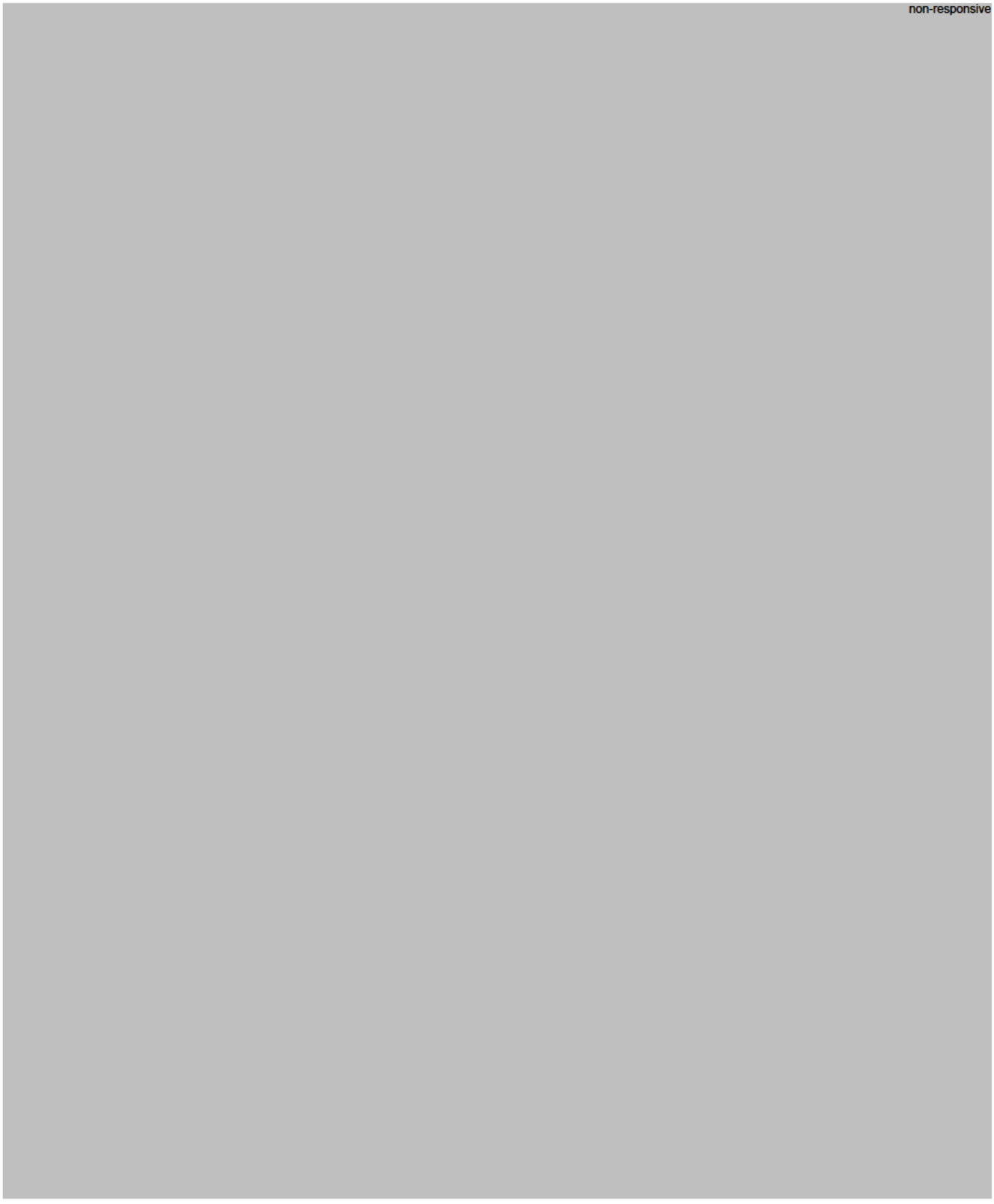
Guests Attending:
Nichella Simms (PMHS)
Erica Radden (PMHS)
Courtney Suggs (OCP)
Donna Snyder (PMHS)
Linda Onaga (DAVP)
Brian Chow (OCP)
Jung Lee (DNCE)
Leslie Chinn (OCP)
Nikolay Nikolov (DPARP)
Karen Hull (DPARP)
L. Fossom (DPP)
Aliza Thompson (DCRP)
Glenn Mannhan (DCRP)
Kofi Ansah (DPP)
Donna Snyder (PMHS)
Amy Talor (PMHS)
Terri Crescenzi (OPT)
Lesley Furlong (DNCE)
Linda Hu (DNCE)
Gilbert Burckart (OCP)
Yodit Belew (OAP)
Gerald Tran (OCP)
Martin Nevit (DTOP)
Jade Pham (DNCE)
Sarah Connelly (DAVP)
Robert Yim (DPARP)
Jing Zhang (DPP)
Nancy Xu (DCRP)
Russell Fortney (DCRP)
Rawa Dwivedi (DCRP)
Jessica Boehmer (DHP)
GT Wharton (OPT)
Angela Men (OCP)

Agenda

10:40 non-responsive
11:00
11:20
11:30

NDA 205382 Umedlidinium Bromide Full Waiver

non-responsive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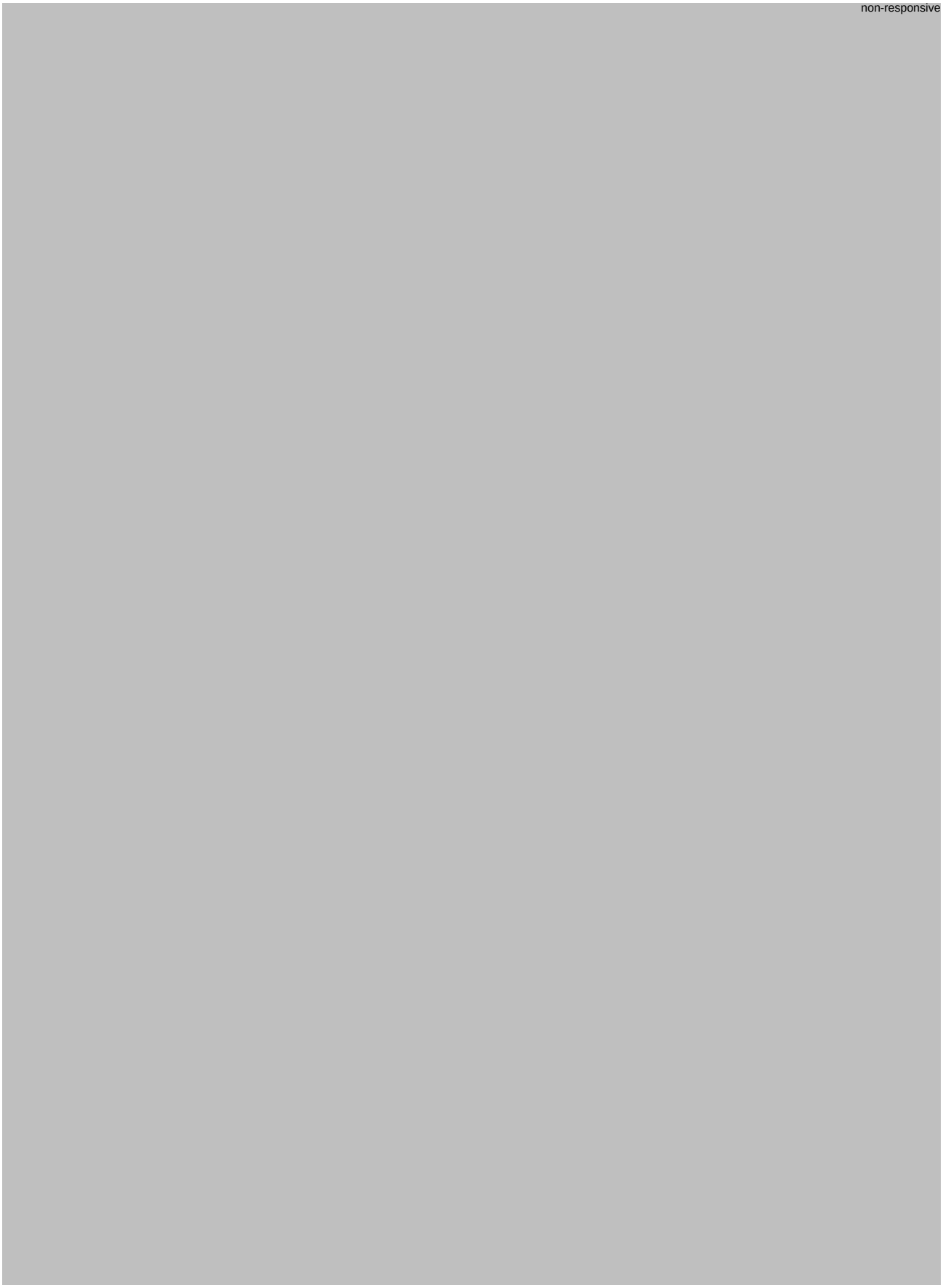
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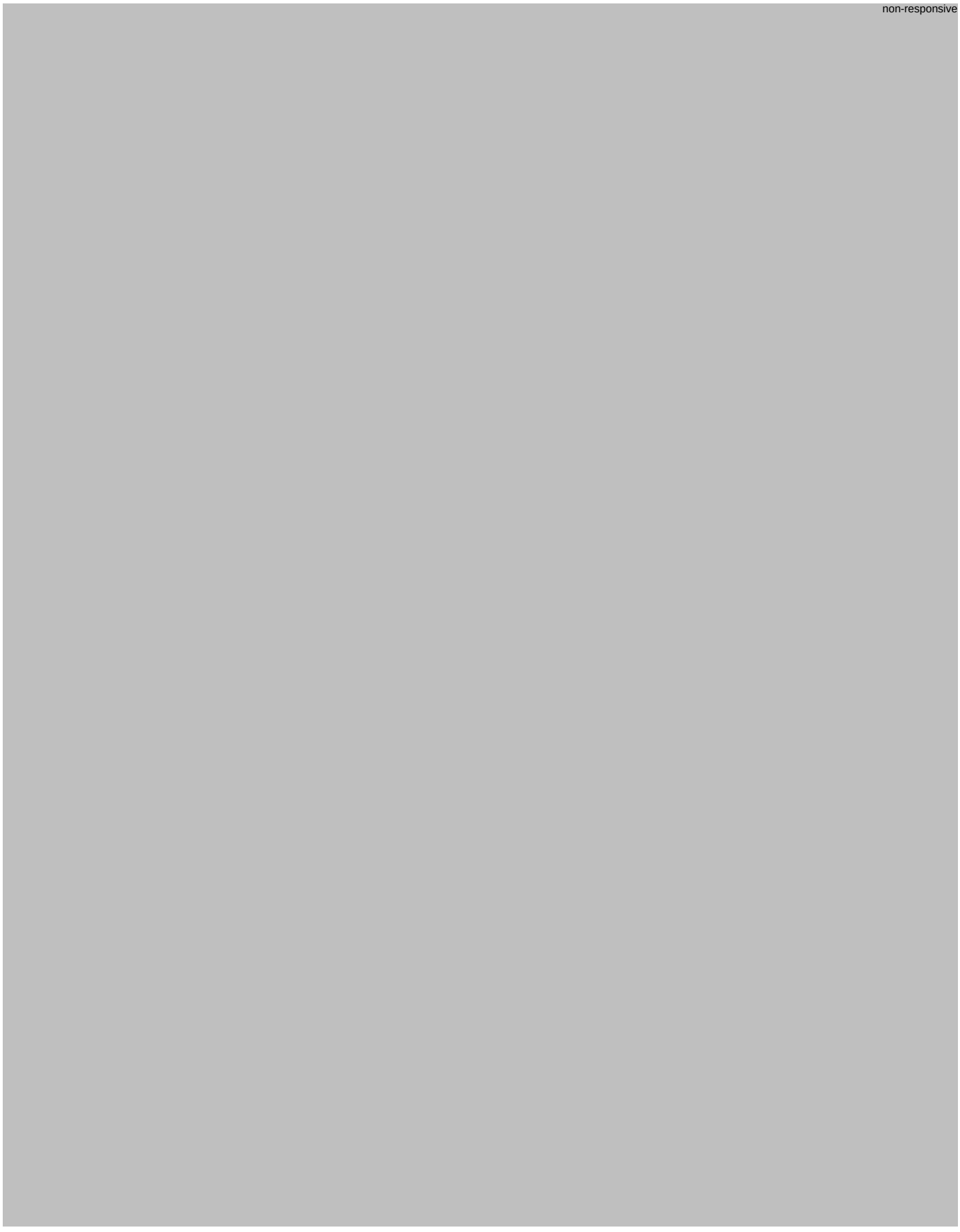
non-responsive

Umeclidinium Bromide Full Waiver

- NDA 205382 seeks marketing approval of the application for Umeclidinium Bromide for COPD.
- The supplement was received on April 30, 2013 and has a PDUFA goal date of April 30, 2014.
- The application triggers PREA as a new active ingredient.
- A full waiver is being requested in all pediatric patients because the disease/condition does not exist in children.

PeRC Recommendations

- The PeRC agreed to the full waiver because the disease/condition does not exist in children.

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/s/

GEORGE E GREELEY
10/01/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205382

INFORMATION REQUEST

Glaxo Group Limited d/b/a GlaxoSmithKline.
Attention: Susan Holmes, M.S.
Director, CMC Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Ms. Holmes:

Please refer to your New Drug Application (NDA) submitted April 29, 2012 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for umeclidinium inhalation powder.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response (preferably by October 10, 2013) in order to continue our evaluation of your NDA.

1. Your drug product specifications table includes a (b) (4) (as noted in footnote L). In Section P.5.6 (Justification of Specifications) you state (3.2.P.5.6.2.8.1):

   > "Tolerance intervals have been calculated using the batches contained within the database described in Section 1."

   The database described in Section 1 includes, in addition to the clinical batches used in Phase III studies, "Primary stability batches including data obtained following storage at the long term storage condition (25°C/60% RH) for up to 12 months within secondary packaging."

   In order for long-term storage stability data to be used to support the calculation of the tolerance interval you must provide an analysis of the test results for all of the samples tested, including an analysis to demonstrate the sources of variability e.g. within batch, between batch, and storage time.

   Alternatively you can amend the drug product specifications table to remove the (b) (4) testing acceptance criterion.

2. Regarding the Dose Content Uniformity and Dose Content Uniformity through Life test:
   a. Prespecify the alternative sample sizes (b) (4)

b. Your sampling approach should be such that the probability of a given batch passing will not change with a change in sample size. (b) (4) [redacted]

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

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
09/26/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205382

FILING COMMUNICATION

GlaxoSmithKline
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Vicki Gunto, Ph.D.,
Director, Global Regulatory Affairs

Dear Dr. Gunto:

Please refer to your New Drug Application (NDA) dated April 29, 2013, received April 30, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for umeclidinium bromide inhalation powder.

We also refer to your amendments dated May 1, 2013.

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**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm . Therefore, the user fee goal date is April 30, 2014.

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 17, 2014. In addition, the planned date for our internal mid-cycle review meeting is September 24, 2012. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Clinical

1. The adequacy of the data to support (b) (4) will be a review issue.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Statistics

2. With respect to the impact of missing data, we do not find the sensitivity analyses you provided for Study 408 to be sufficient. All four multiple imputation approaches (missing at random, copy differences from control, last mean carried forward, and last mean -25 mL/year carried forward) more or less impute post-dropout data by preserving the mean treatment effect that was observed prior to discontinuation. This may not be appropriate, since any positive effects of the bronchodilator on FEV_1 prior to dropout likely declined or went completely away once the patient stopped taking the therapy. We request that you provide results based on additional sensitivity model(s) that do not preserve the pre-dropout treatment effect after patients stop taking the therapy. For example, the "copy reference" and "jump to reference" approaches that you implemented under NDA 203975 are additional models of interest.

Clinical pharmacology

3. Part of Figure 1 for hepatic and renal impairment population in the proposed label is based on UMEC PK data from the UMEC/VI combination arm. Please revise the figure using PK data associated with the UMEC monotherapy.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Excessive length in the HL. The length of the HL section must be less or equal to one-half the page.

2. White space must be present before each major heading in HL.

We request that you resubmit labeling that addresses these issues by July 26, 2013. The resubmitted labeling will be used for further labeling discussions.

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). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), 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.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Angela Ramsey, Senior Program Management Officer at (301) 796-2284.

Sincerely,

{See appended electronic signature page}

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

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/s/

LYDIA I GILBERT MCCLAIN
07/10/2013
Acting Division Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 205382

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Glaxo Group Limited, England
c/o GlaxoSmithKline
Five Moore Drive
Research Triangle Park, NC 27709

ATTENTION: Vicki Gunto
Director, Global Regulatory Affairs

Dear Ms. Gunto:

Please refer to your New Drug Application (NDA) dated April 29, 2013, received April 30, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Umeclidinium Powder for Oral Inhalation, 62.5 mcg.

We also refer to your May 1, 2013, correspondence, received May 1, 2013, requesting review of your proposed proprietary name, (b) (4) Ellipta. We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary name "(b) (4) Ellipta" overstates the efficacy of the product. "(b) (4) easily evokes the word, (b) (4)

Patients with COPD have difficulty effectively exchanging oxygen and CO2, and often engage in a forced expiratory process to facilitate air movement through the lungs. Given that this product is indicated as maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema, the proposed proprietary name implies this product will always (b) (4) or (b) (4) all of the patient's airways to improve airflow obstruction in the lung and allow patients with COPD to breathe easily throughout the day. Without substantial evidence to support such a treatment response, the proposed proprietary name is misleading.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names,*
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Angela Ramsey, at (301) 796-2284.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
06/11/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205382

NDA ACKNOWLEDGMENT

GlaxoSmithKline
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Vicki Gunto, Ph.D.,
Director, Global Regulatory Affairs

Dear Dr. Gunto:

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

Name of Drug Product: umeclidinium bromide inhalation powder

Date of Application: April 29, 20113

Date of Receipt: April 30, 2013

Our Reference Number: NDA 205382

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 June 29, 2013, 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.
If you have any questions, call Angela Ramsey, Senior Program Management Officer, at (301) 796-2284.

Sincerely,

{See appended electronic signature page}

Angela Ramsey R.N., M.S.N.
Senior Program Management Officer
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/

ANGELA H RAMSEY
05/13/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106616

MEETING MINUTES

GlaxoSmithKline
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Attention: Mary Sides
Director

Dear Ms. Sides:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK573719/GW642444.

We also refer to the meeting between representatives of your firm and the FDA on January 18, 2012. The purpose of the meeting was to discuss the progress of the Phase 3 program and discuss the content and format of the non-clinical pharmacology/toxicology, clinical pharmacology, and the clinical efficacy and safety of the planned NDA for COPD.

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 me at (301) 796-4006.

Sincerely,

{See appended electronic signature page}

Eunice Chung-Davies, Pharm.D.
Sr. Regulatory Management Officer
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:	Pre-NDA
Meeting Date and Time:	January 18, 2012; 3:00 P.M. to 4:30 P.M.
Meeting Location:	White Oak Campus Bldg 22 Room 1311
Application Number:	IND 106616
Product Name:	GSK573719/GW642444 (vilanterol)
Indication:	COPD
Sponsor/Applicant Name:	GSK
Meeting Chair:	Badrul Chowdhury, M.D., Ph.D.
Meeting Recorder:	Eunice Chung-Davies, Pharm.D.

FDA ATTENDEES

Badrul Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Jennifer R. Pippins, M.D., MPH., Clinical Reviewer, DPARP
Susan Limb, M.D., Clinical Team Leader, DPARP
Timothy Robison, Ph.D., Nonclinical Team Leader, DPARP
Feng Zhou, M.S., Statistics Reviewer, Division of Biometrics II
Joan Buenconsejo, Ph.D., Acting Statistics Team Leader, Division of Biometrics II
Arun Agrawal, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II
Suresh Doddapaneni, Ph.D., Deputy Director, Division of Clinical Pharmacology II
Teresa McMillan, Pharm.D., Safety Evaluator, Division of Medication Errors Prevention and Analysis
Zachary Oleszcuk, Pharm.D., Safety Team Leader, Division of Medication Errors Prevention and Analysis
Eunice Chung-Davies, Pharm.D., Sr. Regulatory Management Officer, DPARP

SPONSOR ATTENDEES

Darrell Baker, Senior Vice President, Respiratory Medicine Development Center
Jean Brooks, Manager, Respiratory Medicine Development Center Statistics
Sally Bruce, Director, Global Regulatory Affairs
Susan Fayinka, Director, Medicines and Process Delivery
Mauri Fitzgerald, Vice President, Global Regulatory Affairs
Alison Hofmann, MD, Director, Respiratory Medicine Development Center

C. Elaine Jones, Ph.D., Vice President, Medicine Development Leader
Mary Sides, Director, Global Regulatory Affairs

1. BACKGROUND

Ms. Mary Sides of GlaxoSmithKline requested a type B PreNDA meeting with the Division of Pulmonary, Allergy, and Rheumatology Products to discuss the progress of their Phase III program and discuss the content and format of the nonclinical pharmacology/toxicology, clinical pharmacology, and clinical efficacy and safety of the planned NDA for COPD. The meeting was granted on August 10, 2011. Preliminary comments (*in italics*) to GSK's December 12, 2011, briefing package questions (***in bold italics***) were sent to the GSK on January 12, 2012. Any discussion from the January 18, 2012, face to face meeting are in normal font below.

2. DISCUSSION

Introductory Comment:

- *We remind you of the discussion that took place at the EOP2 meeting held on October 29, 2010, at which time we commented on the absence of a clear dose-response based on the phase 2b data, and recommended the evaluation of lower doses, and we note your decision to carry forward two doses of the GSK573719/VI combination (62.5/25 mcg and 125/25 mcg) in the phase 3 program. Without the results of these trials, which are currently ongoing, we are unable to confirm that the appropriate dose and dosing interval have been selected.*
- *The clinical development program for GSK573719/VI must include a full characterization of both of the monotherapy components, including replicate evidence of the efficacy of each of the monotherapies. In addition, substantial evidence of the efficacy and safety of GSK573719/VI as compared to each of the monotherapy components must be provided. Typically, this evidence would come from replicate trials with statistically significant, positive results.*
- *We have concerns regarding your plan to submit the NDA for the GSK573719/VI combination product prior to that for the GSK571319. Typically, the submission of a New Drug Application for a combination product NDA follows the full development of the monotherapies comprising the combination. As we expect that GSK571319 will have been fully characterized for the purposes of the combination program, we recommend that you submit the NDA for GSK571319 first. We also note that the appropriateness of marketing a combination product without component monotherapies available will be a review issue. A relevant patient population for the proposed combination product must be identified.*
- *We recommend that you provide justification for the choice of a placebo-control design in planned studies in the NDA submission.*

Discussion:

The sponsor wished to clarify the Agency's rationale behind the comment, "the appropriateness of the marketing of a combination product without the component monotherapies will be a review issue." FDA stated that this will not be a filing issue. However, whether it is an approval issue will depend on the data. Generally, combination products are intended for patients who do not achieve sufficient benefit from a single

ingredient product. If the single ingredient product is not available, then the intended target population is not immediately apparent.

The sponsor stated that they anticipate that their combination product will be used in the moderate to severe COPD population. They anticipate that trials will demonstrate that use of the combination product in this population results in substantial improvement of airflow that is superior to that obtained with the single ingredient product.

FDA commented that there may be a patient population for whom treatment with the long-acting muscarinic antagonist (LAMA) alone would be suitable. The sponsor stated that they intend to market the LAMA monocomponent. While the LAMA monocomponent may be appropriate for patients with milder COPD, the sponsor anticipates its use primarily as an add-on therapy to existing therapeutics, such as inhaled corticosteroid (ICS)/long-acting beta-agonist (LABA) combination products.

FDA noted the current availability of tiotropium as a LAMA monotherapy. If the clinical program were to provide substantial evidence of benefit for the GSK571319/vilanterol combination over an existing LAMA monotherapy like tiotropium, those results would be useful for identifying an appropriate patient population for the combination. GSK agreed to providing a rationale for the target patient population in the NDA application for FDA's review.

CMC Question from Cover Letter

GSK will request a CMC specific pre-NDA meeting in mid-2012 to discuss CMC aspects of the NDA. GSK would appreciate earlier feedback on a general CMC content question to initiate document preparation as soon as possible. As the Division are aware, two product strengths are currently being studied in Phase 3 clinical trials and the product strength of the to be marketed product has yet to be determined. Therefore, GSK proposes to include full CMC information covering both product strengths in the NDA as these data have contributed significantly to the development and scientific understanding of the product. Does the Agency agree with this approach?

Division Response:

The NDA should include all information for the drug product strength(s)/formulation(s) proposed for marketing. Other strengths/formulations used for clinical studies should be adequately described along with appropriate data, in the P2 (pharmaceutical development) section of the NDA. Provide a table to correlate the relevant information (e.g., strength, batch number, clinical trial number, etc.) for all batches of drug product used in clinical studies.

No discussion occurred.

Section 5: Regulatory

1. ***Does the Division agree with the proposal for submission of the NDA and 120-Day Safety Update for completed and ongoing studies with GSK573719/VI, including***

provision of relevant data with fluticasone furoate/VI Inhalation Powder or VI Inhalation Powder as a monotherapy for (b) (4) COPD to obtain a first-cycle approval (described in Section 5)?

Division Response:

Adequate safety data to support the application is expected at the time of NDA filing. While the proposed content of the NDA submission and 120-day safety update appear reasonable, we note that we will not be able to conduct a substantive review of information submitted at the 120-day safety update; as a result, this additional data has limited capacity to support a regulatory action.

No discussion occurred.

Section 6: Clinical Pharmacology and Biopharmaceutics

2. ***Clinical pharmacology studies examining the bronchodilator properties of GSK573719 and VI in subjects with COPD will be summarised in m.2.7.2. Other pharmacological effects unrelated to efficacy (including heart rate, blood pressure, QTc interval, plasma glucose, and blood potassium) will be discussed in section m.2.7.4. Is this acceptable to the Division?***

Division Response:

Your proposal appears reasonable.

No discussion occurred.

3. ***Does the Division agree that, if the results of study AC4115487 (see Section 3.2.1) provide sufficient evidence that the small pharmacodynamic effect observed between (b) (4) the two-strip configurations of the 62.5mcg and 125mcg GSK573719 monotherapy products is of minimal clinical significance and dose ranging data from the phase IIb studies (AC4113073, AC4113589 and AC4115321) are supportive of the intended marketed dose, that no additional studies are required (b) (4) ?***

Division Response:

As noted previously in the EOP2 meeting, the (b) (4) of GSK573719 when (b) (4) vs. a double-strip device fell in the range of (b) (4)%, which is considered substantial from a CMC perspective and clouds the interpretability of results from the factorial-design trials. We recommended reformulating the monocomparators to be used in the factorial-design trials (b) (4) providing data demonstrating that there is no relevant clinical difference. If you believe that results from study AC4115487 provide that data, submit those data in the NDA. The adequacy of the data will depend on how these data fit into the overall clinical program. For example, data from AC4115487 may be sufficient to bridge between the dose-ranging trials conducted with the double-strip device and the GSK573719 (b) (4) device intended for marketing. On the

other hand, providing sufficient justification for use of (b) (4) *device in the pivotal factorial design poses a higher hurdle.*

Discussion:

FDA asked for clarification of the formulation of the monotherapies used in the pivotal trials, namely, whether or not the monotherapies were (b) (4) double-strip devices. The sponsor replied that they were (b) (4). FDA stated that this may be problematic with regards to the interpretation of data from the factorial-design clinical trials, noting that it is critical that the combination product provide the same amount of drug product as the monotherapies. FDA noted that the difference in (b) (4) for GSK571319 exceeded the upper limit of (b) (4) that previously has been considered to be an acceptable magnitude of difference.

The sponsor stated that their single dose study shows no clinical difference so they believe that their magnitude of difference is potentially reasonable despite the fact that it is outside the Agency's upper limit of (b) (4). The sponsor stated that their clinical program was based on FDA's prior advice against the use of unnecessary excipients in the monoproducts as well as FDA's recommendation for a single, PK bridging trial. Given that the (b) (4) is higher for the monotherapy, the sponsor also noted that difference is to their disadvantage for the purposes of demonstrating superiority of the combination over the monotherapies.

FDA acknowledged that the Agency's current position is a departure from advice previously given. The change in position stems from an effort to maintain consistency across other development programs which have encountered similar issues. FDA requested that the sponsor provide justification for the use (b) (4) device in the factorial design trials in the NDA application. The acceptability of the justification will be a review issue.

4. ***Does the Division agree that the results of the ADME study (AC4112014, described in Section 3.2.2.1) support GSK's proposal to conduct hepatic and renal impairment studies and that product labeling with respect to hepatic and renal impairment will be commensurate with those findings?***

Division Response:

You are proposing to submit (a) PK results of GSK573719 Inhalation Powder, GSK573719/VI Inhalation Powder, and fluticasone furoate/VI in subjects with severe renal impairment and (b) in subjects with moderate hepatic impairment for GSK573719 Inhalation Powder and GSK573719/VI Inhalation Powder and in subjects with mild, moderate, and severe hepatic impairment for fluticasone furoate/VI. You will assume no PK interaction between VI and fluticasone for VI PK conclusions. Further, due to technical difficulties, you are proposing to assess in vitro protein binding of GSK573719 and VI from sourced donors with severe renal impairment in a separate assessment and not assess protein binding of VI in moderate hepatic impairment subjects. Although, it is possible that you may be able to come up with appropriate labeling in renal and hepatic impairment subjects, in light of the several variables involved in this approach and with no data in hand at this time, we are unable to agree.

5. ***Where necessary to more completely describe the clinical pharmacology of VI, data may be used from early phase clinical pharmacology studies in healthy volunteers, COPD patients and asthma patients, using a variety of VI formulations and devices and from studies with fluticasone furoate /VI studies in which only fluticasone furoate /VI treatment arms were tested to describe the pharmacological effects of VI unrelated to efficacy, including heart rate, blood pressure, QTc interval, plasma glucose, and blood potassium. Use of data from these early VI studies and studies with fluticasone/VI studies will be specifically noted in m2.7.2. All clinical pharmacology studies containing VI will be included in m5. Is this acceptable to the Division?***

   Division Response:

   Yes. However, since you are proposing to use data from early studies that used a variety of VI formulations and devices and from studies with fluticasone furoate/VI treatment arms, we recommend that you provide clear explanation in the NDA as to how data from each of these studies is pertinent to the final product.

   No discussion occurred.

Section 7: Summary of Clinical Efficacy

6. ***Does the Division agree with GSK's plans for the integration / pooling of the efficacy data including study grouping, subgroups, and country groupings and studies to be used to support dose and dosing interval justification for GSK573719 and VI which are to be discussed in the Integrated Summary of Efficacy and 2.7.3?***

   Division Response:
   Yes, we agree.

   No discussion occurred.

7. ***Specific to the integration of patient level efficacy data, GSK plans to integrate efficacy data from the four primary efficacy studies conducted for GSK573719/VI Inhalation Powder (DB2113361/ DB2113373 and DB2113360/DB2113374) and not to integrate efficacy data from other studies conducted as part of the GSK573719/VI Inhalation Powder, GSK573719 Inhalation Powder, and fluticasone furoate/VI Inhalation Powder (i.e. data from VI arms) development programs as described in Section 3.1 and Section 7. Does the Division agree with this approach?***

   Division Response:
   While the presentation of pooled efficacy results is at your discretion, we will rely primarily on the efficacy results from the individual trials to support a regulatory action.

   No discussion occurred.

Section 8: Summary of Clinical Safety

8. ***Does the Division agree with GSK's plans for the integration / pooling of the safety data including study grouping, subgroups and country groupings, as discussed in Section 3.1 and Section 8?***

   Division Response:
   Yes, we agree.

   No discussion occurred.

9. ***GSK intends to provide subject level integration for summaries of overall AEs, SAEs, Fatal AEs (deaths), AEs Leading to Withdrawal, Most Frequent AEs and AEs of Special Interest from 13 studies conducted for GSK573719/VI Inhalation Powder, GSK573719 Inhalation Powder, and fluticasone furoate/VI Inhalation Powder that were at least 4 weeks in duration and included a treatment arm for GSK573719/VI Inhalation Powder, GSK573719 Inhalation Powder, and/or VI Inhalation Powder as described in Section 3.1 and Section 8. Does the Division agree with the proposed approach?***

   Division Response:
   Yes, we agree.

   No discussion occurred.

10. ***GSK intends to limit subject level integration of shifts for clinical laboratory tests, ECG and vital sign measurements to five Phase III studies for GSK573719/VI Inhalation Powder (DB2113361, DB2113373, DB2113360, DB2113374, and DB2113359) as described in Section 3.1 and Section 8. Subject level integration of AEs will also be done for these studies. Does the Division agree with the proposed approach?***

    Division Response:
    Yes, we agree.

    No discussion occurred.

11. ***GSK intends to limit subgroup analyses of AEs to five Phase III studies for GSK573719/VI Inhalation Powder (DB2113361, DB2113373, DB2113360, DB2113374, and DB2113359) as described in Section 8. Does the Division agree with the proposed approach?***

    Division Response:
    Yes, we agree.

    No discussion occurred.

12. ***GSK does not intend to describe safety data collected with VI Inhalation Powder in subjects with asthma, obtained as part of the fluticasone furoate/VI Inhalation Powder program. Does the Division agree with the proposed approach?***

Division Response:
No, we do not agree. Include a high-level summary of the safety findings from the asthma program, including deaths, non-fatal SAEs, AEs leading to discontinuation, and common AEs.

Discussion:
The sponsor stated that they would include a summary of the safety of vilanterol in asthma within the Integrated Summary of Safety (ISS), including data on deaths, nonfatal SAEs, AEs, etc., but that they were not planning to include individual study reports. FDA responded that this appears to be reasonable.

13. ***Does the Division agree with the proposed list of adverse events of special interest as described in Section 8?***

Division Response:

In addition to the events you have listed, include an evaluation of the following: pneumonia, events consistent with anticholinergic syndrome (in addition to urinary retention), and intestinal obstruction.

Discussion:
The sponsor stated that they will add pneumonia and intestinal obstruction as FDA suggested. However, the sponsor wished to obtain clarification regarding the inclusion of events consistent with anticholinergic syndrome. FDA responded that we are interested in all anticholinergic symptoms (e.g., dry mouth, constipation, blurry vision, palpitations, tachycardia), and referred the sponsor to the descriptions included in the labels of other products. The sponsor asked whether FDA is also interested in somnolence for LAMAs. FDA responded affirmatively.

14. ***GSK is proposing not to integrate AE data from GSK573719/VI, GSK573719, and relevant fluticasone furoate/VI clinical pharmacology studies with the later phase studies. Where appropriate, AEs from special population, electrocardiographic, and drug-drug interaction clinical pharmacology studies will be summarized in the relevant sections of the ISS. Listings of AEs of special interest and SAEs from all the clinical pharmacology studies will be provided in the NDA submission. Does the Division agree with this proposed approach?***

Division Response:
Yes, we agree.

No discussion occurred.

15. ***GSK intends to include AE reports from the literature as part of the ISS and Summary of Clinical Safety. Does the Division agree that this reporting should be limited to nonclinical data and to orally inhaled long-acting muscarinic antagonist and long-acting beta-agonist clinical data in COPD?***

Division Response:
Provide clarification regarding your plans to submit AE reports from the literature. You propose inclusion of nonclinical data, which is typically not included in the ISS and Summary of Clinical Safety.

No discussion occurred.

16. ***GSK are proposing to provide narratives for all deaths and non-fatal SAEs and for subjects withdrawn from treatment due to an AE for all completed studies. For ongoing studies at the time of submission narratives would not be provided. Does the Division agree with the proposal for provision of narratives in this NDA?***

Division Response:
No, we do not agree. In addition to what you propose, also provide narratives for all deaths and non-fatal SAEs for ongoing studies.

No discussion occurred.

17. ***Some of the planned IIIb studies for GSK573719/VI Inhalation Powder and fluticasone furoate/VI Inhalation Powder (that include a VI alone treatment arm) will be ongoing at the time of the submission of the NDA for GSK573719/VI Inhalation Powder. GSK proposes to include synopses, but not to include data from these ongoing studies in the NDA. Any data for ongoing studies of fluticasone furoate/VI Inhalation Powder (that include a VI alone treatment arm) will be by cross-referenced to the relevant INDs (077855 and 074696). Does the Division agree with this approach?***

Division Response:
Yes, we agree.

No discussion occurred.

18. ***Does the Division agree with GSK's plan for adjudication of SAEs from the Phase IIIa studies conducted for GSK573719/VI Inhalation Powder as described in Section 8?***

Division Response:
In general, we agree. The events chosen for adjudication should be both important and relevant to a LAMA and/or LABA. We recommend you refer to the adjudications conducted previously for other LAMA and LABA COPD products, the details of which are available in the public domain.

Discussion:
The sponsor stated that they plan to adjudicate for deaths, hospitalizations, and intubations and asked whether that would be appropriate. FDA responded affirmatively and added that

an analysis of major adverse cardiac events (MACE) and respiratory-related adverse events such as those conducted in other COPD programs would also be appropriate.

19. ***Does the Division agree that the size of the safety database for GSK573719/VI Inhalation Powder as described in Section 4 will provide an adequate safety database to support the NDA for GSK573719/VI Inhalation Powder?***

Division Response:
While the size of the safety database ultimately depends on the nature of the safety data observed, the current proposal appears to be reasonable.

No discussion occurred.

Section 9: Statistics

20. ***GSK submitted the Summary Document Analysis Plans (SDAP) for the ISE and ISS for Division comment in November 2011. Does the Division agree with the proposed statistical methodology as outlined in the SDAPs and the associated briefing document?***

Division Response:
Yes, we agree. In addition, add the annual rate of exacerbation in "Other endpoints" for the integrated analyses (section 3.2 in SDAP for the ISE).

Discussion:

The sponsor stated that with regard to the annual rates, the majority of their patients withdraw due to exacerbations. However, they do allow for them to stay for the safety analyses. The sponsor asked if they could keep to their original plan to evaluate time to first exacerbation. FDA responded affirmatively.

21. ***Subjects who had previously received GSK573719, VI, GSK573719/VI or fluticasone furoate/VI were not allowed to participate in the phase III program for GSK573719/VI, except for the exercise studies DB2114417 and DB2114418 of cross-over design. The number of subjects participating in more than one study is expected to be small, and may be counted twice in these integrated summaries. Does the Division agree with this approach?***

Division Response:
Yes, we agree. Include a variable (flag) to indicate these patients in the pooled and individual study datasets. Of note, we generally use the results from the individual studies to support any claims in the label. Pooled analyses are not usually very helpful in this regard with the exception of required analyses by subpopulation, like age, sex and race; etc.

No discussion occurred.

Section 11: Non-Clinical Development

22. ***A comprehensive package of nonclinical studies on GSK573719 and GW642444 (as individual NCE's) in accordance with the ICH M3 (R) Guidelines will be available at the time of file. In addition, combination toxicology studies on GSK573719/GW642444 up to one months' duration (rat and dog) and up to 3 months' duration in one species (dog) have been completed. Does the Division agree that no further nonclinical studies are required to support the registration of GSK573719/GW642444 Inhalation Powder?***

Division Response:
We agree that no further nonclinical studies are required to support the registration of GSK573719/GW642444 Inhalation Powder.

For the NDA, provide structures of impurities and intermediates of the drug substance and drug product. Refer to the ICH Guidance for qualification of drug impurities in drug substances [ICH Q3A(R2)] and degradants in drug products [ICH Q3B(R2)]. If applicable, conduct the appropriate toxicity studies to qualify impurities and degradants. Impurities or intermediates that are identified as structural alerts should be at or below acceptable qualification thresholds for genotoxic and carcinogenic impurities as described in the draft FDA Guidance for Industry, "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches" (December 2008) for assessment of impurities to support clinical studies for an IND and NDA.

No discussion occurred.

23. ***Future clinical studies are planned to*** (b) (4)

(b) (4)

Division Response:

(b) (4)

No discussion occurred.

Section 13: Labeling

24. ***GSK intend to describe the Phase IIb dose ranging data for GSK573719 and VI in the Clinical Trials section of the application along with data from the Phase III development program. This includes discussion of the Phase III studies which include a tiotropium arm as these studies are pivotal to the approval of the application (Studies DB2113360 and DB2113374). Does the Division have any comment on the inclusion of the dose-ranging data for GSK573719 and VI and relevant comparator data for tiotropium?***

Division Response:
While it is premature to comment on labeling at this time, we find your proposal to include dose-ranging data in the Clinical Trials section to be reasonable in principle. We note, however, that information regarding an active comparator is typically not included in a product label unless necessary to support the proposed use in the intended patient population. Provide adequate justification in the NDA if you choose to include comparator data for tiotropium in the proposed product label.

No discussion occurred.

25. ***GSK propose to include in the Clinical Trials section a discussion of the results from the primary and secondary endpoints, as well as selected "Other" endpoints such as supplemental*** (b) (4) ***provided statistical significance is achieved. Does the Division have any comment the inclusion of this data?***

Division Response:
It is premature to comment on labeling at this time. Propose the inclusion of information you assess to be necessary to adequately inform the user.

No discussion occurred.

26. ***GSK intend to submit the proposed proprietary name in 1Q 2012. Does the Division have any preliminary comments on the proposed process for review of proprietary names according to the February 2010 guidance for evaluation of proprietary names and when would feedback be expected?***

Division Response:

Submit the proposed name in accordance with Guidance on Complete Submission. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf *For an*

IND, the expected completion date is 180 days from the date of complete submission. If the proposed proprietary name is submitted under the NDA, the expected completion date is 90 days from the date of complete submission.

The proposed proprietary name will also be reviewed 90 days prior to the expected date of approval of the NDA.

We recommend submitting your name as early as possible in the IND phase once your dose has been established.

No discussion occurred.

Section 13: Risk Evaluation and Mitigation Strategy

27. ***Does the Division agree with the proposal to submit a proposed risk evaluation and mitigation strategy (REMS) that is in-line with the current REMS requirements for LABA containing COPD medications?***

Division Response:
It is premature to comment on REMS at this time, prior to an evaluation of the safety profile of the product.

No discussion occurred.

Section 16: GSK573719 Monotherapy

28. ***GSK is planning to submit the NDA for GSK573719 Inhalation Powder subsequent to the GSK573719/VI Inhalation Powder NDA submission. GSK intends to include in the GSK573719 Inhalation Powder NDA data from replicate studies evaluating the efficacy and safety of the addition of (b) (4) in patients with COPD to obtain information for health care professionals should the products be used together. A description of these studies is provided in Section 15 and Appendix 8. Does the Division agree that the conduct of replicate clinical trials evaluating the safety and efficacy (b) (4) alone will support inclusion of data from these studies in the Clinical Trials section of the prescribing information for GSK573719 Inhalation Powder?***

Division Response:
Refer to the Introductory Comment regarding the sequence of NDA submission. Regarding the inclusion of data from trials comparing (b) (4), we believe that such information falls under the practice of medicine and inclusion of data in the label is unlikely to be warranted.

Discussion:

(b) (4)

FDA stated that the Agency will be reluctant to place this type of information in the product label, as the decision to put a (b) (4) falls under the practice of medicine. Trials evaluating (b) (4) may be more appropriate for publication in the medical literature.

The sponsor asked whether there is any way to obtain feedback on the robustness of the proposed trials, as these trials may be used to support promotional materials. FDA responded that the sponsor may submit the protocols for comment. The sponsor also asked if FDA's position would be different if (b) (4) to which FDA replied in the negative.

ADDITIONAL COMMENTS:

1. *Provide all raw data sets, as well as analysis data sets (including all efficacy and safety variables) used to generate the results presented in your study reports. In addition, provide a data definition file (in pdf format or xml format) that includes information on how efficacy variables are derived.*

2. *Include all SAS programs used for creating analysis dataset from submitted raw datasets and all SAS programs used for efficacy and main safety analyses. In addition, provide a document that explains what each SAS programs are used for.*

3. *Provide all analysis data sets and SAS programs used to generate the results in the ISE and ISS reports.*

For more information, refer to
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

3.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

N/A

5.0 ACTION ITEMS

N/A

6.0 ATTACHMENTS AND HANDOUTS

N/A

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

/s/

EUNICE H CHUNG-DAVIES
02/03/2012

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	October 29, 2010; 3-4:30 P.M. E.S.T.
Meeting Location:	White Oak Bldg 22 Room 1309
Application Number:	IND 106,616
Product Name:	GSK573719/GW642444 Inhalation Powder
Received Briefing Package	September 24, 2010
Sponsor Name:	GlaxoSmithKline
Meeting Requestor:	Mary Sides
Meeting Chair:	Badrul A. Chowdhury
Meeting Recorder:	Eunice Chung-Davies

Meeting Attendees:

FDA Attendees

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Susan Limb, M.D., Clinical Team Leader, DPARP

Jennifer R. Pippins, M.D., M.P.H., Clinical Reviewer, DPARP

Molly Topper, Ph.D., Nonclinical Supervisor, DPARP

Tim Robison, Ph.D., Nonclinical Reviewer, DPARP

Joan Buenconsejo, Ph.D., Acting Statistics Team Leader, Division of Biometrics II

Feng Zhou, Ph.D., Statistics Reviewer, Division of Biometrics II

Yun Xu, Ph.D., Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II

Arun Agrawal, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II

Sofia Chaudhry, M.D., Clinical Review, DPARP

Antoine El Hage, Ph.D., Clinical Reviewer, DSI

Eunice Chung-Davies, Pharm.D., Senior Regulatory Management Officer, DPARP

Sponsor Attendees

Darrell Baker, Vice President, Medicine Development Center Head

Jean Brooks, MSc., Associate Director, Biostatistics

Glenn Crater, M.D., Director, Clinical Development

Susan Fayinka, Director, Pharmaceutical Development

Mauri Fitzgerald, Vice President, Global Regulatory Affairs

C. Elaine Jones, Ph.D., Medicine Development Leader, Clinical Development

Chris Kalberg, Ph.D., Director, Clinical Development

Dennis Kelleher, Ph.D., Manager, Clinical Pharmacology, Clinical Development

Mary Sides, Associate Director, Global Regulatory Affairs

Gill Stemp, Manager, Safety Assessment Europe

Andrea Terron, Director, Safety Assessment Europe

1.0 BACKGROUND

Ms. Mary Sides of GSK requested an EOP2 meeting to discuss the nonclinical, clinical and statistical aspects of the Phase III program for GSK573719 Inhalation Powder as a monotherapy and GSK573719/GW642444 Inhalation Powder as a combination for the long-term maintenance of treatment of airflow obstruction and the relief of dyspnea with daily activities, associated with COPD. FDA provided responses (italics) to the sponsor's questions (bold italics) in the briefing package, dated September 24, 2010, on October 27, 2010. Discussion that took place at the October 29, 2010, face-to-face meeting, is in normal font.

2.0 QUESTIONS AND RESPONSES AND DISCUSSION

Nonclinical

Question 9.1.1.

A list of completed, ongoing or proposed non-clinical studies for the individual components, GSK573719 and GW642444, alone and in combination is provided in attachment 2. Are the data from the non-clinical toxicology studies adequate to support initiation of the proposed Phase III clinical trials with the combination product and subsequent registration of the combination product?

FDA Response:

The data appears to be inadequate at this time with specific reference to the histopathological examinations of organs and tissues in the 13-week toxicology study with the combination of GSK573719 and GW642444 in dogs.

This study was intended to determine if the observed toxic effects observed with the combination of GSK573719 + GW642444 are consistent with toxic effects observed with monoproducts alone (i.e., there is no evidence of additive or synergistic toxic effects). Further, the study should attempt to identify a NOAEL.

Several findings were identified at increased incidences in the lungs, larynx, and trachea from dogs that received the combination of GSK573719 + GW642444 at a dose of 177/183 µg/kg/day (Group 5); however, lower dose groups were not examined in order to determine if a NOAEL could be identified. Further, it is noted that pre-adaptation or tolerance phase was used for Group 5, which might have potentially protected animals from subsequent exposure to higher doses. Groups 3 and 4 need to be examined to ensure that there were no additional findings due to the use of a tolerance phase for Group 5.

Organ/Tissue	Finding

Lung	perivascular/peribronchial/subpleural inflammatory cell infiltrate, G1
Lung	aggregates of alveolar macrophages
Larynx	mucosa: mixed inflammatory cell infiltrate, G1-G2
Trachea	mucosa: mixed inflammatory cell infiltrate, G1

Organs and tissues from dogs that received monoproducts (GSK573719 or GW642444 alone) were, in general, not submitted to the histopathological examination. This makes the direct comparison of findings with the combination product and monoproducts difficult or essentially impossible. The only potential comparisons are to rely on findings from other toxicology studies with monoproducts alone; however, these studies were conducted under differing experimental conditions and doses. This renders the comparisons inexact and inadequate.

Provide histopathological examinations of all tissues for combination groups that received 23/29 and 60/72 µg/kg/day (Groups 3 and 4). The control group (Group 1) needs to be reexamined by the pathologist along with drug treatment groups in order to have a valid comparison. Tissues, in which findings were identified for Groups 3, 4, or 5, should also be examined for monoproducts groups (Groups 6 and 7).

Question 9.1.2.

Inhaled combination toxicity studies with GSK573719 and GW642444 of up to 28 days duration in the rat and dog and up to 13 weeks duration in the dog have been completed. A further 28-day toxicity in the dog is ongoing and data will be available prior to the start of the Phase III trials. Does the Agency agree that, based on results of these combination studies, that no further nonclinical studies on the combination are required to support Phase III or registration?

FDA Response:

We cannot provide a definitive response to this question at this time. The need for any additional nonclinical studies will be assessed following review of the histopathology data for the 13-week combination toxicology study in dogs requested in Question 9.1.1 and the 28-day combination study in dogs to determine the effect of a pre-adaptation phase.

Question 9.1.3.

Interstitial, bronchoalveolar and granulomatous inflammation in the lung were observed at all doses in the dog 28-day study. Due to the histopathological appearance of the lesions, it was considered likely that this lung pathology was a result of accidental inhalation and deposition of exogenous material in the lung. This hypothesis has been further substantiated in subsequent studies in the dog with

GSK573719 alone or in combination with GW642444. Does the Division agree that the induction of granulomas in the dog has been adequately explained and resolved?

FDA Response:

We agree that the induction of granulomas in the dog has been adequately explained and resolved.

Question 9.1.4.

GSK have conducted 28-day and 13-week dog combination toxicology studies evaluating GSK573719/GW642444 in combination at various dose levels. A subsequent 28-day dog combination study is ongoing to assess the effect of a pre-adaptation phase used in the previous dog combination studies on cardiovascular function/parameters; the study report will be submitted within 30 days of initiating the long-term safety study (i.e. mid Nov 2010). Given that for the proposed Phase III clinical dose (125mcg), adequate safety margins already exists from a non-pre-adapted dose in the 13 week combination study at the 1:1 ratio, GSK believe it is safe to proceed with combination clinical studies longer than 12 weeks duration. Does the Division agree?

FDA Response:

We cannot provide a definitive response to this question at this time. The adequacy of nonclinical support for combination clinical studies longer than 12 weeks duration will be assessed following review of the histopathology data for the 13-week combination toxicology study in dogs requested in Question 9.1.1 and the 28-day combination study in dogs to determine the effect of a pre-adaptation phase.

The proposed clinical doses of GSK573719 and GW642444 in the combination product need to be adequately supported by NOAELs identified in the 6-month rat and 9-month dog toxicology studies with the individual monoproducts as well as the 13-week combination toxicology study in the dog. A NOAEL for the 13-week combination toxicity study has not yet been established.

Discussion:

The Sponsor expressed their thinking that the nonclinical information in their briefing package was comprehensive enough to start Phase 3 studies in humans. They noted that histopathological findings in the 3 month combination study were consistent with findings for each of the monoproducts alone and there was no evidence for any additive or synergistic effect with the combination. Further, the observed findings were not considered adverse. Thus, they did not believe that there was any need to examine additional groups in the combination study. FDA responded that we have expressed numerous concerns regarding the use of a pre-adaptation or tolerance phase for Group 5 as this might lead to protective effects for various tissues and mask any potential toxic effects of the combination. The primary concern was for the heart; however, protective effects for other tissues could not be excluded. FDA further stated that the sponsor should

have examined Groups 3 and 4 to ensure the pre-adaptation or tolerance phase used for Group 5 did not mask any potential toxic effects of the combination. The 28-day dog study was designed to assess the effects of the pre-adaptation phase with specific reference to the heart. It might provide supportive data for the use of Group 5 from the 3-month combination study; however, it does not alleviate the need to examine all tissues from Groups 3 and 4. The data from the 28-day study is unknown at this time.

The sponsor agreed to examine all the tissues for Groups 3 and 4 in the 13 week combination study with dogs. As stated in the response to Question 9.1.l., tissues in which findings were identified for Groups 3, 4, or 5, should also be examined for monoproducts groups (Groups 6 and 7). The FDA agreed. It was also confirmed that the 28-day dog study to assess the effects of pre-adaptation should be submitted prior to the human study protocol.

The sponsor inquired how long it would take for FDA to review the data if they submit the data by the end of November with the clinical trial. FDA discouraged the sponsor from submitting the clinical protocol without prior agreement that the nonclinical data are adequate. FDA stated that it could not pinpoint a time, however, the nonclinical reviewer will give it high priority and review the data as soon as it is submitted.

The sponsor stated that their intent is to start their study in humans as soon as possible after the animal data is complete. FDA acknowledged this.

Clinical Pharmacology

Question 9.2.1.

Does the Division agree that the clinical pharmacology program completed and ongoing to date when combined with the proposed studies to be conducted during Phase III will be adequate to describe the clinical pharmacology, potential for drug-drug interactions, and co-variant pharmacokinetics of GSK573719 Inhalation Powder and the combination product GSK573719/GW642444 Inhalation Powder?

FDA Response:

Yes, your program appears acceptable.

Discussion:

No discussion required

Question 9.2.2.

Does the Division agree that the results of the verapamil drug interaction study

DB2113950 adequately describes the low probability of a clinically significant drug-drug interaction between Pgp substrate inhibitors and GSK573719 such that no additional drug-interaction studies are required and the exclusion of strong Pgp inhibitors is not required in Phase III studies for GSK573719 Inhalation Powder and GSK573719/GW642444 Inhalation Powder?

FDA Response:

Yes, your rationale appears acceptable.

Discussion:

No discussion required

Question 9.2.3.

Does the Division agree the results of study AC4110106, a study of repeat inhaled doses of GSK573719 in a healthy population of cytochrome P450 2D6 poor metabolizers, adequately describe the low probability of a clinically significant drug-drug interaction with concomitant use of GSK573719 Inhalation Powder and 2D6 inhibitors and that no additional studies are required and the exclusion of 2D6 poor metabolizers is not required in Phase III studies for GSK573719 Inhalation Powder and GSK573719/GW642444 Inhalation Powder?

FDA Response:

Yes, your rationale appears acceptable.

Discussion:

No discussion required

Clinical

Question 9.3.1.

Does the Division agree that the completed Phase IIb studies for GSK573719 Inhalation Powder provide adequate data to demonstrate a once-daily dosing interval?

FDA Response:

No, we do not agree. Confirmation of the dosing interval should be preceded by adequate dose-ranging. See our response to Question 9.3.2.

Discussion:

The sponsor asked what the FDA is looking for with regard to the determination of nominal dose and dosing interval. FDA replied that, as stated in the response to Question 9.3.2, there seems to be no clear discrimination among doses in terms of trough FEV1. In the absence of a demonstrated dose response, it is difficult for FDA to draw conclusions about the appropriateness of the sponsor's proposed nominal dose and dosing interval.

Focusing on dosing interval, the sponsor commented that the 62.5 mcg twice daily dose did not perform better than the once daily dose, and added that anti-cholinergic products tend to have a flat dose response curve. FDA acknowledged that the information provided by the sponsor is supportive of a once daily dosing interval; however, in the absence of a demonstrated dose response, there is a concern that the once daily dosing interval may be the result of a nominal dose that is higher than necessary. The sponsor stated that the totality of the data demonstrates that 62.5 mcg is not as effective as 125 mcg.

FDA acknowledged that there are not many examples of anti-cholinergic products and that it is uncertain if a clear dose response curve can be demonstrated for this class of therapeutics. Nevertheless, what is certain is that at some dose, the product will not work. It remains important to obtain some sense of dose response in order to address whether the chosen dose is at the optimal portion of the dose response curve. FDA further stated that dose selection needs to be considered in the context of heightened concerns about anti-cholinergic safety; the safety of tiotropium is still an open question. If a safety issue is identified with the proposed 125 mcg dose, the Division will question whether lower doses may have had more acceptable safety profiles with similar efficacy. In addition, dose selection influenced by the goal of demonstrating superiority to another product, which is a goal that the sponsor may or may not have, can complicate matters. The sponsor stated that their dose selection is not based on a goal of demonstrating superiority to tiotropium, rather, the development program includes trials comparing the proposed product to tiotropium because of European regulatory requirements.

FDA summarized its view on a path forward: generation of a good FEV1 dose response curve in the patient population of interest. Demonstration of an ineffective dose would also aid in supporting the sponsor's choice of dose.

The sponsor expressed that the 62.5 dose data was characterized by a high degree of variability; FDA responded that trough FEV1 tends to be a variable measure, however, we would take into account the entire FEV1 curve in our review. FDA noted that exploring a nominal dose and dose frequency at the same time can be very difficult; it is preferable to explore nominal dose and dosing frequency in a sequential fashion (first nominal dose, then dosing frequency). The sponsor asked whether they could establish a nominal dose based on the results of a single dose study. FDA responded that this was a reasonable approach FDA suggested a cross-over study, using either ipratropium or tiotropium as a benchmark to assure assay sensitivity. Enrichment of the population for anti-cholinergic sensitivity may also assist in demonstration of a dose response. The sponsor referred to a single dose study that evaluated the 30 mcg, 60 mcg, and 125 mcg doses in COPD patients, stating that the lowest dose did not demonstrate efficacy, while the two higher doses did. The sponsor added that in a single dose, healthy, ipratropium-responsive volunteer study, no effect was observed at the 10 mcg or 20 mcg dosing

levels. FDA agreed that these were supportive data, but noted that these data would be more convincing in a COPD population, who can be quite sensitive to anti-cholinergic effects.

Question 9.3.2.

Does the Division agree that the 125mcg once-daily dose of GSK573719 Inhalation Powder is the optimal dose to evaluate individually and in combination with the LABA GW642444 Inhalation Powder in Phase III?

FDA Response:

No, we do not agree. The summary information provided indicates that no clear dose response was observed in terms of trough FEV1, the proposed primary efficacy variable for the pivotal phase 3 trials. We recommend exploration of lower doses. Assess the full time profile FEV_1 curve after dosing, rather than relying only on one time point at trough. Consider assessing the nominal dose first, then exploring the dosing frequency.

Discussion:

See discussion in 9.3.1.

Question 9.3.3.

Does the Division agree that the Phase I and IIa data for GSK573719 Inhalation Powder in combination with GW642444 Inhalation Powder provide an appropriate basis for progression to Phase III for GSK573719/GW642444 Inhalation Powder?

FDA Response:

From a clinical perspective, pending resolution of issues raised in response to your questions 9.3.1 and 9.3.2 above, the proposal appears reasonable. Also see the response to 9.1.1 regarding the adequacy of nonclinical data to support dosing in the Phase 3 trials.

Discussion:

See discussion in 9.3.1.

Question 9.3.4.

Does the Division agree that based on findings from clinical studies conducted to date for GSK573179 Inhalation Powder and GSK573719/GW642444 Inhalation Powder, no further assessment of the gall bladder is required in clinical trials other than standard adverse event monitoring?

FDA Response:

Yes, we agree.

Discussion:

No discussion required.

Question 9.3.5.

Does the Division agree that enrolment of women of childbearing potential who have a negative pregnancy test at screening and are using appropriate contraceptive methods is acceptable in the proposed Phase III studies?

FDA Response:

Yes, the proposed enrollment of women of childbearing potential who have a negative pregnancy test at screening and are using appropriate contraception is acceptable.

Discussion:

No discussion required.

Question 9.3.6.

Does the Division agree that conducting replicate 6-month pivotal studies evaluating GSK573719/GW642444 Inhalation Powder, GSK573719 Inhalation Powder, GW642444 Inhalation Powder, and placebo within each study:

a. are sufficient to fulfill the requirements of 21 CFR 300.50 for fixed-combination prescription drugs,

b. are sufficient to demonstrate the efficacy of the GSK573719 Inhalation Powder and GSK573719/GW642444 Inhalation Powder, and

c. support the proposed indication for both GSK573719 Inhalation Powder and GSK573719/GW642444 Inhalation Powder for the long-term maintenance treatment of airflow obstruction associated with COPD, including emphysema and chronic bronchitis?

FDA Response:

The general trial design of the proposed replicate 6-month trials appears reasonable. We note the choice of trough FEV1 as the primary endpoint. We ask that you justify the use of this endpoint in the NDA submission. While the choice of primary endpoint is at

your discretion, we remind you that the totality of the data will be examined during NDA review including post-dose serial FEV1 time curves and supportive non-spirometric parameters.

In addition, we have the following comments about the proposed Phase 3 program:

1) *As previously discussed during the June 8, 2010, meeting for the related ICS/LABA product (fluticasone furoate/vilanterol; IND 77,855), we remind you that dose selection for the LABA component of the combination should be supported by robust pharmacodynamic information in a bronchodilator-sensitive population.*
2) *The generalizability of the data to a broad COPD population, including both patients with emphysema and those with chronic bronchitis, will depend on the characteristics of the patient population enrolled.*

Discussion:

No discussion required.

Question 9.3.7.

Does the Division agree that the primary endpoint of trough FEV1 proposed for the replicate 6-month pivotal studies is adequate for evaluation of 1) the individual products and 2) the combination product to demonstrate that the individual products contribute to the efficacy of the combination product?

FDA Response:

See our response to Question 9.3.6.

Discussion:

No discussion required.

Question 9.3.8.

Does the Division agree that the size of the database, the length of patient exposure, and the proposed safety monitoring, including the extent of cardiovascular safety monitoring, will provide an adequate safety database to support the NDA for GSK573719/GW642444 Inhalation Powder and GSK573719 Inhalation Powder?

FDA Response:

While the proposed safety database appears reasonable at this time, the adequacy of the safety database will depend on the totality of the data. Additional information may be required depending on the nature of the safety findings observed during Phase 3.

Discussion:

No discussion required.

Question 9.3.9.

Does the Division agree that 1) subjects who participated in previous GW642444 studies are eligible to participate in any of the proposed Phase III studies for GSK573719/GW642444 Inhalation Powder and 2) subjects who participated in previous studies for GSK573719 Inhalation Powder are eligible to only participate in the Phase III studies comparing GSK573719/GW642444 Inhalation Powder and tiotropium?

FDA Response:

We prefer that you enroll treatment-naïve patients in your pivotal Phase 3 clinical trials.

Discussion:

No discussion required.

Question 9.3.10.

Does the Divison agree that the measures proposed to ensure a consistent standard of care across regions in the proposed global, multicenter Phase III studies are adequate to allow these data to support approval for the use of GSK573719/GW642444 Inhalation Powder and GSK573719 Inhalation Powder in a US population?

FDA Response:

The generalizability of the data generated by the Phase 3 trials, which draw only 30% of their total enrollment from North America, to the U.S. population will be a review issue. Ensure adequate representation of patients of African descent in your program.

Discussion:

The sponsor clarified that the study will draw approximately 20-25% of its population from America, and that this group will be representative of the United States population.

The sponsor stated that based on prior experience, the proportion of African Americans recruited is expected to be quite low (approximately 1-2%). This is despite efforts to improve the recruitment of African American patients in the U.S. One attempt to address this lack of diversity will be the recruitment of European patients of African descent. The

sponsor also stated that they will be recruiting South American and Asian patients. FDA stated that the issue of adequately diverse representation in clinical trials has been widely discussed in public forums, and that the Agency would be remiss to not continue bringing it to the attention of sponsors. Nevertheless, FDA stated that it understands the difficulties faced by the sponsor and that the proposed approach is reasonable.

Question 9.3.11.

Does the Division agree that a GW642444 arm is not required in the 12 month safety study DB2113359?

FDA Response:

Yes, we agree.

Discussion:

No discussion required.

Question 9.3.12.

Does the Division agree that the replicate 6-month studies comparing GSK573719/GW642444 Inhalation Powder to tiotropium via the HandiHaler are adequately designed, including the blinding strategy, (b) (4)

FDA Response:

A demonstration of superiority to an active comparator such as tiotropium is not a regulatory requirement and appears intended primarily for promotional purposes. Therefore, we have no comment on the proposed trial design. However, we caution you that the intention to demonstrate superiority to an active comparator may compromise the selection of an optimally safe dose.

Discussion:

No discussion required.

Question 9.3.13.

GSK plan to evaluate patient ease of use of the Novel DPI and the HandiHaler in the 6-month studies comparing GSK573719/GW642444 Inhalation Powder to tiotropium.

Does the Division agree that the proposed approach to evaluate patient ease of use (b) (4)

FDA Response:

We are unable to comment on the acceptability of the proposed approach based on the information provided. For advisory comments, we recommend that you submit the following information:

1) *The questionnaire to evaluate patient ease of use of the novel DPI compared to Handihaler*
2) *The study protocol which describes the target population and manner in which the questionnaire will be administered* (b) (4)

Discussion:

No discussion required.

Question 9.3.14.

Does the Division agree that the replicate exercise studies comparing GSK573719/GW642444 Inhalation Powder, GSK573719 Inhalation Powder, GW642444 Inhalation Powder, and placebo are adequately designed (b) (4)

FDA Response:

We note that exercise endurance is multi-factorial and influenced by many factors, including ones unrelated to COPD. As a result, it will be difficult to attribute changes in exercise endurance time solely to a beneficial effect of the proposed product on the lungs. Other factors which may confound exercise capacity, such as cardiovascular fitness, muscle tone, joint mobility, and balance, will need to be addressed.

Discussion:

The sponsor wished to obtain feedback on the choice of endurance shuttle test for the proposed trial, commenting that this assessment would be more useful in the evaluation of COPD patients and less artificial than a treadmill test or other exercise challenge models. FDA noted that while the shuttle test has some advantages, at the same time it is still dependent on patient motivation. FDA stated that our comments were not focused on the choice of instrument, but rather on the general challenges (b) (4)

FDA stated that it will be important to connect any effects of the proposed product on exercise to its bronchodilatory effect. Moreover, given that this is new territory, the topic would be discussed in a public forum.

Question 9.3.15.

Does the Division agree that the data from the dose-ranging studies for GSK573719 Inhalation Powder (which contains two strips, i.e. an active strip and a nonactive strip) can be utilized to select a single dose to progress to Phase III pivotal studies for both the single-strip Novel DPI for the monotherapy product and a two-strip Novel DPI for GSK573719/GW642444 Inhalation Powder?

FDA Response:

Based on the information provided, we note differences in the aerodynamic particle size distribution (APSD) in the presence and absence of a non-active strip. Given these differences, we have concerns that the use of a single-strip comparator in the factorial design pivotal trials for GSK573719/GW642444 will not be appropriate for satisfying the requirements of the Combination Rule.

Dose ranging information obtained from the two-strip device may be used to support dose selection for a single-strip monotherapy product; however, clinical bridging data will be required to characterize and support the differences between the two-strip and single-strip products. Should you choose to develop a single-strip monotherapy product for marketing, additional safety information may be required depending on the extent of the differences.

Discussion:

The sponsor inquired why the use of a single-strip comparator in the factorial design pivotal trials for GSK573719/GW642444 would impact the ability to satisfy the combination rule. FDA stated that the (b) (4) Hence, the interpretability of data from the factorial design pivotal trial would be clouded.

The sponsor stated that they could add the second (nonactive) strip to the monotherapy device, noting, however, that this would expose users to unnecessary excipient, and that previous guidance from FDA had discouraged this. FDA responded that the previous guidance was provided prior to data being available regarding this pharmaceutical interaction. FDA outlined two options open to the sponsor: adding in a second non-active strip to the monotherapy, or obtaining bridging data to justify reliance on the data generated by the single-strip monotherapy device. The sponsor noted that the (b) (4) monotherapy device actually puts the sponsor at a disadvantage, making it more difficult to demonstrate superiority of the combination product to monotherapy. FDA reiterated that choosing to use the single-strip monotherapy device will result in data that is difficult to interpret, moreover, also at issue

is the difficulty that would be faced by providers and patients when switching from the combination product to monotherapy.

(b) (4)

from a CMC perspective. FDA will require data demonstrating that there is no relevant clinical difference; such data may be obtained from a single dose PK/PD study.

Question 9.3.16.

Does the Division agree with GSK's proposal to compare the two-strip Novel DPI for GSK573719/GW642444 Inhalation Powder with the single strip Novel DPI for the monotherapy products in the pivotal Phase III studies to support registration of GSK573719/GW642444 Inhalation Powder and GSK573719 Inhalation Powder?

FDA Response:

See our response to 9.13.15.

Discussion:

No discussion required.

Question 9.3.17.

Does the Division agree that the population pharmacokinetics sampling to be conducted during the planned Phase III studies will be adequate to evaluate population co-variants; e.g. age and gender among the general population of prescribed patients?

FDA Response:

Yes, your program appears acceptable.

Discussion:

No discussion required.

Question 9.3.18.

(b) (4)

(b) (4)

[redacted]

FDA Response:

In your Phase 3 studies, your calculated sample size of 1005 subjects in Study DB2113361/3373, and 292 subjects in Study DB2113360/3374 is acceptable. Assuming your analysis population consists of all randomized subjects and taking into consideration your proposal to handle missing data, sample size need not be increased to allow for dropouts. Otherwise, increasing the sample size is reasonable to allow adequate safety data. Of note, the study has to demonstrate clinically meaningful and statistically significant treatment differences on the primary efficacy endpoint of FEV_1.

We noted that your sample size of 190 subjects was calculated based on a two-sample t-test for the exercise endurance study. Because this is a crossover design study, applying a two-sample t-test is not recommended.

Discussion:

The sponsor stated that they plan to increase the sample size to allow for patient dropouts. They also stated that given their primary endpoint is at the end of the treatment (Visit 9), missing data due to patient dropout will be a problem even if they apply mixed model repeated measures.

The Division stated that we understand the potential loss of power due to patient dropout. However, because the Sponsor is applying mixed model repeated measures that uses all observed data from all randomized patients to analyze their primary endpoint, we do not agree with the reason for inflating the sample size.

Nonetheless, increasing the sample size is acceptable and the Division reminded the Sponsor that our assessment will not just be on the statistical significance, but also on the clinical meaningfulness of the treatment effect.

Question 9.3.19.

GSK intend to conduct a clinical study to evaluate the safety of fluticasone furoate/GW642444 Inhalation Powder and GSK573719/GW642444 Inhalation Powder given concomitantly in patients with COPD. Does the Division have any feedback on the design of the study?

FDA Response:

We have no comments at this time.

Discussion:

No discussion required.

Labeling

Question 9.4.1.

Does the Division have any preliminary comments on the draft wording for the INDICATIONS AND USAGE section and the DOSAGE AND ADMINISTRATION section of the package inserts for GSK573719/GW642444 Inhalation Powder and GSK573719 Inhalation Powder?

FDA Response:

The evaluation of dyspnea presents many challenges, and the successful development of a patient reported outcome instrument to measure dyspnea and/or shortness of breath is without precedent. We refer you to the meeting of the Pulmonary-Allergy Drugs Advisory Committee held on September 6, 2002, as well as the May 10, 2010, discussion of the SOBDA instrument (IND 50,703), which addressed the difficulties associated with attempts to measure dyspnea and to claim dyspnea as an indication.

Discussion:

No discussion required.

Question 9.4.2.

Does the Division have any preliminary comments on inclusion of studies from the Phase III development program in the clinical trials section of the labelling for GSK573719/GW642444 Inhalation Powder and GSK573719 Inhalation Powder?

FDA Response:

We have no specific comments at this time. In general, we note that the inclusion of active comparator data will be a review issue.

Discussion:

No discussion required.

ADDITIONAL COMMENTS

Statistics Comments:

1. *You propose to apply Mixed Model Repeated Measures to evaluate treatment difference at Visit 9 (Day 169). In general, this approach is generally acceptable. However, we would like to caution you that the reasons for dropout may vary for which some may likely be due to treatment-related adverse events. Therefore it may be difficult to justify the assumption of missing data at random.*

   In the protocol, discuss potential mechanisms which may cause FEV_1 data to be missing, and how those mechanisms affected your selection of the primary analysis method. We also recommend that you outline additional analyses to gauge the sensitivity of your primary analysis method to violations of the assumed missing data mechanism. In addition, provide a plan on how you will integrate and explain the results from all these sensitivity analyses; in particular, if the results are in a different direction from the result of the primary analysis.

   Refer to the National Research Council of the National Academy's report, titled "The Prevention and Treatment of Missing Data in Clinical Trials" for further information.

Discussion:

The Sponsor stated that they understood our comments and will be providing a more detailed description of their approach to handle missing data in their protocols. They asked the Division if we have further suggestions on how to handle missing data. The Division replied that we do not have any specific advice on what methods to use. We noted from their synopsis that they plan to use last observation carried forward approach to impute missing data as part of their sensitivity analysis. Unless they have sound justification, we cautioned them about the use of LOCF, in particular when there are treatment-related dropouts. We refer them again to the NAS report for more information about missing data.

2. *You stated that you are anticipating a 30% dropout rate. We recommend that the reasons for discontinuation be clearly documented to avoid less informative terms such as 'lost to follow-up', 'patient/investigator decision,' 'withdraw consent', etc. If a patient is 'lost to follow-up,' you should provide a plan for attempting to contact the patient so that a more informative category can be assigned.*

3. *In the briefing package, you stated that "all available data collected until the time of study discontinuation will be included in the intent-to-treat analysis for subjects who withdraw from the study." In your protocol, clarify if you intend to use the data collected after patient withdraws from treatment.*

Discussion:

The Sponsor clarified that if a patient drops out of the study, they will conduct a follow-up visit/assessment within 30 days either by bringing the patient in or by phone. They do not plan to include any data collected after a patient drops out in the efficacy analysis. The sponsor asked whether this is the information that FDA is looking for. FDA stated affirmatively and that it was not clear from the package. FDA further stated that the sponsor should try to prevent loss to follow up and to clearly document the reasons for dropout (e.g. adverse event or lack of efficacy). The sponsor acknowledged this and indicated that this is what they intend to do. FDA further advised the sponsor to make sure that the informed consent form is very clear and ensure that the patient is aware of their expectations in order to prevent missing data.

Additional Discussion:

The sponsor inquired about what FDA's thoughts were on long acting muscarinic antagonists (LAMAs) and intranasal corticosteroids (ICSs) in combination for asthma. FDA responded that this topic has been brought up in many forums and it remains an open question. While the scientific community generally views LAMAs as having poor efficacy for asthma, there is some support for the use of LAMA/ICS combinations, particularly among patients with severe asthma. FDA raised the issue that perhaps this severe population is actually comprised of individuals with COPD, as opposed to true asthmatics. Hence, it would be important for the sponsor to clearly define the patient population being targeted for a proposed LAMA/ICS product.

The sponsor inquired about whether a pediatric plan would be needed for this COPD program. FDA responded that a COPD program will not require a pediatric plan.

The sponsor inquired about whether a large safety trial will be required to support product registration for a COPD indication. FDA responded that this issue would require internal discussion. The sponsor also noted that if the LAMA/LABA and LAMA/ICS products were both available, some providers and COPD patients might choose to use the products concurrently; the sponsor asked FDA what would be required to address this issue. FDA responded that this topic would be best discussed at a later time.

The Division of Scientific Investigations provided documents to the sponsor describing a voluntary pilot program to which they are being invited.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

4.0 ACTION ITEMS

5.0 ATTACHMENTS AND HANDOUTS

Drafted by: Eunice Chung-Davies/November 1, 2010

Initialed by: Timothy Robison/November 2, 2010
Molly Topper/November 2, 2010
Joan Buenconsejo/November 5, 2010
Jennifer Pippins/ November 5, 2010
Susan Limb/ November 5, 2010
Badrul A. Chowdhury/November 17, 2010

Finalized by: EChung-Davies/November 17, 2010

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/s/

EUNICE H CHUNG-DAVIES
11/17/2010

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205382

LATE-CYCLE MEETING MINUTES

GlaxoSmithKline
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Vicki Gunto, Ph.D.,
Director, Global Regulatory Affairs

Dear Dr. Gunto:

Please refer to your New Drug Application (NDA) dated April 29, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Incruse Ellipta (umeclidinium bromide) Inhalation powder.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on February 5, 2014.

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

If you have any questions, call Angela Ramsey, Senior Program Management Officer at (301) 796-2284.

Sincerely,

{See appended electronic signature page}

Susan Limb, M.D.
Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: February 5, 2014
Meeting Location: Teleconference

Application Number: 205382
Product Name: Incruse Ellipta (umeclidinium bromide) inhalation powder
Applicant Name: GlaxoSmithKline

Meeting Chair: Susan Limb, M.D.
Meeting Recorder: Angela Ramsey, R.N., M.S.N

FDA ATTENDEES

Susan Limb, MD, Clinical Team Leader
Jennifer Pippins, MD, Clinical Reviewer
Ruthanna Davi, Ph.D., Statistical Reviewer
Gregory Levin, Ph.D., Statistical Reviewer
Arthur Shaw, Ph.D., Quality Reviewer
Lissa C. Owens, Pharm.D., Safety Evaluator, Office of Medication Error Prevention and Risk
Jianmeng Chen, Ph.D., Clinical Pharmacology Reviewer
Timothy Robison, Ph.D., Pharmacology Toxicology Team Leader

(b) (6)

APPLICANT ATTENDEES

Vicki Gunto, Ph.D,

BACKGROUND

NDA 205382 was submitted on April 29, 2013 for Incruse Ellipta (umeclidinium bromide) inhalation powder.

Proposed indication(s): COPD

PDUFA goal date: April 30, 2014

FDA issued a Background Package in preparation for this meeting on January 15, 2014.

DISCUSSION

1. Introductory Comments – 5 minutes (RPM/CDTL)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – None

   Discussion: ***No discussion occurred.***

3. Information Requests – None

   Discussion: ***No discussion occurred.***

4. Discussion of Upcoming Advisory Committee Meeting – Not applicable

   Discussion: ***No discussion occurred.***

5. Postmarketing Requirements/Postmarketing Commitments
   - None anticipated

   Discussion**:** ***No discussion occurred****.*

6. REMS or Other Risk Management Actions
   - None anticipated

   Discussion**:** ***No discussion occurred****.*

7. Clinical/Statistics – None

   Discussion: ***No discussion occurred.***

8. Additional Applicant Data – None

   Discussion: ***No discussion occurred.***

9. Major labeling issues – None

   Discussion: ***No discussion occurred.***

10. Discussion of Minor Review Issues – None

    Discussion: ***No discussion occurred.***

11. Review Plans – 5 minutes
    a. Completion of reviews and consults
    b. Labeling discussions (as needed)

Discussion: ***The Division noted no change in the PDUFA goal date.***

12. Wrap-up and Action Items – 5 minutes

Discussion: ***No discussion occurred.***

Additional discussion points proposed by GSK:

- Label – Table 1 (confirmation of Table source)

  Discussion: ***GSK requested clarification of the request for references in table 1 in order to gain an understanding for future submissions. The Division noted GSK's changes to the description preceding the table in their January 15, 2014, version of the label; the adverse events are now based on a pooling of three, rather than four, trials. A new reference table corresponding to the 3-trial pooling should be submitted.***

- Label – (b) (4)

  (b) (4)

- Package art – inclusion of dose on all carton panels

  Discussion: ***The Division stated it is acceptable to not include the product strength, 62.5 mcg, on all carton panels, in keeping with the carton labels for Breo Ellipta and Anoro Ellipta. The Division brought to GSK's attention minor editorial differences (e.g., the phonetic spelling of Ellipta) between the three labels that have been introduced with the FDA edits communicated on January 29, 2014, and recommends harmonization of the labels at some point in the future.***

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

ANGELA H RAMSEY
02/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205382

LATE CYCLE MEETING
BACKGROUND PACKAGE

GlaxoSmithKline
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Vicki Gunto, Ph.D.,
Director, Global Regulatory Affairs

Dear Dr. Gunto:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Incruse Ellipta (umeclidinium bromide) inhalation powder

We also refer to the Late-Cycle Meeting (LCM) scheduled for February 5, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Angela Ramsey Senior Program Management Officer, at (301) 796-2284.

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

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	February 5, 2014
Meeting Location:	FDA White Oak, Building 22, Conference Room 1419
Application Number:	NDA 205382
Product Name:	umeclidinium bromide
Indication:	maintenance treatment of patients with Chronic Obstructive Pulmonary Disease including chronic bronchitis and emphysema
Sponsor/Applicant Name:	Glaxo Group, (d/b/a GSK)

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

No substantive review issues have been identified. While the primary, secondary, and tertiary reviews are pending at this time, the major aspects of the review have been previously addressed in the reviews for NDA 203975, umeclidinium/vilanterol.

ADVISORY COMMITTEE MEETING

As umeclidinium was already discussed at the September 10, 2013, advisory committee meeting in the context of the umeclidinium/vilanterol application, a separate advisory committee meeting for umeclidinium was not be convened.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – None

3. Information Requests – None

4. Discussion of Upcoming Advisory Committee Meeting – Not applicable

5. Postmarketing Requirements/Postmarketing Commitments
   - None anticipated

6. REMS or Other Risk Management Actions
   - None anticipated

7. Clinical/Statistics – None

8. Additional Applicant Data – None

9. Major labeling issues – None

10. Discussion of Minor Review Issues – None

11. Review Plans – 5 minutes

- Completion of reviews and consults
- Labeling discussions (as needed)

12. Wrap-up and Action Items – 5 minutes

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/s/

BADRUL A CHOWDHURY
01/15/2014