

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204275Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 204275

SUPPL #

HFD # 570

Trade Name Breo Ellipta

Generic Name fluticasone furoate/vilanterol

Applicant Name GlaxoSmithKline

Approval Date, If Known May 10, 2013

### 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#

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# 22051 Veramyst

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:

Trials HZC112206, HZC112207, HZC102871 and HCZ102970

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:

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:

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"):

Trials HZC112206, HZC112207, HZC102871 and HCZ102970

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 # 77855            YES             ! NO   
! Explain:

Investigation #2  
IND # 77855            YES             ! NO   
! Explain:

Investigation #3  
IND # 77855            YES             ! NO   
! Explain:

Investigation #4  
IND # 77855            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:

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Name of person completing form: Angela Ramsey R.N., M.S.N  
Title: Senior Program Management Officer

Date: May 10, 2013

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

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANGELA H RAMSEY  
05/10/2013

BADRUL A CHOWDHURY  
05/10/2013

## DEBARMENT CERTIFICATION

GlaxoSmithKline certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application (NDA 204275 Original NDA for BREO ELLIPTA (fluticasone furoate 100/vilanterol 25) for the treatment of chronic obstructive pulmonary disease (COPD).



Craig Wozniak

June 2012

Head, Americas Clinical Operations

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # 204275 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Breo Ellipta Established/Proper Name: fluticasone furoate/vilanterol Dosage Form: Inhalation Powder		Applicant: GlaxoSmithKline Agent for Applicant (if applicable):
RPM: Angela Ramsey		Division: DPARP
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)  Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>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.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is May 10, 2013</li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None

<sup>e</sup> **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists documents to be included in the Action Package.

<sup>2</sup> 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).

<p>❖ 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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics<sup>3</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span>  <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span>  <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span></p> <p>Subpart I <span style="margin-left: 200px;">Subpart H</span>  <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR <span style="margin-left: 100px;">REMS: <input type="checkbox"/> MedGuide</span>  <input type="checkbox"/> Submitted in response to a PMC <span style="margin-left: 100px;"><input type="checkbox"/> Communication Plan</span>  <input type="checkbox"/> Submitted in response to a Pediatric Written Request <span style="margin-left: 100px;"><input type="checkbox"/> ETASU</span>  <span style="margin-left: 300px;"><input checked="" type="checkbox"/> MedGuide w/o REMS</span>  <span style="margin-left: 300px;"><input checked="" type="checkbox"/> REMS not required</span></p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>• Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>• Press Office notified of action (by OEP)</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>• Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>NDA only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

Copy of this Action Package Checklist <sup>4</sup>	Included
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s): 5/12/13
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	5/8/13
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	7/12/12
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	NA

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input checked="" type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	5/6/13
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	7/12/12
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	5/8/13 (carton); 4/26/13 (container)
<ul style="list-style-type: none"> <li>❖ Proprietary Name               <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	Acceptable: 3/1/13 2/28/13
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 9/18/12 <input checked="" type="checkbox"/> DMEPA 4/9/13 <input checked="" type="checkbox"/> DMPP/PLT 4/5/13 <input checked="" type="checkbox"/> ODPD (DDMAC) 4/9/13; 4/4/13 <input checked="" type="checkbox"/> SEALD 5/6/13 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	9/18/12
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP               <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)               <ul style="list-style-type: none"> <li>• Date reviewed by PeRC April 3, 2013- Pediatric waiver granted If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

* Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	3/27/13; 3/26/13; 3/22/13; 3/5/13; 1/10/13; 1/8/13; 1/7/13; 12/10/12; 11/15/12; 10/24/12; 10/11/12; 9/19/12 7/24/12
❖ Internal memoranda, telecons, etc.	12/14/12
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>• Regulatory Briefing <i>(indicate date of mtg)</i></li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i></li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i></li> </ul>	<input type="checkbox"/> No mtg 7/13/11 (COPD) & 10/12/11 (Asthma)
<ul style="list-style-type: none"> <li>• EOP2 meeting <i>(indicate date of mtg)</i></li> </ul>	<input type="checkbox"/> No mtg 3/31/09 (Asthma) 6/17/09 ( COPD); CMC-only EOP2: 3/31/09
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i></li> </ul>	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	4/17/13
<ul style="list-style-type: none"> <li>• 48-hour alert or minutes, if available <i>(do not include transcript)</i></li> </ul>	
<b>Decisional and Summary Memos</b>	
Office Director Decisional Memo <i>(indicate date for each review)</i>	<input type="checkbox"/> None 5/10/13
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 5/9/13
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 4/1/13
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>• Clinical Team Leader Review(s) <i>(indicate date for each review)</i></li> </ul>	See CDTL review
<ul style="list-style-type: none"> <li>• Clinical review(s) <i>(indicate date for each review)</i></li> </ul>	3/18/13; 9/4/12
<ul style="list-style-type: none"> <li>• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i></li> </ul>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	3/18/13 pg 15
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input type="checkbox"/> None 3/28/13; 12/12/12; 12/07/12; 10/31/12
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None- REMS not recommended 4/22/13
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested 4/16/13 3/15/13
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 3/18/13; 9/5/12
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 3/18/13; 9/11/12
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 5/8/13
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 3/22/13
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/22/13; 3/12/13; 2/14/13; 8/30/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input type="checkbox"/> No carc 4/10/12
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 11/30/12 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
<b>Product Quality Discipline Reviews</b>	
<ul style="list-style-type: none"> <li>• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i></li> </ul>	<input type="checkbox"/> None 5/9/13
<ul style="list-style-type: none"> <li>• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i></li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i></li> </ul>	<input type="checkbox"/> None 4/30/13; 3/18/13; 12/13/12; 11/29/12; 9/5/12
<ul style="list-style-type: none"> <li>❖ Microbiology Reviews                             <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility &amp; pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i></li> <li><input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i></li> </ul> </li> </ul>	<input type="checkbox"/> Not needed 11/27/12
<ul style="list-style-type: none"> <li>❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i></li> </ul>	<input type="checkbox"/> None 4/11/13; 3/18/13; 3/13/13
<ul style="list-style-type: none"> <li>❖ Environmental Assessment (check one) (original and supplemental applications)</li> </ul>	
<ul style="list-style-type: none"> <li><input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i></li> </ul>	3/18/13 pg 233
<ul style="list-style-type: none"> <li><input type="checkbox"/> Review &amp; FONSI <i>(indicate date of review)</i></li> </ul>	
<ul style="list-style-type: none"> <li><input type="checkbox"/> Review &amp; Environmental Impact Statement <i>(indicate date of each review)</i></li> </ul>	
<b>Facilities Review/Inspection</b>	
<ul style="list-style-type: none"> <li><input type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(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<sup>7</sup>)</i></li> </ul>	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<ul style="list-style-type: none"> <li><input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i></li> </ul>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> <li>❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i></li> </ul>	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>7</sup> 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.

## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.



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

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**FACSIMILE TRANSMITTAL SHEET**

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**Date:** May 7, 2013

<b>To:</b> Patrick Wire	<b>From:</b> Angela Ramsey Senior Program Management Officer
<b>Company:</b> GlaxoSmithKline	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 919-315-0033	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> : 919-483-7650	<b>Phone number:</b> 301-796-2284
<b>Subject:</b> NDA 204275 Breo Ellipta labeling fax # 4	

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

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**Comments:**

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**Document to be mailed:** YES XNO

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NDA 204275

We continue our review of the labeling in your submission dated, May 6, 2013, to NDA 204275. The FDA proposed insertions are underlined and deletions are in strikeouts. Submit responses via email to [angela.ramsey@fda.hhs.gov](mailto:angela.ramsey@fda.hhs.gov) by COB Wednesday, May 8, 2013.

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

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/s/  
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ANGELA H RAMSEY  
05/07/2013



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

**Memorandum of Facsimile Correspondence**

Date: May 2, 2013

To: Patrick Wire

Company: GlaxoSmithKline

Fax: 919-315-0033

Phone: 919-483-7650

From: Angela Ramsey, RN, MSN  
Senior Program Management Officer  
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 204275 Breo Ellipta Labeling fax# 3

# of Pages:

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If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPAP, Silver Spring, MD 20993.

Thank you.

We continue our review of the labeling in your submission dated, April 26, 2013, to NDA 204275. The FDA proposed insertions are underlined and deletions are in strikeouts. We have the following comment to the labeling:

Clarify if the Institutional Pack described is available for prescribing by practitioners

Submit responses via email to [angela.ramsey@fda.hhs.gov](mailto:angela.ramsey@fda.hhs.gov) by Monday, May 6, 2013.

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

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/s/  
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ANGELA H RAMSEY  
05/02/2013



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

**Memorandum of Facsimile Correspondence**

Date: March 27, 2013

To: Patrick Wire

Company: GlaxoSmithKline

Fax: 919-315-0033

Phone: 919-483-7650

From: Angela Ramsey, RN, MSN  
Senior Program Management Officer  
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 204275 Breo Ellipta Labeling Recommendations

# of Pages:

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Thank you.

NDA 204275  
Breo Ellipta  
GSK

We have begun our review of the labeling in your submission dated, October 12, 2012, to NDA 204275. The FDA proposed insertions are underlined and deletions are in strike-out. These comments are not all-inclusive and we will have additional comments and/or requests as we continue our review of the label. We have the following comments and/or requests for revisions to the labeling:

1. Table of Contents: Update Section 14 of the table with the appropriate sub-headings.
2. Revise all figures in black and white.
3. Section 12.3, Clinical pharmacology:
  - a. Figure 1. Update figure, put forest plot for FF and VI side by side, with one recommendation column. Final figure should have column1: population description; column2: PK; column3: FF forest plot; column 4: VI forest plot; column 5: recommendation.
  - b. Figure 2. Update figure, put forest plot for FF and VI side by side, with one recommendation column. Final figure should have column1: Interacting Drug; column2: PK; column3: FF forest plot; column 4: VI forest plot; column 5: recommendation
4. Section 13.2, Animal Toxicology and/or Pharmacology: Delete the section.
5. Section 14.1, Dose Ranging Trials: Insert figures from Trial B2C111045 showing the difference from placebo in change from baseline FEV<sub>1</sub> (ml) over time at Day 1 and Day 28.
6. Section 14.2, Confirmatory Trials, Lung Function: Insert figures from trial HCZ112207 of post-dose serial FEV<sub>1</sub> in ml on Day 1 and Day 168.
7. Throughout the label, there are inconsistencies with font (headings change from Arial to New Roman Times). Be consistent with use of the fonts.

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/s/  
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ANGELA H RAMSEY  
03/26/2013



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

**Memorandum of Facsimile Correspondence**

Date: April 16, 2013

To: Patrick Wire

Company: GlaxoSmithKline

Fax: 919-315-0033

Phone: 919-483-7650

From: Angela Ramsey, RN, MSN  
Senior Program Management Officer  
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 204275 Breo Ellipta Labeling fax# 2

# of Pages:

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Thank you.

We continue our review of the labeling in your submission dated, April 9, 2013, to NDA 204275. The FDA proposed insertions are underlined and deletions are in strikeouts. These comments are not all-inclusive and we will have additional comments and/or requests as we continue our review of the label.

We have the following comments and/or requests for revisions to the labeling:

#### 1. All Container Labels

- Revise the word 'Ellipta' in the proprietary name so that it is presented in the same color as the word 'Breo'. As presented the word Ellipta utilizes a (b) (4) font over the blue background and is difficult to read.
- Unbold the statement 'Rx Only', as presented this statement competes for prominence with the proprietary name.

#### 2. All Carton Labeling

- See bullets above for 1. All Container Labels
- Remove the Theravance logo from the principle display panel to decrease clutter.
- As presented, the directions on the side panel may cause confusion as patients may read across the line. Revise these to be presented in a stepwise manner that reads from left to right and top to bottom omitting the line in the middle. See example below:
  1. OPEN
    - Slide the cover down until you hear a "click"  
*Add existing graphic*
  2. INHALE
    - While holding the inhaler....
    - Don't breathe out...
    - Put the mouthpiece...
    - Take one long...  
*Add existing graphic*
    - Remove the inhaler....
    - You may not be able...
  3. CLOSE
    - Then slide the cover .....
    - Remember to....
- Revise the carton label to include a directive for patients to read the complete IFU

3. Insert figures as outlined in the revised medication guide. Formatting (e.g., lines) may remain from the original version. These should be removed where appropriate.

#### 4. Section 12 clinical pharmacology

- 12.2 Pharmacodynamics, Cardiovascular effects: Usually only one QT parameter is listed in the label to avoid confusion. QT-IRT analysis indicated that QTcF is the proper parameter here.
- 12.3 Pharmacokinetics, Elimination, Vilanterol: HT “4.6 to 6.4 hours” is generated in study HZA102932, a single dose study of vilanterol 100mcg. Derive the half life from multiple dose vilanterol (25mcg) studies as the information is more relevant.

## 5. Highlights

- Insert white space before each heading
- Submit waiver request for 1/2 page highlights requirement

## Medication Guide

- Insert web address in the Medication Guide

## 6. Remove line numbering from the label

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

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/s/  
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ANGELA H RAMSEY  
04/16/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 27, 2013

TO: GlaxoSmithKline

THROUGH: **Patrick Wire**

FROM: Angela Ramsey

SUBJECT: **Breo Ellipta Labeling fax dated, March 26, 2013**

APPLICATION/DRUG: **NDA 204275/Breo Ellipta (fluticasone furoate/vilanterol)**

GSK was informed that there was a missed edit to page 2 of the labeling fax #1 dated, March 26, 2013. CDR Ramsey sent the corrected version dated, March 27, 2013 via fax. The attachment below contains the corrected version.



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

**Memorandum of Facsimile Correspondence**

Date: March 27, 2013

To: Patrick Wire

Company: GlaxoSmithKline

Fax: 919-315-0033

Phone: 919-483-7650

From: Angela Ramsey, RN, MSN  
Senior Program Management Officer  
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 204275 Breo Ellipta Labeling Recommendations

# of Pages:

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Thank you.

NDA 204275  
Breo Ellipta  
GSK

We have begun our review of the labeling in your submission dated, October 12, 2012, to NDA 204275. The FDA proposed insertions are underlined and deletions are in strike-out. These comments are not all-inclusive and we will have additional comments and/or requests as we continue our review of the label. We have the following comments and/or requests for revisions to the labeling:

1. Table of Contents: Update Section 14 of the table with the appropriate sub-headings.
2. Revise all figures in black and white.
3. Section 12.3, Clinical pharmacology:
  - a. Figure 1. Update figure, put forest plot for FF and VI side by side, with one recommendation column. Final figure should have column1: population description; column2: PK; column3: FF forest plot; column 4: VI forest plot; column 5: recommendation.
  - b. Figure 2. Update figure, put forest plot for FF and VI side by side, with one recommendation column. Final figure should have column1: Interacting Drug; column2: PK; column3: FF forest plot; column 4: VI forest plot; column 5: recommendation
4. Section 13.2, Animal Toxicology and/or Pharmacology: Delete the section.
5. Section 14.1, Dose Ranging Trials: Insert figures from Trial B2C111045 showing the difference from placebo in change from baseline FEV<sub>1</sub> (ml) over time at Day 1 and Day 28.
6. Section 14.2, Confirmatory Trials, Lung Function: Insert figures from trial HCZ112207 of post-dose serial FEV<sub>1</sub> in ml on Day 1 and Day 168.
7. Throughout the label, there are inconsistencies with font (headings change from Arial to New Roman Times). Be consistent with use of the fonts.

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

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/s/  
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ANGELA H RAMSEY  
03/27/2013



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

**Memorandum of Facsimile Correspondence**

Date: March 26, 2013

To: Patrick Wire

Company: GlaxoSmithKline

Fax: 919-315-0033

Phone: 919-483-7650

From: Angela Ramsey, RN, MSN  
Senior Program Management Officer  
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 204275 Breo Ellipta Labeling Recommendations

# of Pages:

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Thank you.

NDA 204275  
Breo Ellipta  
GSK

We have begun our review of the labeling in your submission dated, October 12, 2013, to NDA 204275. The FDA proposed insertions are underlined and deletions are in strike-out. These comments are not all-inclusive and we will have additional comments and/or requests as we continue our review of the label. We have the following comments and/or requests for revisions to the labeling:

1. Table of Contents: Update Section 14 of the table with the appropriate sub-headings.
2. Revise all figures in black and white.
3. Section 12.3, Clinical pharmacology:
  - a. Figure 1. Update figure, put forest plot for FF and VI side by side, with one recommendation column. Final figure should have column1: population description; column2: PK; column3: FF forest plot; column 4: VI forest plot; column 5: recommendation.
  - b. Figure 2. Update figure, put forest plot for FF and VI side by side, with one recommendation column. Final figure should have column1: Interacting Drug; column2: PK; column3: FF forest plot; column 4: VI forest plot; column 5: recommendation
4. Section 14.1, Dose Ranging Trials: Insert figures from Trial B2C111045 showing the difference from placebo in change from baseline FEV<sub>1</sub> (ml) over time at Day 1 and Day 28.
5. Section 14.2, Confirmatory Trials, Lung Function: Insert figures from trial HCZ112207 of post-dose serial FEV<sub>1</sub> in ml on Day 1 and Day 168.
6. Throughout the label, there are inconsistencies with font (headings change from Arial to New Roman Times). Be consistent with use of the fonts.

Submit revised labeling by April 2, 2013 via email to [angela.ramsey@fda.hhs.gov](mailto:angela.ramsey@fda.hhs.gov) and officially to the NDA.

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

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/s/  
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ANGELA H RAMSEY  
03/26/2013



NDA 204275

**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 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BREO™ ELLIPTA™ (fluticasone furoate/vilanterol) 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 March 29, 2013) in order to continue our evaluation of your NDA.

1. Your response submitted on 12-Mar-2013 to Question 1 regarding your proposal (b) (4)  
(b) (4)  
in APSD testing is not warranted.

However, in order to accommodate the reasonable analytical variations that may be observed during APSD testing, and as a resolution to this issue, we propose to adjust the acceptable limits of the fluticasone furoate and vilanterol APSD test attributes as shown below:

Test Parameters	GSK Proposed Acceptance Criteria (micrograms) <sup>a</sup>	Agency Proposed Acceptance Criteria
-----------------	--	-------------------------------------

(b) (4)		
---------	--	--

Confirm that you agree with our proposal of the adjusted acceptance criteria and update your NDA accordingly.

- Your response submitted on 12-Mar-2013 to Question 5 regarding your possible post-approval change of sample size in DCU testing using the PTIT approach is not acceptable. Your response used an incorrect statement to support your proposal under negotiation.

In the response, you claimed that “The Two 1-Sided PTIT Procedure with 87.5% Coverage, 95% Confidence and a 1:3 Tier Ratio is designed (b) (4)

To assess the probability you claimed, the two one-sided hypotheses can be set up as:

$$H_0^U: \Pr(X \geq U) \geq P_U \text{ versus } H_a^U: \Pr(X \geq U) < P_U \quad (1)$$

$$H_0^L: \Pr(X \leq L) \geq P_L \text{ versus } H_a^L: \Pr(X \leq L) < P_L \quad (2)$$

Where X is the random variable for delivery dose throughout the life of usage of the inhaler, L=80, U=120, and  $P_U=P_L=(b) (4)$

We will use tier 1 as an example to illustrate our reasoning (b) (4)

$\alpha_1$  is type I error rate, the probability of rejecting  $H_0^U$  and  $H_0^L$  (i.e. complies) when  $H_0^U$  or  $H_0^L$  is true (i.e. not complies).  $(1-\alpha_1)*100\%$  is the probability of not rejecting  $H_0^U$  and  $H_0^L$  (i.e. not complies) when  $H_0^U$  or  $H_0^L$  is true (i.e. not complies). Clearly, the confidence level  $(1-\alpha_1)*100\%$  is not the probability of rejecting  $H_0^U$  and  $H_0^L$  under  $H_a^U$  and  $H_a^L$  are true (i.e. complies) (b) (4)

Hence your k values (tolerance factors) for different sample sizes are derived on the basis of (b) (4). However, (b) (4) is not a concern from a practical point of view (b) (4)

Hence the k-values should be derived based on maintaining 90% power for a different sample size such that the alternative sample-size test should have a 90% passing probability to pass at the quality standard at which the test for the 20/60 sample size plan (20 at 1st tier, 60 at 2nd tier) has a 90% probability of at least 87.5% coverage with 95% confidence level tolerance interval for the total of 60 samples falling between 80% and 120% of label claim.

To resolve the issue, you may not change the currently proposed sample size of 20 for Tier 1 and (b) (4) for Tier 2 testing without prior agreement or approval from the Agency. Alternatively,

you may choose the sample sizes, but the test with the alternative sample size should have a 90% passing probability to pass at the quality standard at which the test for the 20/60 sample size plan (20 at 1st tier, 60 at 2nd tier) has a 90% probability of at least 87.5% coverage with 95% confidence level tolerance interval for the total of 60 samples falling between 80% and 120% of label claim.

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/  
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YOUBANG LIU  
03/22/2013

PRASAD PERI  
03/22/2013



NDA 204275

**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 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BREO™ ELLIPTA™ (fluticasone furoate/vilanterol) 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 March 12, 2013) in order to continue our evaluation of your NDA.

1. Your drug product specifications table includes [REDACTED] (b) (4)  
APSD testing (as noted in footnote L) [REDACTED] (b) (4)  
[REDACTED]  
Update the drug product specifications table [REDACTED] (b) (4)  
[REDACTED]
2. In the container closure section (P.7.), the method for determination of particulates only quantifies particulates from the inhaler [REDACTED] (b) (4) Justify the rationale [REDACTED] (b) (4)  
[REDACTED]
3. Submit the actual reference standard information to the corresponding drug substance and drug product sections.
4. In your responses to the Agency's information requests and comments (dated 10/17/2013 and 2/7/2013), you submitted technical information and updates into Section 1.11 of the eCTD. Note that the technical information must be submitted to the appropriate sections of the eCTD. Provide the information in the appropriate sections of the NDA.
5. Your response (dated 7-Feb-2013) to item 9 of the Agency's information requests regarding the alternative sample sizes and the corresponding k-values for emitted dose uniformity testing is not acceptable. As indicated by the Operating Characteristic (OC) curve you provided, your possible sampling approach (of an alternative sample size at a 1:3 ratio between the sample sizes for the first and second tier) allows increased passing probability of a given batch with sheer increase in sample size. This is not acceptable. To resolve the issue,

you may confirm not to change the currently proposed sample size of 20 for Tier 1 and (b) (4) for Tier 2 testing without prior agreement or approval from the Agency. Alternatively, you may choose the sample sizes, but the alternative sample-size test should have a 90% passing probability to pass at the quality standard at which the test for the 20/60 sample size plan (20 at 1st tier, 60 at 2nd tier) has a 90% probability of at least 87.5% coverage with 95% confidence level tolerance interval for the total of 60 samples falling between 80% and 120% of label claim.

6. Your response indicates (b) (4)

Hence, it is recommended to follow guidelines in CFR 314.70 regarding notification of changes to this procedure. (b) (4)

At a minimum, the protocol should include:

- a) A general description of analyzer, software, and interface
- b) Rules of selection of spectra for calibration, testing, and validation sets
- c) Approaches for selection of critical model parameters
- d) Validation acceptance criteria
- e) Proposed notification approach

7. Based on the submitted data we have determined that the water activity as measured by NIR (b) (4) during test time frame. (b) (4)

8. The following comments pertain to labeling of cartons and container
- a) At the side of the packaging carton, the wording of “visit xxxx.com” is too prominent compared to the required information, decrease the font size for this wording.
  - b) The word “Theravance” and the star like artwork on the packaging cartons have no clear relevance to the product except occupying space. Justify their presence or remove them. You may use the space to enlarge the font of the required information.

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/  
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PRASAD PERI  
03/05/2013



NDA 204275

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Glaxo Group Limited, England d/b/a GlaxoSmithKline  
c/o GlaxoSmithKline  
Five Moore Drive  
P.O. Box 13398  
Research Triangle Park, NC 27709

ATTENTION: Patrick D. Wire, PharmD  
Product Director, Respiratory Group  
US Regulatory Affairs

Dear Dr. Wire:

Please refer to your New Drug Application (NDA) dated July 11, 2012, received July 12, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Furoate and Vilanterol Powder for Inhalation , 100 mcg/25 mcg.

We also refer to your December 6, 2012, correspondence, received December 6, 2012, requesting review of your proposed proprietary name, Breo Ellipta. We have completed our review of the proposed proprietary name, Breo Ellipta and have concluded that it is acceptable.

The proposed proprietary name, Breo Ellipta, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. (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 **any** of the proposed product characteristics as stated in your December 6, 2012, 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 Taylor, PharmD, MPH  
Deputy Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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KELLIE A TAYLOR  
03/01/2013



NDA 204275

**METHODS VALIDATION  
MATERIALS RECEIVED**

GlaxoSmithKline  
Attention: Patrick D. Wire, Director, Regulatory Affairs  
Five Moore Drive  
P.O. Box 13398  
Research Triangle Park, NC 27709  
FAX: (919) 315-0033

Dear Patrick Wire:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BREO Ellipta Inhalation Powder, 100/25 mcg and to our November 26, 2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on January 10, 2013, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email ([Michael.Trehy@fda.hhs.gov](mailto:Michael.Trehy@fda.hhs.gov)).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy, Ph.D.  
MVP Coordinator  
Division of Pharmaceutical Analysis  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
01/10/2013



NDA 204275

**INFORMATION REQUEST**

Glaxo Group Limited d/b/a GlaxoSmithKline.  
Attention: Susan Holmes  
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 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BREO™ ELLIPTA™ (fluticasone furoate/vilanterol) 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 February 8th, 2013) in order to continue our evaluation of your NDA.

1. Revise the specification for micronized fluticasone furoate (FF) to remove the footnote 5, as this is inconsistent with cGMP regulations (i.e., 21 CFR 211.84(d)(2)). Revise NDA 22051 accordingly as well.
2. Your tiered microbial limit testing approach should be applied only to stability testing. Add your in-process microbial limit testing to the specifications table as release testing and footnote it as conducted during in process testing.
3. The summaries of analytical methods submitted are helpful for an initial evaluation. However, some summaries do not have sufficient details for the Agency to make a knowledgeable assessment of the method(s) or to repeat the method(s). To facilitate our review, provide an actual copy of each test method used in your release and stability testing, and clearly identify each method with a unique method ID and version number. Revise the drug specifications sheet to include these method identifications.
4. The FF and VI (Vilanterol) Identity and Content Uniformity of Emitted Dose by HPLC method describes (b) (4)  
[REDACTED] Such a description may be confusing and not easy for an analyst new to the method to follow, therefore we recommend that you include as part of the method, a table to illustrate which doses are collected in the

method. An example of such a table is shown below for your consideration, if the method does not already contain a table with this information.

	Dose No																													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Inhaler 1	*			*																										
Inhaler 2							*				*																			
Inhaler 3													*			*														
Inhaler 4																		*			*									
Inhaler 5																											*			*
Inhaler 6	*			*																										
Inhaler 7							*				*																			
Inhaler 8													*			*														
Inhaler 9																			*			*								
Inhaler 10																											*			*

5. Your drug product APSD method noted that (b) (4)  

The Agency does not agree with this approach. You should include appropriate investigation procedures to identify the cause of the failure. Testing of a new inhaler can only occur if such failure is not due to product quality/performance issue. You should also specify that the testing of a new inhaler can only take place a single time for each release/stability testing point per batch.
  
6. Provide the following information regarding your Near Infrared (NIR) method used for water activity determination —
  - a. The instrument listed for water activity measurement is a “Perkin-Elmer Spectrum 400, Frontier (b) (4)”. Discuss what is considered (b) (4)
  - b. For the analytical method for determining the water activity of blisters, specify the environmental conditions in the method (e.g., temperature and relative humidity) under which the test is conducted.
  - c. Please submit a comparison of water activity measured by your NIR procedure and a dedicated water activity analyzer. The comparison should be performed (b) (4)
  
7. The Agency notes that you have indicated in section P.3.3 that regulatory action for minor post approval changes to processing parameters (PP) would be taken in conformance with regulations and guidance. We would like to remind you that, if a change to an PP has a substantial or moderate potential impact to product quality (e.g., as might occur in the case of changes beyond ranges previously studied), you should conform to the requirements for regulatory notification as described in CFR 314.70 (b) or (c).

8. Provide in vitro dose delivery data demonstrating the effect of a mis-use scenario where the mouthpiece cover is only partially indexed.
9. Prespecify the alternative sample sizes and the corresponding k-values (the tolerance coefficient). You may propose extending the two, 1-sided PTIT procedure at sample size (b) (4) by intersecting with the OC curve (b) (4) for the two, 1-sided PTIT procedure at a pre-specified acceptance probability, e.g., 90%.

If you have any questions, contact 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/  
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PRASAD PERI  
01/08/2013



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** January 7, 2013

<b>To:</b> Patrick Wire	<b>From:</b> <b>Angela Ramsey</b>
<b>Company:</b> GlaxoSmithKline	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 919-315-0033	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 919-483-7650	<b>Phone number:</b> 301-796-2300
<b>Subject:</b> NDA 204275 Breo Ellipta (fluticasone furoate/vilanterol) Inhalation Powder	

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

**Comments:**

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Your submission dated July 12, 2012, to NDA 204275, is currently under review. We have the following comments or request(s) for information:

On page 36 of the SAP for Study HZC112206, you describe in “high level” language the approaches to your sensitivity analyses. We request that you submit detailed statistical models corresponding to your general language for the MAR and CDC approaches.

For example, in the case of MAR, you seem to be saying that the imputations will be done for each group separately, i.e. using data from only the respective group. Also, you seem to indicate that both MAR and CDC approaches will be done by fitting a different MI model to each cohort. However you do not state whether the final analysis will be the usual MMRM model. In addition we request that you specify the model and prior distributions used to impute the data.

For the CDC approach, please submit the specific manner in which you use the placebo data (presumably placebo completers) to impute values for active treatment. The same questions, as above, about the use of MI models apply to the CDC method. Specify how you handled missing data in the placebo group.

We request a response by close of business Wednesday, January 9, 2013, to facilitate our review. If you have any questions, please contact Angela Ramsey, Regulatory Project Manager, at 301-796-2284.

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/s/  
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ANGELA H RAMSEY  
01/07/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 13, 2012

TO: GlaxoSmith Kline (GSK)

THROUGH: **Patrick Wire**

FROM: Angela Ramsey

SUBJECT: **Mid-Cycle Communication**

APPLICATION/DRUG: **NDA 204275**

The Division requested a teleconference with GSK to provide a Mid-Cycle review update for Breo Ellipta (fluticasone furoate/vilanterol) Inhalation Powder in the treatment of COPD. The Division commented that the reviews are ongoing and some preliminary thoughts are as follows:

- Strength of the efficacy data is a potential concern due to the inconsistent data among the four pivotal studies
- Safety profile is consistent with other products in the same class, therefore, no major safety issues noted
- No other potential concerns noted with other disciplines.

The Division opened the discussion for any further clarification. GSK questioned whether the inconsistent data is limited to the lung function or does it include the exacerbation data as well. The Division noted concerns with the inconsistencies in both lung function and exacerbation data and whether there is enough evidence to support benefit of the combination over vilanterol alone. The Division will seek potential input during the Advisory Committee (AC) meeting in March. The Division will follow-up with GSK as needed in preparation for the AC.

GSK acknowledged re-submission of tradename request for Breo Ellipta and receipt of CMC/Biopharm IR fax dated, December 10, 2012.

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/s/  
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ANGELA H RAMSEY  
12/14/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: December 10, 2012**

<b>To:</b> Patrick Wire	<b>From:</b> Angela Ramsey
<b>Company:</b> GlaxoSmithKline	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 919-315-0033	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 919-483-7650	<b>Phone number:</b> 301-796-2300
<b>Subject:</b> NDA 204275 Breo Ellipta (fluticasone furoate/vilanterol) Inhalation Powder	

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

**Comments:**

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Your submission dated July 12, 2012, to NDA 204-275, is currently under review. We have the following requests for information:

Human Factors:

You reported that you conducted several formative studies that included patients (ages 7 -83 years) and patients with limited grip function and manual dexterity. Another study was conducted with pediatrics to determine whether the inhaler could be used by children unsupported by an adult. In addition, your validation study included 47 inhaler users (12 – 55+ years of age) and 15 professional/lay caregivers. Please address the following:

1. Indicate the smallest pediatric age that you expect to use the proposed product. Your validation study was conducted with users with the age 12 and above but prior formative studies were conducted with users with the age of 7 and above.
2. The validation study report was not clear on whether pediatric users (ages <18) were able to use the product independently or with the assistance of a caregivers. If caregiver assistance was provided in this study, describe the use scenario and the nature of assistance provided. If assistance is required for use with this product, ensure that the product labeling/instructions for use and your communication to prescribing physicians clearly specify this requirement.
3. Clarify whether the validation study report included users who might have manual dexterity limitations. Provide a characterization of potential limitations with COPD patients, and indicate how your product design has been validated to safeguard against potential use related issues that might occur with patients whose limitations might be more severe than others.

Biopharmaceutics

4. Provide information on the solubility differences of [REDACTED] (b) (4) fluticasone furoate and vilanterol. Explain how these differences, if any, could impact the drug product mean residence time in the lungs and the rate and extend of absorption.
5. If available, provide dissolution profile comparisons for batches tested in phase 3 pivotal trials vs. commercial batches using the investigational or other dissolution method.

We request a response by close of business Friday, December 14, 2012, to facilitate our review. If you have any questions, please contact Angela Ramsey, Regulatory Project Manager, at 301-796-2284.

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/s/  
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ANGELA H RAMSEY  
12/10/2012

## **Executive CAC**

**Date of Meeting: November 27, 2012**

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair  
Abby Jacobs, Ph.D., OND IO, Member  
Paul Brown, Ph.D., OND IO, Member  
Lynnda Reid, Ph.D., DRUP, Alternate Member  
Luqi Pei, Ph.D., DPARP, Presenting Reviewer

Author of Draft: Luqi Pei, Ph.D.

**The following information reflects a brief summary of the Committee discussion and its recommendations.**

NDA #: NDA 204,275  
Drug Name: Vilanterol (GW642444)  
Sponsor: GSK

### **Background:**

Vilanterol is a long acting beta 2 adrenergic agonist being developed as a component of a therapy (Breo Ellipta) for chronic obstructive pulmonary disease. Breo Ellipta is a dry powder inhaler using fluticasone and vilanterol as the active pharmaceutical ingredients. This meeting evaluated the carcinogenicity potential of vilanterol only because the Committee evaluated the carcinogenicity potential of fluticasone previously during the review of NDA 22-051.

The evaluation of the carcinogenicity potential of vilanterol included a battery of genetic toxicity testing and traditional 2-year bioassays in rats and mice. In the genetic toxicity testing battery, vilanterol tested negative in the following assays: bacterial mutation assay in *S. typhimurium* and *E. coli* (Ames test), rat bone marrow micronucleus assay, in vitro unscheduled DNA synthesis (UDS) assay, and Syrian Hamster embryonic (SHE) cell transformation assay. Vilanterol tested equivocal in the mouse lymphoma assay.

The bioassays were 2-year inhalation carcinogenicity studies of vilanterol in mice and rats. Animals were exposed to various doses of vilanterol daily for up to 104 weeks. Vilanterol was delivered by nose-only inhalation exposure for 60 minutes per day. The Executive CAC concurred with the dose selection for each study and the dose adjustments during the study in rats. Final reports of the studies were submitted in the NDA submission.

### **Rat Carcinogenicity Study**

Sprague-Dawley rats (60/sex/dose) were exposed by nose-only inhalation to vehicle (C), which was lactose powder, low-dose (LD), mid dose (MD), mid-high dose (HD-1), and high dose (HD-2) of vilanterol for up to 104 weeks. Specifically, males were treated with 0, 10.5, 84.4, 223, or 657- $\mu$ g/kg/day vilanterol (achieved doses) for 101 weeks. Females

were exposed to the same doses for 85 weeks and dose adjustments were made subsequently due to excessive mortalities in the vilanterol-treated groups. The dose adjustments consisted of the following: dosing was discontinued in the HD-1 and HD-2 groups and vilanterol doses in the LD and MD groups were reduced to 3.5 and 28.2 µg/kg/day, respectively. The three top-dose groups were terminated during weeks 95 – 96 when the number of survivors reached 15/group.

Both male and female rats had dose-related mortality ( $P < 0.01$ ) and shortened latency to pituitary neoplasms, which were considered to be the cause of death, although the increases in overall tumor incidence did not reach the statistically significant level of 0.01 for the common tumor. Control incidences were 70% for males and 90% for females. The three highest dose groups of females also had increased incidences of mesovarian leiomyomas. Table 1 presents the leiomyoma incidences in the mesovarian ligament in rats. Figure 1 presents the time-course of pituitary adenoma-related deaths in males as an example.

Table 1: Mesovarian Leiomyoma Incidences in Rats

Sex	Incidence (p-value)				
	0	10.5/3.5	84.4/28.2	223	657
F	0/60	0/60	5/60 (0.007)	4/60 (0.020)	4/60 (0.020)

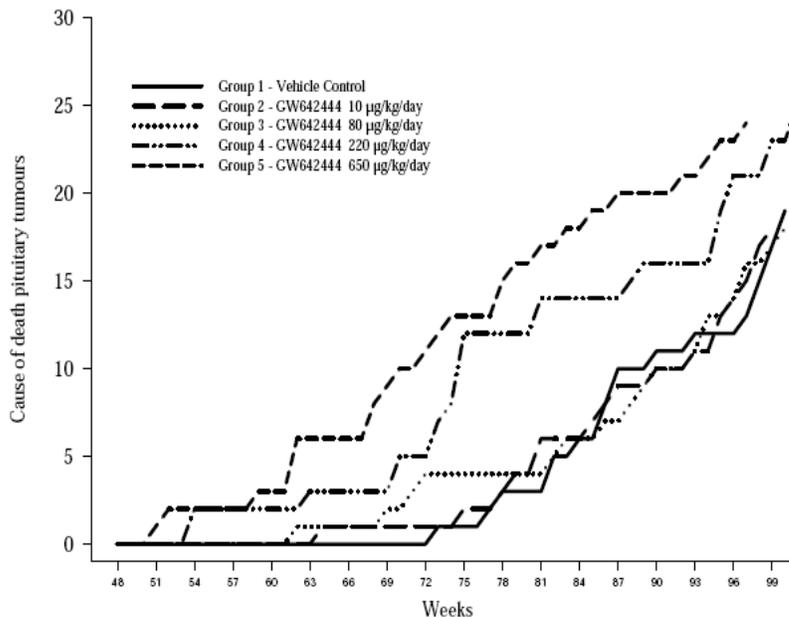


Figure 1: Pituitary tumor-related deaths in male rats.

### Mouse Carcinogenicity Study

Mice (84/sex/dose, CD-1) were treated by nose-only inhalation with 0 (C), 6 (LD-1), 62 (LD-2), 615 (MD), 6,150 (HD-1), or 29,500 (HD-2)-µg/kg/day vilanterol (achieved doses) for 101 – 104 weeks. The HD-2 female group showed a statistically significant increase in ovarian tubulostromal adenoma ( $p = 0.014$ ) (incidence: 0/84, 0/83, 1/84, 0/84, 2/84 and

6/83 in the C, LD-1, LD-2, MD, HD-1 and HD-2, respectively). Although, the four top-dose groups in females showed numerical increases in the incidence of leiomyomas and leiomyosarcomas in the uterus, alone or in combination, none of the increases reached the statistically significant level of  $p < 0.01$ .

Table 2: Incidences of Tubulostromal Adenomas in Ovaries in Female Mice

	Vilanterol ( $\mu\text{g}/\text{kg}/\text{day}$ )					
	0	6	62	615	6150	29,500
Incidence (overall)	0/84	0/83	1/84	0/84	2/84	6/83
P-value (vs. vehicle)	-	-	0.500	-	0.249	0.0137

### Executive CAC Recommendations and Conclusions:

#### *Rat study:*

1. The Committee agreed that the study was acceptable.
2. The Committee considered the following neoplasms to be clearly drug-related:
  - Adenomas of the pituitary gland in males and females (based on dose-related decreases in tumor latency associated with increased lethality)
  - Leiomyomas of mesovarian ligaments in females.

#### *Mouse study:*

- The Committee agreed that the study was acceptable.
- The Committee considered the tubulostromal adenomas in the ovaries to be drug related.

David Jacobson-Kram, Ph.D.  
Chair, Executive CAC

cc:\n  
/Division File, DPARP  
/TRobison, DPARP  
/LPei, DPARP  
/ARamsey/PM, DPARP  
/ASeifried, OND IO

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/s/  
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ADELE S SEIFRIED  
11/30/2012

DAVID JACOBSON KRAM  
11/30/2012



NDA 204275

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

GlaxoSmithKline  
Attention: Patrick D. Wire  
Director, Regulatory Affairs  
P.O. Box 13398  
Research Triangle Park, NC 27709

Dear Patrick D. Wire:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BREO Ellipta (Fluticasone furoate and Vilanterol Trifenatate) Inhalation Powder, 100/25 mcg.

We will be performing methods validation studies on BREO Ellipta (Fluticasone furoate and Vilanterol Trifenatate) Inhalation Powder, 100/25 mcg, as described in NDA 204275.

In order to perform the necessary testing, we request the following sample materials and equipments:

**Method, current version**

Determination of Vilanterol drug-related impurities content in Fluticasone furoate/Vilanterol inhalation powder by HPLC

**Samples and Reference Standards**

- (b) (4) vilanterol trifenate reference standard
- (b) (4) fluticasone furoate reference standard
- (b) (4) impurity
- (b) (4) lactose monohydrate/magnesium stearate
- (b) (4) blister packs of Fluticasone furoate/Vilanterol inhalation powder

**Equipment**

- 1 XBridge C18 3.5 micron, 150 x 4.6 mm column

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: Sample Custodian  
1114 Market Street, Room 1002  
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy  
MVP coordinator  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
11/26/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: November 15, 2012**

<b>To:</b> Patrick Wire	<b>Angela Ramsey</b>
	<b>From:</b>
<b>Company:</b> GlaxoSmithKline	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 919-315-0033	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 919-483-7650	<b>Phone number:</b> 301-796-2300
<b>Subject:</b> NDA 204275 Breo Ellipta (fluticasone furoate/vilanterol) Inhalation Powder	

**Total no. of pages including cover:** 2      3

**Comments:**

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**Document to be mailed:**                      YES                      xNO

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NDA 204275

Your submission dated July 12, 2012, to NDA 204-275, is currently under review. We have the following request for information:

1. Provide your analysis of the co-primary endpoints, weighted mean FEV1 and trough FEV1, by GOLD category for trials HZC112206 and HZC112207.

To facilitate our review, we request a response by Monday, December 3, 2012. If you have any questions, please contact Angela Ramsey, Regulatory Project Manager, at 301-796-2284.

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/s/  
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ANGELA H RAMSEY  
11/15/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: October 24, 2012**

<b>To:</b> Patrick Wire	<b>From:</b> Angela Ramsey
<b>Company:</b> GlaxoSmithKline	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 919-315-0033	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 919-483-7650	<b>Phone number:</b> 301-796-2300

**Subject:** NDA 204275 Breo Ellipta (fluticasone furoate/vilanterol) Inhalation Powder

**Total no. of pages including cover:** 2      3

**Comments:**

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NDA 204275

Your submission dated July 12, 2012, to NDA 204-275, is currently under review. We have the following request for information:

1. For the All Studies pooled dataset, provide the exposure adjusted rate for the following Adverse Events of Special Interest as defined by the Preferred Terms included in Appendix 2:
  - Pneumonia
  - Cardiovascular Effects
  - Bone disorders

We request a response by close of business Monday, November 5, 2012, to facilitate our review. If you have any questions, please contact Angela Ramsey, Regulatory Project Manager, at 301-796-2284.

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/s/  
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ANGELA H RAMSEY  
10/24/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: October 11, 2012**

<b>To:</b> Patrick Wire	<b>From:</b> Angela Ramsey
<b>Company:</b> GlaxoSmithKline	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 919-315-0033	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 919-483-7650	<b>Phone number:</b> 301-796-2300
<b>Subject:</b> NDA 204275 Breo Ellipta	

**Total no. of pages including  
 cover:** 2

**Comments:**

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Your submission dated July 12, 2012, to NDA 204-275 is currently under review. We have the following request for information:

1. We note inconsistencies between the bone fracture data presented in the Integrated Summary of Safety Tables 2.160 and 2.190. Some of these differences may be due to the different Preferred Terms included in Appendix 2 defining the Adverse Events of Special Interest; however, it is unclear if the terms used account for all of the differences.

For instance, the number of ankle fractures listed in Table 2.190 is one event each in the FF/VI 50/25, FF/VI 100/25, and FF/VI 200/25 treatments groups, but the FF/VI 100/25 and 200/25 treatment groups have zero ankle fracture events in Table 2.160.

In addition, there are differences in the total number of fractures reported. For instance, in Table 2.160 there are 14 total fractures for the FF/VI 50/25 group (24 bone disorders events minus 2 skeletal injuries, 5 osteoporosis and 5 osteopenia events). However, in Table 2.190 there are a total of 15 fracture incidents for this same treatment group. Provide clarification of these discrepancies.

We request a response by close of business Friday, October 26, 2012. If you have any questions, please contact Angela Ramsey, Regulatory Project Manager, at 301-796-2284.

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/s/  
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ANGELA H RAMSEY  
10/11/2012



NDA 204275

**NDA ACKNOWLEDGMENT**

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

Attention: Patrick Wire, Pharm.D.  
Product Director, Respiratory Group

Dear Dr. Wire:

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: Breo Ellipta (fluticasone furoate/vilanterol) Inhalation Powder

Date of Application: July 11, 2012

Date of Receipt: July 12, 2012

Our Reference Number: NDA 204275

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 September 10, 2012, 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](mailto: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 Regulatory Project Manager, at (301) 796-2284.

Sincerely,

*{See appended electronic signature page}*  
Angela Ramsey R.N., M.S.N  
Senior Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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ANGELA H RAMSEY  
07/24/2012



NDA 204275

**FILING COMMUNICATION**

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

Attention: Patrick Wire, Pharm.D.  
Product Director, Respiratory Group

Dear Dr. Wire:

Please refer to your New Drug Application (NDA) dated July 11, 2012, received July 12, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Breo Ellipta (fluticasone furoate and vilanterol) Inhalation Powder.

We also refer to your amendments dated July 12, and August 13, 16, 27, and 29, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is May 12, 2013.

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, midcycle, 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 March 31, 2013.

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

Clinical

1. We note inconsistencies in your pivotal phase 3 trial results, particularly as they relate to the benefit of fluticasone furoate/vilanterol over vilanterol alone. Whether the data sufficiently support the benefit of the combination product over vilanterol alone will be a review issue.

Nonclinical

2. The evaluation and interpretation of the 2-yr carcinogenicity studies could be review issues. Specifically, validity of the 2-yr mouse carcinogenicity study and the significance of pituitary tumors in rats will be determined during the review.

We request that you submit the following information:

Quality

3. Modify your drug product specifications [REDACTED] (b) (4)  
[REDACTED]
4. Separate acceptance criteria are proposed for the Aerodynamic Particle Size Distribution specifications for release and through life. The release specifications may be considered in house specifications; clarify that the regulatory specifications are the “through life” specifications.
5. Provide information pertaining to any different inhaler designs used in clinical studies prior to phase IIb, and provide summary comparative performance data with later designs.
6. Provide a description of the labeling process for your drug product.
7. Update your methods validation section by providing a tabular list of all samples and standards (including the numbers/amounts of each to be included), as well as Material Safety Data Sheets for the standards.
8. Provide 4 samples of the drug product.

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.

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

1. Excessive length in the Highlights section of the label. The length of the HL section must be less or equal to one-half the page.
2. Please revise label to include intrinsic and extrinsic factor information in a forest plot as shown in the following reference:  
*Essential Pharmacokinetic Information for Drug Dosage Decisions: A Concise Visual Presentation in the Drug Label. Clinical Pharmacology & Therapeutics. Sep 2011; 90(3): 471-474.*

We request that you resubmit labeling that addresses these issues by October 12, 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) and Medication Guide. 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 Medication Guide 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/  
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BADRUL A CHOWDHURY  
09/19/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 77855

**MEETING MINUTES**

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

Attention: Christopher J. Stotka, Pharm.D.  
Director, Respiratory  
US Regulatory Affairs

Dear Dr Stotka:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GW685698/GW642444 Inhalation Powder.

We also refer to the meeting between representatives of your firm and the FDA on October 12, 2011. The purpose of the meeting was to discuss plans for NDA submission for fluticasone furoate/vilanterol in the treatment of Asthma.

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) 796-796-2284.

Sincerely,

*{See appended electronic signature page}*

Angela Ramsey, RN, MSN  
Senior Regulatory Project Manager  
Division of Pulmonary, Allergy and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** October 12, 2011 at 11:00- 12:00 EST  
**Meeting Location:** FDA White Oak Building 22, Conference Room: 1417

**Application Number:** IND 77855  
**Product Name:** GW685698/GW642444 Inhalation Powder.

**Indication:** Asthma  
**Sponsor/Applicant Name:** GlaxoSmithKline

**Meeting Chair:** Badrul A. Chowdhury, M.D., Ph.D., Division Director  
**Meeting Recorder:** Angela Ramsey, RN, MSN, Senior Regulatory Project

**FDA ATTENDEES**

Badrul A. Chowdhury, M.D., Ph.D., Division Director  
Angela Ramsey, RN, MSN, Senior Regulatory Project  
Brian Porter, M.D., Clinical Reviewer  
Susan Limb, M.D., Clinical Team Leader  
Craig M. Bertha, PhD, Quality Reviewer  
Prasad Peri, PhD, Quality Branch Chief  
Sally Seymour, M.D., Deputy Director for Safety  
Joan Buenconsejo, Ph.D., Statistician  
Ying Fan, Ph.D., Clinical Pharmacology Reviewer  
Partha Roy, Ph.D., Senior Clinical Pharmacology Reviewer

**SPONSOR ATTENDEES**

Brett Haumann, M.D., Medicines Development Leader  
Darrell Baker, SVP Respiratory Medicines Development  
Mauri Fitzgerald, VP, Global Regulatory Affairs  
Loretta Jacques, Ph.D., Director, Clinical Development  
Sally Lettis, Ph.D., Director, Statistics and Programming  
Patrick Wire, PharmD., Group Director, Global Regulatory Affairs  
Christopher Stotka, PharmD., Director, Global Regulatory Affairs

## BACKGROUND

GlaxoSmithKline (GSK) submitted a Type B meeting request dated, July 26, 2011, to discuss plans for NDA submission for fluticasone furoate/vilanterol inhalation powder in the treatment of asthma. GSK submitted background material dated, September 12, 2011. Upon review of the material, the Division responded via secure email on October 7, 2011. GSK requested to continue the face-to-face meeting to discuss questions 3, 4, 6, 10 and the additional comment regarding datasets.

The content of the email is below. Any discussions that occurred during the meeting are captured directly under the relevant response. The sponsor's questions are in ***bold italics***; the Division's response is in *italics*; and the discussion is in normal font.

## DISCUSSION

### *Introductory Comment*

(b) (4)



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/s/  
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ANGELA H RAMSEY  
10/27/2011

9/14/11



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 77855

**MEETING MINUTES**

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

Attention: Sue Holmes, M.S.  
Director  
Global Pre-Approval, CMC Regulatory Affairs

Dear Ms Holmes:

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

We also refer to the meeting between representatives of your firm and the FDA on September 14, 2011. The purpose of the meeting was to discuss CMC aspects for your planned NDA submission for fluticasone/vilanterol in the treatment of 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) 796-2284.

Sincerely,

*{See appended electronic signature page}*

Angela Ramsey, RN, MSN  
Senior Regulatory Project Manager Division of  
Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** September 14, 2011  
**Meeting Location:** White Oak Building 22, Conference Room: 1417

**Application Number:** 77855  
**Product Name:** fluticasone furoate/vilanterol.  
**Indication:** COPD  
**Sponsor/Applicant Name:** GlaxoSmithKline

**Meeting Chair:** Prasad Peri  
**Meeting Recorder:** Angela Ramsey

**FDA ATTENDEES**

Craig M. Bertha, PhD, Quality Reviewer  
Alan Schroeder, Ph.D., CMC Lead  
Prasad Peri, PhD, Quality Branch Chief  
Brian Porter, M.D., Clinical Reviewer  
Susan Limb, M.D., Clinical Team Leader  
Angela Ramsey, RN, MSN, Senior Regulatory Project

**SPONSOR ATTENDEES**

Jason Creasey, Manager, Shared Project Technical Services  
Mike Denham, Director, Statistics and Programming  
Karl Ennis, Manager, Inhaled Product Analysis  
Susan Holmes, Director, CMC Regulatory Affairs  
Paul Johnson, Director, Medicine and Process Development  
Richard Walker, Manager, DPI Delivery Systems  
Mark Whitaker, Director, Inhaled Product Development

## BACKGROUND

GlaxoSmithKline (GSK) submitted a Type B meeting request dated, April 19, 2011, to discuss the chemistry aspects for their planned NDA submission for fluticasone furoate/vilanterol in the treatment of COPD. GSK submitted their briefing package material dated, August 15, 2011. Upon review of the material, the Division responded via secure email on September 12, 2011. GSK requested to continue with the face-to-face meeting to clarify questions 11, 16, 17, 22, 23, and the additional comment.

The content of the email is below. Any discussions that occurred during the meeting are captured directly under the relevant response. The sponsor's questions are in *bold italics*; the Division's response is in *italics*; and the discussion is in normal font.

## DISCUSSION

### Drug Substance: Vilanterol Trifenatate

#### Question 1

***Does the Agency agree that it is appropriate to file the vilanterol trifenatate drug substance information using a DMF [REDACTED] (b) (4)?***

#### FDA Response

*It is acceptable for you provide a letter of authorization in the application and in a type II DMF that has been assigned a number by the Agency, for the vilanterol trifenatate drug substance information. The NDA should still include the specifications used for acceptance of the vilanterol trifenatate, with all of the parameters appropriate for the dosage form.*

#### Discussion

No Discussion occurred.

#### Question 2

***GSK considers [REDACTED] (b) (4) [REDACTED] Does the Agency agree?***

#### FDA Response

*The general approach taken [REDACTED] (b) (4) appears to be reasonable. A detailed evaluation [REDACTED] (b) (4) will be done at the time of our review of the NDA.*

#### Discussion

No discussion occurred.

**Question 3**

*GSK is complying with the three conditions outlined by the Agency at the End of Phase 2 meeting. Can the Agency confirm acceptability of the proposed [REDACTED] (b) (4)?*

**FDA Response**

*Based on the generally described stipulations outlined in 2.2 (p. 9), we confirm the acceptability [REDACTED] (b) (4)*

*However, we may have comments [REDACTED] (b) (4) upon the full evaluation during the NDA review (see response to question 2).*

**Discussion**

No discussion occurred.

**Drug Substance: Fluticasone Furoate**

**Question 4**

*Does the Agency agree that it is appropriate to cross-reference fluticasone furoate information approved under NDA 22-051, Veramyst Nasal Spray, and to only provide additional fluticasone furoate information specific to Fluticasone Furoate/Vilanterol Inhalation Powder in the NDA for Fluticasone Furoate/Vilanterol Inhalation Powder?*

**FDA Response**

We agree.

**Discussion**

No discussion occurred.

**Drug Product:**

**Question 5**

*Although it is proposed to market only one drug product strength for the COPD indication, GSK intends to provide CMC information in the COPD NDA for all 3 drug product strengths evaluated in Phase 3 clinical studies [REDACTED] (b) (4)*

*[REDACTED] Does the Agency agree with this approach?*

**FDA Response**

*We agree with this approach.*

**Discussion**

No discussion occurred.

Question 6

(b) (4)

*Does the Agency agree?*

FDA Response

Your application of a risk management approach (b) (4)

(b) (4)  
is reasonable. Include in your application your definition of Proven Acceptable Ranges and how you intend to use them related to post-approval changes. Also, we agree (b) (4)

Discussion

No discussion occurred.

Question 7

*Does the Agency agree that the batches described are suitable for inclusion in the database used to justify acceptance criteria for the specification tests for Fluticasone Furoate/Vilanterol Inhalation Powder?*

FDA Response

We agree, as long as batches (b) (4)  
(b) (4) are not included in the database.

Discussion

No discussion occurred.

Question 8

*GSK believes that the PTI Test provides a more discriminating assessment of dose uniformity than the Zero Tolerance approach defined in the FDA's November 1998 Draft Guidance for Industry - Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products - Chemistry, Manufacturing, and Controls and intends to apply the criteria outlined in the FDA's October 25, 2005 Advisory Committee of Pharmaceutical Science proposal for Parametric Tolerance Interval Test (PTI Test) criteria. Has the Agency's perspective changed in the interim particularly with respect to the suitability of the coverage and goalposts proposed to assure content uniformity of the emitted dose for inhaled drug products?*

FDA Response

No, our perspective has not changed.

Discussion

No discussion occurred.

Question 9

*GSK proposes to use (b) (4) to assure the control of APSD in the commercial products. GSK recognises that (b) (4) will be a review issue however, in order to present data in the appropriate format in the NDA, GSK would like the Agency to highlight any concerns with the APSD (b) (4) proposed?*

FDA Response

*The use (b) (4) is consistent with our recommendations for the number that could be used for the APSD acceptance criteria. (b) (4)*

Discussion

No discussion occurred.

Question 10

*Does the Agency agree with the statistical approach proposed for setting the acceptance criteria for APSD?*

FDA Response

*The evaluation of your statistical approach used to derive and justify the proposed acceptance criteria will be done during the review of the application. Without full evaluation of the APSD data in the context of the product stability and in consultation, as necessary, with the other members of the review team, it is premature to comment on the statistical approach that you propose to use.*

Discussion

GSK asked if it would be possible to have an interactive dialog in general during review of the NDA and specifically with regard to the statistical approach that they plan to use to justify and set the APSD acceptance criteria. The CMC team indicated that they would not hesitate to contact GSK if they were to have an important question during the review. With respect to the statistical approach for the APSD acceptance criteria, the CMC indicated that this can not be reviewed by itself without consideration of the actual data that are obtained for that test parameter.

Question 11

*GSK proposes to control content uniformity of the product (b) (4)*

*The suitability of each batch is confirmed by application of the emitted dose test and PTIT*

*criteria as part of batch release testing. Does the Agency agree with the proposed approach or have any comments?*

FDA Response

*You have presented data in the package to support your assertion that for a series of batches, you have been able to achieve uniformity of the formulation* (b) (4)

*Therefore, you propose that effective control of formulation drug content uniformity will be achieved* (b) (4)

*We do not agree* (b) (4)

*You are encouraged to include as a part of your drug content uniformity control strategy, appropriate in-process testing* (b) (4)

Discussion

GSK will revise proposed control strategy and include (b) (4) as recommended by the Division. Testing will be described in detail in the NDA submission. GSK intends to use the same data and the mean to provide assay data and asked whether this would be acceptable to the Division. The Division responded that GSK's proposal is acceptable.

Question 12

*GSK proposes to apply acceptance criteria for drug content and drug-related impurities in the specification* (b) (4) *A test and acceptance criteria for drug-related impurities in drug substance will be performed at release. Does the Agency have any comments on this approach?*

FDA Response

*The label claim strength for inhalation powder drug products is the metered dose. In this case that is the amount of drug in the blisters. Therefore, as per 21 CFR 211.165(a), an assay test is to be performed to determine the strength for each drug product batch at the time of release.*

(b) (4)  
*In order to support your proposal, include in the NDA, a summary of the risk assessment that you performed for potential situations* (b) (4)

*and the way in which these would be detected or avoided. The Agency will consider your comprehensive presentation at the time of NDA evaluation to determine if your proposal* (b) (4) *is warranted.*

Discussion

No discussion occurred.

**Question 13**

**Does the Agency agree** [REDACTED] (b) (4) [REDACTED] ?

FDA Response

[REDACTED] (b) (4) [REDACTED]  
[REDACTED]  
[REDACTED] Whether the associated data demonstrate that there would be some value [REDACTED] (b) (4) [REDACTED] will be evaluated at the time of NDA review. The justification for the absence of such a test in the drug product specification can be included in the P.5.6 section of the NDA.

Discussion

No discussion occurred.

**Question 14**

**Would the Agency find animations of the inhaler operation useful and is a storage disk a suitable means of submitting such information to the Agency?**

FDA Response

Yes, these would likely be useful for our understanding of the inhaler operation.

Discussion

No discussion occurred.

**Question 15**

**Does the Agency agree that a Human Factors – User Error study, in conjunction with robustness testing and the pre-defined [REDACTED] (b) (4) [REDACTED] protocol to demonstrate the in-vitro pharmaceutical performance is unaffected by this improvement, are appropriate to support implementation of the audible click at launch?**

FDA Response

We agree. Refer to the draft guidance Applying Human Factors and Usability Engineering to Optimize Medical Device Design (June 2011) and ISO 14791:2007, Medical Devices – Application of Risk Management to Medical Devices.

Discussion

No discussion occurred.

**Question 16**

***Does the Agency agree with the proposal for the control of leachables in Fluticasone Furoate/Vilanterol Inhalation Powder?***

**FDA Response**

*The data that you have provided regarding the extractables/leachables and the correlation will be evaluated at the time of NDA review in light of the PQRI and Agency recommendations.*

*However, apart from safety concerns for potential leachables, the Agency has consistently recommended that applicants have some method and associated acceptance criteria for assuring the batch-to-batch compositional consistency of the critical components of the DPI which are likely linked to reproducible drug product performance. In the past, routine extractables profiling (with multiple solvent-based extraction) has been one method by which this was done, although there may be alternate appropriate methods. In the NDA you will need to address how you will assure the compositional consistency of the important device components.*

**Discussion**

GSK acknowledged the Division's concerns for a method to examine compositional consistency of the critical device component (e.g. mouthpiece). GSK proposes (b) (4) and feels that this will meet the Division's requirements. But in addition, GSK proposed (b) (4). The Division asked that GSK also provide some data (b) (4).

**Question 17**

***GSK intends to use the (b) (4) foil laminate tray for the commercial product. Does the Agency agree that the data package proposed for the file is sufficient to demonstrate that the secondary packaging used to date ((b) (4) tray) are fully representative of the intended commercial product?***

**FDA Response**

*We generally recommend that the primary stability batches of drug product have the configuration of the final to-be-marketed drug product.*

*We acknowledge that you are now proposing a third version of the secondary protective packaging ((b) (4) foil trays).*

*As you propose (b) (4) with the new (b) (4) tray, additional information to what has been provided in this meeting package will need to be included in the NDA to allow us to determine if the product with the (b) (4) trays can be considered to be representative of product with the (b) (4) trays. This information includes:*

*Updated comparative moisture vapor transmission rate and pack relative humidity data for the two protective packaging tray versions*

*Results of all seal integrity testing that was performed in-process for the two different tray versions*

*Comparison of the qualified sealing conditions (i.e., temperatures, speeds) for each of the tray versions*

*A comparison of the composition of the materials of construction both tray versions,  
[REDACTED] (b) (4)  
[REDACTED] (reference to DMFs may be appropriate)*

*Refer to the response to Question 19 below.*

Discussion

GSK referred to table 48 ( pg 1184 in background material) and clarified their intention is to provide 3 months of moisture vapor transmission data at 40°C/75%RH to support the switch from the (b) (4) to the (b) (4) trays, as well as 6 months of 40°C/75%RH pack relative humidity data comparing the two protective packaging types. No additional data are planned to be submitted during the review period. The Division stated the proposed plan seems appropriate.

GSK also clarified that they have pack integrity data which assesses the integrity of the seal of the protective packaging .GSK will provide data for both (b) (4) tray versions to demonstrate similarity. The Division found the proposal acceptable.

Question 18

*Does the Agency agree with the proposal to update the stability data during the first 100 days post NDA filing?*

FDA Response

*It is unclear if you are proposing to submit the stability update during the first 100 days after the submission or the filing of the NDA. If you truly mean the filing of the NDA, then receipt of the stability update could be as late as 175 days into the review cycle. In such a case we do not agree with the proposal. However, if your 100 day window refers to your submission date, then you may update the stability data as proposed. However, although we would make every effort to include these updated data in our evaluation, depending on our available resources, we can not guarantee that we would be able to review amendments that arrive after the original submission. In such a case, our decisions may then need to be based on our evaluation of the data provided in the original submission alone.*

Discussion

No discussion occurred.

Question 19

*Does the Agency agree with the proposal that there is no requirement to provide additional stability data in the (b) (4) tray at time of file and that stability data on the (b) (4) tray will be generated for the annual post-approval stability commitment?*

FDA Response

*It is premature to agree with the proposal until we have evaluated all of the information and data for the two types of trays (see response to question 17) and conclude that the (b) (4) trays are representative of the (b) (4) trays. However, based on the limited data provided in the meeting package it appears that your approach will be acceptable.*

Discussion

No discussion occurred.

Question 20

*Does the Agency agree that the shelf-life for the commercial product can be defined on the longest term stability data (b) (4) ?*

FDA Response

*Although it is premature to agree to your proposal, based on the limited information provided it seems likely that the shelf-life can be defined based on the drug product (b) (4) if it is confirmed that the product in the (b) (4) tray will be representative of the commercial product in the (b) (4) tray (see responses to questions 17 and 19) and if we determine that the stability data (particularly the pack RH data) for the product in the (b) (4) tray are comparable to that for the product (b) (4),*

*We also ask that you provide the results of your statistical analyses of the long term stability data for any trending parameters that support your proposed shelf-life period.*

Discussion

No discussion occurred.

Question 21

*Does the Agency agree (b) (4) ?*

FDA Response

*Although you may have data that demonstrate that your product routinely does not display any significant change in dosing variability with time, this does not mean that such changes can not occur for some reason at a later time. We do not agree with your belief (b) (4) : Apply acceptance criteria for individual delivered dose uniformity during the testing of your routine annual stability batches.*

Discussion

No discussion occurred.

**Question 22**

***GSK intends to provide the stability data in the format as described. Does the Agency agree that the supplied format is acceptable [REDACTED] (b) (4) [REDACTED] ?***

**FDA Response**

*No, we do not agree with the format and it would greatly expedite our review if you would provide the following as well:*

*For both the delivered dose uniformity (DDU) and aerodynamic particle size distribution (APSD) group tabular data, provide the individual data as opposed to the ranges, along with the standard deviation observed for each determination.*

*Provide plots of the mean stage-by-stage APSD data as a function of time for the product stored under long term, accelerated, and in-use stability conditions so that profile changes that may be masked by the groupings will be evident.*

*Provide plots of the mean and individual stability data for the most important (i.e., delivered dose uniformity (DDU), APSD groupings) and any trending parameters, if applicable, for the each storage condition. If possible, include mean and individual data on the same plots.*

*The use of colored plots is encouraged as is the inclusion of the proposed acceptance criteria on the plots for reference.*

**Discussion**

GSK will provide data plots in the format requested by the Division, and ask whether the Division would like to see individual data. The Division would like to see each result in order to see changes in variability. GSK proposed to provide an Excel spreadsheet with individual data and a summary table in the NDA submission. The Division commented that as long as the data are present and a graphical presentation is available, that would be sufficient to expedite our review. The Division emphasized that due to the size of the application, that graphical presentations and summaries will be important in helping streamline the CMC review.

**General/Regional:**

**Question 23**

***For the demonstrator inhalers, GSK does not propose to generate registration information for submission in the NDA for Fluticasone Furoate/Vilanterol Inhalation Powder. Does the Agency agree that this is not required? If required, what specific information would the Agency expect to be submitted?***

FDA Response

*We assume that "demonstration inhalers" do not contain any formulation components (no actives or inactives) and that these would be identical to the devices used for the to-be-marketed drug product. If that is correct, no registration information need be provided.*

Discussion

GSK proposed two variants of demonstration devices as an educational component for providers.

[REDACTED] (b) (4)  
The Division confirmed that no registration information would then be required for the NDA submission for these demonstration devices. GSK will submit samples to the Division once available.

Question 24

*GSK proposes* [REDACTED] (b) (4)

[REDACTED] Does the Agency agree?

FDA Response

*No, we do not agree. Provide the batch production record for each batch that is used to conduct a primary stability study as required by the regulations.*

Additional Comment

*Each batch of drug product must be tested for microbiological quality and foreign particulates, i.e., a "complies if tested" approach is not acceptable for any important quality parameter that is part of the specification [see 21 CFR 211.165].*

Discussion

GSK intends to ensure microbiological quality of every batch using a 2 tier approach:

- Tier 1: Water activity determination
- Tier 2: Microbiological testing of the finished product

This will be backed up by microbial controls on the incoming raw materials and microbiological testing during drug filling.

GSK clarified that this approach is testing/control of the finished product, not skip lot testing. The Division commented that this approach is reasonable, but acceptance of details will be a review issue.

The Division proposed that all batches are tested for foreign particulate matter for the NDA submission. GSK agreed that this will be done at release.

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/s/  
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ANGELA H RAMSEY  
09/23/2011



IND 77855

**MEETING MINUTES**

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

Attention: Patrick Wire  
Product Director, US Regulatory Affairs

Dear Mr Wire:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GW685698X/GW642444 Inhalation Powder.

We also refer to the meeting between representatives of your firm and the FDA on July 13, 2011. The purpose of the meeting was to discuss data supporting the use of FF/VI inhalation powder in the treatment of COPD and asthma.

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) 796-2284.

Sincerely,

*{See appended electronic signature page}*  
Angela Ramsey RN, MSN  
Senior Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre- NDA

**Meeting Date and Time:** July 13, 2011  
**Meeting Location:** White Oak, Building 22, Conference Room 1417

**Application Number:** 77855  
**Product Name:** GW685698X/GW642444 Inhalation Powder.  
**Indication:** Treatment of Asthma and COPD  
**Sponsor/Applicant Name:** GlaxoSmithKline

**Meeting Chair:** Badrul Chowdhury, M.D., Ph.D.  
**Meeting Recorder:** Angela Ramsey RN, MSN

**FDA ATTENDEES**

Badrul A. Chowdhury, M.D., Ph.D, Division Director  
Susan Limb, M.D., Clinical Team Leader  
Brian Porter, M.D., Ph.D., M.P.H., Clinical Reviewer  
Molly Shea, Ph.D., Pharmacology/Toxicology Supervisor  
Asoke Mukherjee, Ph.D., Pharmacologist/Toxicologist Reviewer  
Joan Buenconsejo, Ph. D., Mathematical Statistician Team Leader  
David Hoberman, Statistical Reviewer

**SPONSOR ATTENDEES**

Brett Haumann, MD- Medicine Development Leader  
Darrell Baker- VP Medicine Development- Respiratory  
Courtney Crim, MD- Director, Clinical Development  
Loretta Jacques- Director, Clinical Development  
Mauri Fitzgerald- VP, Global Regulatory Affairs  
Chris Powell- VP, pre-clinical toxicology  
Julie Anderson- Director, Statistics  
Patrick Wire- Director, Global Regulatory Affairs

## BACKGROUND

GlaxoSmithKline (GSK) submitted Type B meeting request dated, March 1, 2011, to discuss data to support the use of FF/VI inhalation powder in the treatment of COPD and Asthma. GSK submitted their briefing package dated, June 14, 2011. Upon review of the material, the Division responded via secured email on July 6, 2011. GSK requested to continue the face-to-face meeting to discuss Introductory Comments, the additional question submitted on July 5, 2011, and responses to questions 6, 19, 20, 22, 23, and 24.

### \*Introductory Comment:

*Preliminary review of the data from the completed lung function trials raises concerns regarding the lack of robust results to support the proposed bronchodilation indication and satisfy the Combination Rule [21 CFR 300.50]. Only the lowest dose, fluticasone furoate/vilanterol (FF/VI) 50/25 mcg, showed a statistically significant benefit in terms of trough FEV1 over VI, and there does not appear to be a replicated comparison of FF/VI 50/25 to placebo in the clinical program. Trough FEV1 data for FF/VI 100/25 and 200/25 compared to VI were not supportive. The ongoing COPD exacerbation trials may provide efficacy support for the addition of FF to VI, but positive exacerbation results will be problematic in the context of the negative lung function results observed to date, as was previously discussed during the June 17, 2009, End-of-Phase 2 meeting. Furthermore, it is uncertain that the exacerbation trials will provide sufficient data to distinguish and justify multiple dose levels of FF/VI for COPD. The completed lung function trials do not appear to justify multiple dose levels.*

*These concerns are accentuated by the proposed sequence of NDA submissions for the FF/VI, FF, and VI products. In the past, the development of inhaled corticosteroid/long-acting beta-agonist (ICS/LABA) combination products in COPD has been preceded by development and approval of the monocomponents and the combination in asthma. Experience in an asthma population informs COPD dose selection for each monocomponent and provides relevant safety information. Subsequent development of the LABA monocomponent in COPD confirms dose selection for COPD. A program for the ICS/LABA combination in COPD can then rely on the totality of this information to help establish the relative benefit of ICS plus LABA over LABA alone.*

*The proposed submission of the FF/VI NDA for COPD inverts this regulatory precedent, and therefore, does not benefit from a previously established body of information for the monocomponents and the combination. Whether the proposed inclusion of other supportive information will compensate is uncertain and will be a review issue.*

*In addition, the Division recommends that the development program address potential ethical concerns regarding the use of placebo controls and maintaining the standard of care in clinical trials. This topic is the subject of ongoing discussion within and outside the Agency. In particular, we note the availability of other products approved for the reduction of COPD exacerbations, which may be a consideration for the ongoing year-long exacerbation trials.*

Discussion:

GSK has the potential to extract additional 12 month data but asked whether the Division would accept lung function data in the exacerbation study to meet the Combination Rule. The Division's intent is to satisfy the Combination Rule, but with clinical judgment. The Division stated that GSK's attempt (b) (4) is a difficult task to accomplish. The Division stated that the dose aspect of the LABA is in question and whether the dose is appropriate in COPD population. Lung function can not determine this in COPD, but can in the asthma. There is no prior precedence of dose that would determine COPD exacerbation. The Division stated that the proposed program lacks support for an exacerbation claim. The Division recommended that GSK determine a dose for asthma to support a COPD indication or submit data to support asthma for COPD indication. The Division asked if GSK had considered submitting 2 NDAs at the same time. GSK concluded that they would prefer to continue with the exacerbation study, generate additional lung function data and provide enough data to support COPD and Asthma (b) (4)

**Section 5: Regulatory**

**Question #1**

***Does the Division agree with the proposal for submission of the NDA and 120-Day Safety Update, as described in Section 5, for completed and ongoing studies?***

**FDA Response:**

*While the proposal is acceptable in terms of structuring the content of the application, we have overriding concerns regarding the proposed application. See the Introductory Comment.*

**Discussion:**

No discussion occurred.

**Question #2**

***The pharmacokinetics of FF and VI presented in m.2.7.2 will focus on data derived from studies conducted with the FF/VI Investigational Product Inhaler. Other supporting data from early studies with FF alone and VI (GW642444M) alone that used other inhaler types or other routes of administration (intravenous and oral) will be used for pharmacokinetic characterisation where applicable. Pharmacokinetic data from early clinical pharmacology studies with the (b) (4) (GW642444H) are not directly relevant to the FF/VI Investigational Product Inhaler and therefore will not be described in m.2.7.2. The full study reports from these investigations will be included in m5 and the pharmacokinetic data from these studies will be available in the study reports. The safety data from all studies conducted with GW642444H will be described in the ISS and m.2.7.4. Is this acceptable to the Division?***

FDA Response:

*Your approach seems reasonable. You stated that other supporting data from early studies with FF alone and VI alone that used other inhaler types or other routes of administration will be used for pharmacokinetics characterization where applicable. We recommend that when you are doing this, you provide clear explanation in the NDA as to how data from each of these studies is pertinent to the final product.*

Discussion:

No discussion occurred.

Question #3

***The pharmacokinetics of FF and VI in the target patient population (COPD) will be fully described in m.2.7.2. In addition FF and VI pharmacokinetic data in subjects with asthma from the supporting HPA axis (HZA106851) and long term safety that included LOCSIII assessments (HZA106839) studies will also be described in m.2.7.2. This will enable comparison of systemic exposure to FF and VI between subjects with COPD and asthma to demonstrate the relevance of this safety data to subjects with COPD. Pharmacokinetic data from other studies in subjects with asthma, including paediatrics, will not be described m.2.7.2. The Pharmacokinetic data from these studies will be available in the study reports that will be included in m5. Is this acceptable to the Division?***

FDA Response:

*Your approach seems acceptable.*

Discussion:

No discussion occurred.

Question #4

***Early clinical pharmacology studies examining the anti-inflammatory activity of FF in subjects with asthma and the bronchodilator properties of VI in subjects with COPD, together with the bronchoprotection studies with FF/VI Investigational Product Inhaler in subjects with asthma, will be summarised in m.2.7.2. Results of the thorough QT study will also be presented m.2.7.2. Early clinical pharmacology studies assessing the bronchodilator effects of VI and GW642444H in subjects with asthma will not be described in m.2.7.2. Other pharmacological effects unrelated to efficacy (including heart rate, blood pressure, QTc interval, blood potassium and serum and urine cortisol) will be discussed in section m.2.7.4. Is this acceptable to the Division?***

FDA Response:

*Your approach appears acceptable. For submission of the thorough QT study report, we recommend that you include the following items:*

- *Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed Electronic copy of the study report*

- *Electronic or hard copy of the clinical protocol*
- *Electronic or hard copy of the Investigator's Brochure*
- *Annotated CRF*
- *A data definition file which describes the contents of the electronic data sets*
- *Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses*
- *Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)*
- *Data set whose QT/QTc values are the average of the above replicates at each nominal time point*
- *Narrative summaries and case report forms for any*
  - *Deaths*
  - *Serious adverse events*
  - *Episodes of ventricular tachycardia or fibrillation*
  - *Episodes of syncope*
  - *Episodes of seizure*
  - *Adverse events resulting in the subject discontinuing from the study*
- *ECG waveforms to the ECG warehouse ([www.ecgwarehouse.com](http://www.ecgwarehouse.com))*
- *A completed Highlights of Clinical Pharmacology Table*

Discussion:

No discussion occurred.

**Section 7: Clinical Studies – Summary of Clinical Efficacy**

**Question #5**

***Section 7 of this Briefing Document outlines how GSK plans for the integration / pooling of the efficacy data including study grouping, subgroups, country groupings, analysis plans, and dose justification support. Does the Division agree with the proposals?***

**FDA Response:**

*The proposed pooling of efficacy data as secondary support is at your discretion. The review of efficacy data to support approval will be based on the individual trials.*

Discussion:

No discussion occurred.

**Question #6**

*The data in HZC112206 and HZC112207 consistently demonstrated that VI provides significant contribution to the combination in terms of lung function improvement and while there were inconsistent statistical effects on the FF contribution the magnitude was within the range seen with other ICS/LABA combinations approved for COPD. GSK propose that the contribution of the ICS is best demonstrated in the 1 year exacerbation studies (HZC102871 and HZC102970) where the contribution of FF to the combination can both be demonstrated by the difference in exacerbation rates and, as these studies are also measuring trough FEV<sub>1</sub>, can further define the contribution of FF to changes in lung function. Does the Division agree that this approach will satisfy the combination rule for provision of effectiveness of the combination of FF/VI Inhalation powder?*

**FDA Response:**

*While the ongoing COPD exacerbation trials may provide efficacy support for the addition of FF to VI, the extent to which data from this trial can support the bronchodilation indication in addition to an exacerbation claim is uncertain. Positive exacerbation results will be problematic in the context of the negative lung function results observed to date, as was previously discussed during the June 17, 2009, End-of-Phase 2 meeting. See the Introductory Comment.*

**Discussion:**

See Discussion in Introductory Comment

**Section 8: Clinical Studies – Summary of Clinical Safety**

**Question #7**

*Section 8 of this Briefing Document outlines how GSK plans for the integration / pooling of the safety data including the grouping of COPD studies and the grouping of Asthma studies, mono component data, subgroups, analysis plans, and dose justification support. Does the Division agree with the proposals?*

**FDA Response:**

*The proposed plan for the pooling of safety data from the FF/VI clinical program is acceptable.*

**Discussion:**

No discussion occurred.

**Question #8**

*Does the Division agree with the classification, analysis and reporting of GSK's predefined Adverse Events of special interest?*

**FDA Response:**

*The proposed reporting of AEs of special interest is acceptable. We also recommend evaluation of COPD exacerbations as a safety outcome.*

Discussion:

GSK clarified that they will be looking at COPD exacerbations from a safety and efficacy standpoint.

**Question #9**

***Adverse events and SAE reports of pneumonia in the primary COPD phase III studies will be further characterized by describing those with compatible chest radiographs; in particular, studies HZC102970 and HZC102871, in which chest x-rays were required per protocol for all moderate or severe exacerbations as well as AE and SAE reports of pneumonia. Does the Division agree that this approach is adequate to describe this specific adverse event of special interest?***

FDA Response:

*The approach to characterizing and reporting radiographically confirmed and unconfirmed pneumonia-related AEs and SAEs in the long-term COPD exacerbation trials HZC102970 and HZC102871 is acceptable.*

Discussion:

No discussion occurred.

**Question# 10**

***Does the Division agree that the ECG assessments in the clinical trials in conjunction with the thorough QTc study constitute adequate assessment of QT prolongation potential?***

FDA Response:

*The proposed assessment of potential QT prolongation by FF/VI and its monocomponents is acceptable.*

Discussion:

No discussion occurred.

**Question #11**

***We intend to include AE reports from the literature as part of the ISS and SCS. Does the Division agree that this reporting should be limited to nonclinical data and to orally inhaled FF/VI clinical data?***

FDA Response:

*The proposed approach to the literature review for drug-related adverse events is acceptable.*

Discussion:

No discussion occurred.

**Question #12**

***GSK are proposing to provide narratives for all fatal and non-fatal SAEs and for subject 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?***

**FDA Response:**

*The proposed plan is acceptable.*

**Discussion:**

No discussion occurred.

**Question #13**

***The intent of the current NDA is to seek approval of an indication for FF/VI Inhalation Powder in patients with COPD. However, we believe it is also important to thoroughly analyze and understand the safety of FF/VI in patients with asthma at the time of the COPD NDA.***

***(b) (4) at this time we purpose to provide an Integrated Summary of Safety of all available asthma data in addition to an Integrated Summary of Safety of all COPD data. Furthermore, in m2.7.4 of the NDA we propose to summarize the COPD safety data and only briefly discuss the relevant asthma data. Does the Division agree with the proposed approach?***

**FDA Response:**

*While the proposed approach is acceptable in terms of structuring the content of the application, we have overriding concerns regarding the proposed application. See the Introductory Comment.*

**Discussion:**

No discussion occurred.

**Question #14**

***Over 800 subjects with COPD are planned to receive VI Inhalation Powder 25mcg QD as monotherapy in the ongoing, Phase III clinical development program for GSK573719/VI Inhalation Powder (a combination of VI and the long-acting muscarinic antagonist GSK573719). These studies will all be ongoing at the time of the submission of the NDA for FF/VI Inhalation Powder. GSK propose not to include data from the ongoing GSK573719/VI program in the NDA but incorporate the data by cross-reference to the relevant INDs ( (b) (4) 074696). Does the Division agree with this approach?***

**FDA Response:**

*The proposal to cross-reference safety data from ongoing trials of the GSK573719/VI combination product is acceptable*

Discussion:

No discussion occurred.

**Question #15**

***GSK will have a blinded committee adjudicate SAE data from the studies in the FF/VI asthma program as detailed in Section 8.2.2.3. Does the Division have any additional input for this process?***

FDA Response:

*The Division has no additional input at this time regarding the blinded adjudication process for SAEs in the FF/VI asthma program. However, it is unclear why a blinded adjudication process is not also proposed for SAEs in the COPD development program.*

Discussion:

GSK stated that they will do other things to address AES in COPD such as chest x-rays and all will go to the adjudication committee.

**Additional question submitted on July 5, 2011**

***A COPD phase IIIb study, HZC113107, "A 12-Week Study to Evaluate the 24 Hour Pulmonary Function of Fluticasone Furoate (FF)/Vilanterol (VI) Inhalation Powder (FF/VI Inhalation Powder) Once Daily Compared with Salmeterol/Fluticasone Propionate (FP) Inhalation Powder Twice Daily in Subjects with Chronic Obstructive Pulmonary Disease" (GSK Document Number: RM2010/00157/03) originally planned to read out after COPD NDA submission will now report out in time for inclusion in the COPD NDA. At the time of our submission of the briefing document this study was not included as a completed study and there we propose the following for incorporation of the study results in the proposed NDA.***



***Does the agency agree with these proposals?***

FDA Response:

*No, we do not agree. We recommend that the results for HZC113107 be submitted as an individual study report without integration in the ISS (b) (4). Include in your submission the raw (SDTM) and the analysis and reporting (analysis-ready) datasets that were used to generate the results presented in your study report for HZC113107, as well as define.pdf that includes complete information on how variables were derived from the SDTM data (b) (4).*

*Include the programs used for creating main efficacy analysis datasets from submitted raw datasets and the programs used for the efficacy and main safety analyses.*

Discussion:

See discussion in question 19.

**Section 9: Statistics**

**Question #16**

***GSK submitted Summary Document Analysis Plans for the ISE for COPD to IND 077855 on 11 March 2011 (Serial No. 0291) and for the ISS for COPD to IND 077855 on 24 March 2011 (Serial No. 0296). Does the FDA agree with the proposed statistical methodology for examining subgroups as outlined in Section 9 of this briefing document and described more fully in Section 8.4 of the SDAP for the ISE and in Sections 8.5 of the SDAPs for safety?***

FDA Response:

*The proposed statistical methodology for examining subgroups as described in Sections 8.4, 10.1.1.1, and 10.1.3.1 of the SDAP for the ISE is reasonable.*

*Your approach for summarizing AEs by subgroups as described in Section 8.5 of the SDAP for the ISS is reasonable.*

Discussion:

No discussion occurred.

**Question #17**

***Does FDA have any further comments on the statistical analysis methods proposed in the SDAPs for the ISE for COPD or ISS for COPD or asthma?***

FDA Response:

*We do not have any additional comments on the statistical analysis methods proposed in the SDAP for the ISE except to note that 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 age, sex and race. Additional analyses may be performed using pooled data; however, little weight will be given to the results from these analyses.*

*We do not have any additional comments on the analysis methods proposed in the SDAP for the ISS.*

Discussion:

No discussion occurred.

**Question #18**

***GSK is proposing to create cross-study summaries of AEs of special interest and SAEs from clinical pharmacology studies conducted with the Investigational Product Inhaler in healthy subjects as this is the most relevant data for the submission. Other clinical pharmacology studies will be excluded from these summaries as they used a range of different inhalers, formulations and routes of administration. However, listings of AEs of special interest and SAEs from all the clinical pharmacology studies will be provided in the NDA submission. Does the agency have any comments on this proposal?***

FDA Response:

*The proposed approach for safety reporting of SAEs and AEs of special interest from clinical pharmacology trials is acceptable.*

Discussion:

No discussion occurred.

**Question #19**

***FDA endorses the standard format called Study Data Tabulation Model (SDTM), developed by the Clinical Data Interchange Standards Consortium (CDISC). Sponsors of human drug clinical trials can use SDTM to submit data to the Agency. Are the Statistical Reviewers in agreement with the content, structure and format of the dataset and associated documentation as described in Section 9 of this briefing document?***

FDA Response:

*Your proposal to submit CDISC SDTM is acceptable. It is our understanding that you are also submitting analysis and reporting datasets that were used to generate the results presented in your study report, as well as define.pdf that contains metadata and links to the annotated CRF. Your metadata should include complete information on how variables were derived from the SDTM data and should contain links to the annotated CRF when possible. In addition, submit a Reviewer's Guide, if available.*

*Refer to the Study Data Tabulation Model Metadata Submission Guidelines (SDTM-MSG) at <http://www.cdisc.org/msg-draft> for more information.*

*Include the programs used for creating main efficacy analysis datasets from submitted raw datasets and the programs used for the efficacy and main safety analyses.*

Discussion:

GSK explained that the datasets (i.e. original and analysis-ready datasets) they used to analyze and generate the results in their study reports are based on GSK data standards format and is NOT based on the CDISC (SDTM/ADaM) format. However, they converted some of their legacy data using the SDTM format and they are seeking our advice if they need to submit CDISC compliant datasets in their NDA application or can they submit all their legacy datasets, along with the converted data. The sponsor added that because they plan to submit NDA next year and their program is large, they will not be able to convert all their data to an SDTM format in time of submission. They also inquired what the current data submission requirement is.

The Division explained that currently there is no requirement for them to submit CDISC (SDTM/ADaM) compliant datasets (at least in this medical division), in particular, when the CDISC datasets are product of data conversion. However, for future clinical development programs, they should plan their protocols and design their case report forms with CDISC standard in mind. In their submission, they should submit all the legacy datasets and analysis data sets that were used to generate the results in their study reports, with full description (in the define file) on how they derived variables.

GSK clarified whether they should continue converting their legacy datasets to the SDTM format and we responded that we will seek clarification from the Data Standards team and will include their response as a post-meeting comment.

Data Standards Team Response: At this time, there is no regulatory requirement for standard data. Data sets that you submit must support the analyses contained in the study reports. Because of challenges and complexity of converting data - such as converted data that does not accurately support analyses presented in the study reports, there is currently no requirement for you to continue converting your legacy datasets to CDISC (SDTM or ADaM) format in your current program. We recommend that as part of your NDA submission, include the already-converted datasets in order for us to test the datasets and provide you with feedback regarding your converted datasets. Of note, we will not be using these converted datasets in our review.

We strongly encourage you to consider the implementation and use of data standards (i.e. CDISC format) in your new clinical programs as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies.

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

**Question #20:**

***Do the Statistical Reviewers have other comments regarding any dataset (Analysis & Reporting, Data Listing, Analysis or SDTM or those for population PK, PK/PD or dose-response) or presentation of the metadata?***

FDA Response:

*All datasets and the final analysis dataset used for model development and validation should be submitted as SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).*

Discussion:

See discussion in question 19.

Question #21

*As this will be the first GSK submission to the Pulmonary Division to include CDISC SDTM datasets, it would be helpful if the Division would receive a test transfer and confirm that it is satisfactory. Would this be acceptable?*

FDA Response:

*Your proposal to submit a sample SDTM prior to live submission is acceptable. You should go to the following link on how to submit a sample SDTM submission to the FDA for review. The process allows you to review the resulting validation error report and make appropriate changes to the dataset prior to submission. This is similar to the existing eCTD test submission process with the exception that test submission data needs to be submitted via CD/DVD, and cannot come in through the Gateway.*

*<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>*

Discussion:

No discussion occurred.

Section 11: Nonclinical

Question #22

*In the carcinogenicity studies, the ovarian findings in female rats are consistent with those seen with other  $\beta$ 2 adrenoceptor agonists and are considered related to a pharmacologically-mediated hastening of rodent-specific reproductive senescence. Findings from a 26-week hormonal investigative study in female rats which showed elevated estradiol levels and secondary hormonal changes support this conclusion. GSK believe that no further non-clinical or clinical investigational studies related to endocrine status are necessary to support the proposed NDA. Does the Division agree?*

FDA Response:

*No additional nonclinical studies to assess endocrine status are considered necessary. However, as your question relates to tumor findings in the carcinogenicity studies, we remind you that*

*review and discussions with the Executive Carcinogenicity Assessment Committee of the completed carcinogenicity study reports are necessary prior to concurring with any tumor findings.*

Discussion:

The Division clarified that in addition to need for nonclinical studies, there was no need for clinical studies as well.

Question #23

***As with other  $\beta_2$ -adrenoceptor agonists and in agreement with published data, the incidence and growth / progression of benign pituitary adenoma in male and female rats are considered to be influenced by increased bodyweight gain in young animals and a sustained increase in food consumption. Additionally, the elevated levels of estradiol are considered to contribute to the development of pituitary tumors in females leading to an apparent increased susceptibility. GSK believe that no further non-clinical or clinical investigational studies are required to support the proposed NDA in relation to the pituitary findings. Does the Division agree?***

FDA Response:

*No additional nonclinical studies in relation to pituitary findings are considered necessary. See the response to question #22.*

Discussion:

See discussion in question 24.

Question #24

***As previously communicated to the Carcinogenicity Assessment Committee (CAC) / Agency, in the carcinogenicity studies there were non-treatment related findings (convulsions in vehicle and GW642444-treated rats; abdominal distension in vehicle and GW642444-treated mice). Since some dose groups in both studies were dosed for at least 100 weeks (minimum dosing duration 86 weeks followed by termination at Weeks 95 or 96) with at least 15/sex/group surviving to termination, and the observed pattern of tumours was characteristic of those previously reported for the marketed  $B_2$ -agonists: salmeterol and formoterol (mice: leiomyoma and leiomyosarcoma of uterus, rat: leiomyoma of mesovarian ligament and pituitary adenoma), GSK believe both studies have demonstrated the ability to detect an increased incidence of tumours and therefore, the studies are valid – does the Division agree?***

FDA Response:

*We cannot agree at this time. Review and discussions with the Executive Carcinogenicity Assessment Committee of the completed carcinogenicity study reports are necessary prior to concurring with the validity of your carcinogenicity studies. We recommend that you submit the completed carcinogenicity study reports and appropriate SAS data sets for review under the IND before submission of the NDA. Provide appropriate historical control data for the species from the test laboratory to address any potential findings in your studies.*

**Additional Nonclinical Comments:**

*For the NDA, qualify any impurity exceeding ICH Q3A(R) and Q3B(R) guidelines.*

**Discussion:**

The Division clarified that the historical control data for tumor incidences should represent a life time duration for the test species and strain. The Sponsor inquired if it would help the Division in analyzing the carcinogenicity data, if they provided comparative LABA carcinogenicity data. The Sponsor indicated that there may be an earlier-onset of tumor formation than other LABAs but no new tumor types were recognized. The Division explained that the carcinogenicity section of the label will be based on the individual drugs for this IND/NDA and will not include comparisons to other LABA. However, the sponsor can submit carcinogenicity information data for other LABA for a comparison. The Division reaffirmed that the carcinogenicity studies can be submitted to the IND or to the NDA. At the IND stage, the Division may complete the review prior to NDA submission depending on workload.

**Section 12.2: Labeling**

**Question #25**

***Does the Division have any preliminary comments on the proposed proprietary name at this time?***

**FDA Response:**

*The Division has no preliminary comments at this time.*

**Discussion:**

No discussion occurred.

**Section 13: Risk Evaluation and Mitigation Strategy**

**Question #26**

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

**FDA Response:**

*The proposal is acceptable*

**Discussion:**

No discussion occurred.

**Section 14.2: eCTD Format of the NDA**

**Question #27eSub**

***The specifications and file formats that GSK proposes to use are as noted in Section 14.2. These items are fully consistent with the FDA's guidance documents as referenced within Section 14.2. Does the Division agree that these specifications and file formats are acceptable for this NDA?***

**FDA Response:**

***The proposed formats are acceptable.***

**Discussion:**

No discussion occurred.

**Question #28eSub**

***Since the submission will include datasets, as outlined in Section 9.2, GSK does not intend to submit CRF tabulations / Patient Profiles. Does the Division agree with this approach?***

**FDA Response:**

***This approach is acceptable.***

**Discussion:**

No discussion occurred.

**Question #29eSub**

***Does the Division agree with the level of hyperlinking proposed for the NDA?***

**FDA Response:**

***The approach for hyperlinking the proposed NDA is acceptable.***

**Discussion:**

No discussion occurred.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANGELA H RAMSEY  
07/25/2011

6/17/09



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 77855

GlaxoSmithKline  
Five Moore Drive  
PO Box 13398  
Research Triangle Park, NC 27709

Attention: Lorna Wilson  
Director, US Regulatory Affairs

Dear Ms. Wilson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GW685698/GW64244 Inhalation Powder.

We also refer to the meeting between representatives of your firm and the FDA on June 17, 2009. The purpose of the meeting was to discuss adequacy of safety database to support proceeding to Phase III in Asthma.

A copy of the official minutes of the meeting is attached 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) 796-2284.

Sincerely,

*{See appended electronic signature page}*

Angela Robinson, RN, MSN  
Senior Regulatory Project Manager  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** June 17, 2009  
**TIME:** 1:00- 2:30 pm EST  
**LOCATION:** White Oak, Bldg 22, Conference Room 1417  
**APPLICATION:** IND 77855  
**DRUG NAME:** GW685698/GW64244 Inhalation Powder  
**TYPE OF MEETING:** EOP II

**MEETING CHAIR:** Badrul Chowdhury

**MEETING RECORDER:** Angela Robinson

**FDA ATTENDEES:** Division of Pulmonary and Allergy Products

Badrul A. Chowdhury, M.D., Ph.D., Director  
Angela Robinson, RN, MSN, Senior Regulatory Project Manager  
Anthony Durmowicz, MD, Clinical Team Leader  
Anya Harry, MD, Clinical Reviewer  
Molly Shea, Acting Pharmacology/Toxicology Team Leader  
Lawrence Sancilio, Ph.D., Pharmacologist/Toxicologist Reviewer  
Prasad Peri, PhD, Pharmaceutical Assessment Lead  
Qian H. Li, Sc.D., Statistical Team Leader  
Dongmei Liu, Statistical Reviewer  
Sally Choe, Ph.D, Clinical Pharmacology Team Leader  
Ying Fan, Ph.D, Clinical Pharmacology Reviewer

**EXTERNAL CONSTITUENT ATTENDEES: GlaxoSmithKline**

Brett Haumann, M.D., Respiratory Development  
Elaine Jones, Ph.D., Vice President , Regulatory Affairs  
Darrell Baker, Senior Vice President, Respiratory Development  
Courtney Crim, M.D., Director, Clinical Development  
Kate Knobil, Vice President, Global Clinical  
Lorna Wilson, Director, Regulatory Affairs  
Susan Holmes, Associate Director, Global Pre-Approval, CMC  
Regulatory Affairs  
Loretta Jacques, Director, Clinical Development  
Sally Lettis, Director, Statistics

**BACKGROUND:**

GlaxoSmithKline submitted a Type B meeting request dated, September 30, 2008 to discuss End-of-Phase II development plans for GW685698/GW642444 Inhalation Powder for asthma and COPD indications. GSK submitted a request dated, January 6, 2009 to separate the meetings by indications and an additional meeting was scheduled for June 17, 2009 for COPD.

The briefing package was submitted on May 15, 2009. Upon review of the material, the Division responded via fax on June 16, 2009. GSK requested to continue with the face-to-face meeting as scheduled to discuss CMC additional comment, Clinical Pharmacology question 1, Clinical questions 3, 5, 4, 15, 10, and 11, Statistical questions 3 and 4 and if time permits, clarification on Division's response to question #8 from March 31, 2009 EOP2 meeting.

The content of the fax is below. Any discussions that occurred during the meeting are captured directly under the relevant response. The sponsor's questions are in ***bold italic***; the Division's response is in *italics*; and the discussion is in normal font.

**Additional Comment**

***Prior to the initiation of the phase 3 trials, it is important that you provide results of in vitro performance tests (APSD and DDU, both through device life) to confirm that there is no unexpected interaction resulting in differences in performance between the monotherapy products and the combination drug product. This should be shown for all strengths of the product used in the phase 3 clinical trials.***

***Clarify the configuration of the placebo product that will be used in the phase 3 clinical trials.***

**Discussion:**

GSK asked the Division to clarify if the Division has specific concerns because this sort of information was provided earlier. The Division asked GSK to submit the above mentioned in vitro CMC information, or provide reference in previous IND submissions that contained the requested in vitro data. The division reiterated that it would be helpful and would prefer stage by stage (b) (4) data and not just (b) (4) data. GSK is in agreement.

**Clinical Pharmacology:**

**Question #1:**

***Does the Division agree that the proposed dose proportionality study is adequate to support registration for (b) (4) COPD?***

**FDA Response:**

***Based on your dose proportionality study design, include the therapeutic dose range of the product in your proposed dose proportionality study. In addressing your bio-analytical concerns, you can try (b) (4)***

Discussion

GSK asked the Division if unable to detect drug concentration levels at proposed therapeutic dose range, whether the Division would still want to include these doses in the dose proportionality study.

The Division [REDACTED] (b) (4) [REDACTED] asked GSK to include the proposed therapeutic dose range in the dose proportionality study. If it is unable to detect drug concentration, the sponsor needs to provide justification. GSK agreed that they will attempt to include proposed therapeutic dose in the dose proportionality study.

Clinical:

Question #3

***Does the Division agree that the 25mcg dose of GW642444 is the appropriate total daily dose to carry into the COPD Phase III studies in combination with fluticasone furoate and as the individual LABA component treatment arm and that no other doses need to be investigated in Phase III?***

FDA Response:

*We do not necessarily agree. The dose of GW642444 to be used in the combination product will be contingent upon its safety and efficacy profile as a single agent in patients with COPD. Because you are choosing to develop the single ingredient LABA and the LABA/ICS combination for COPD concurrently and because clinical trials to support the dose and dosing frequency of GW642444 have yet to be completed, we cannot address if the 25 mcg dose is an appropriate single dose for Phase 3 studies. As has been previously conveyed, you may want to consider inclusion of more than one dose of GW642444 in your Phase 3 trials.*

Question #5:

***Does the Division agree that the Phase I and Phase II data with fluticasone furoate and GW642444, alone and in combination, provide an appropriate basis for progression to Phase III studies in COPD?***

FDA Response:

*We do not necessarily agree. You have not yet adequately identified the dose and dosing interval of GW642444 (see response to Question 3).*

Discussion:

GSK stated that the QD versus BID study is not completed, but they believe that 25 mcg is the lowest effective dose when comparing 25 mcg to 50 mcg. GSK asked what does the Division feels is missing. The Division stated that it is not as confident that the 25 mcg dose is the lowest effective LABA dose as it appears that the 12.5 mcg dose performed as well if not nominally better than the 25 mcg dose in patients with asthma while the 25 mcg dose performed better in the COPD study. Thus, the results are inconsistent across patient populations. The Division stated it may have to deal with the potential of approving different doses of LABA in COPD than for asthma which has not previously been done. The Division indicated that if the GSK proves

that asthma and COPD require different dosing, the Division would review the data. The Division recommended finding dose and dose frequency in a bronchodilator responsive population by assessing 25 mcg total daily doses divided BID versus QD dosing. GSK was in agreement.

**Question #4:**

***Does the Division agree that the 50, 100 and 200mcg doses of fluticasone furoate are the appropriate once-daily doses to carry into the COPD Phase III studies in combination with GW642444 and as the individual ICS component treatment arms? Moreover, as the 100mcg dose of fluticasone furoate is expected to be the lowest effective monotherapy dose and in the combination product, does the Division agree that only the 100mcg monotherapy dose needs to be replicated in the 6-month clinical studies?***

**FDA Response:**

*Your dose selection appears reasonable. In your asthma program, in which you plan to develop several ICS/LABA combinations with more than one strength of ICS, the efficacy of the lowest monotherapy dose should be supported with replicative data. Any higher dose would have to show substantial benefit above that of the lower dose. For your COPD program, the concept is similar except that it appears you plan to develop only one strength of ICS for the combination. If that is the case, then the selected dose of ICS should be supported with replicative efficacy data, and also the selected dose of ICS should be supported by adequate scientific reasoning.*

**Discussion:**

*See responses to your alternative proposal in the attachment.*

**Question 15:**

***Does the Division agree that***

(b) (4)

***the two replicate 12 month exacerbation studies will be adequate to support the proposed indication of maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema. [The proposed indication to reduce exacerbations of COPD in patients with a history of exacerbations would still come from the two replicate 12 month exacerbation studies as per the briefing document].***

**FDA Response:**

*No we do not agree. Efficacy for both the bronchodilator and reduction in exacerbation claims need to be demonstrated in a robust fashion with replicative clinical trials supporting each claim.*

**Discussion:**

GSK provided additional study proposal (see attachment). The Division will review and provide an addendum.

**Question 10:**

***GSK plans to conduct a study*** [REDACTED] (b) (4)

[REDACTED] ***Does the Division agree?***

**FDA Response:**

*It is premature to comment on post-marketing commitments until review of safety and efficacy data from future proposed clinical trials.*

**Discussion:**

The Division instructed GSK to wait until the dose is identified before assessing bone density. GSK agreed with the Division.

**Question 11:**

***Due to the high background incidence of cataracts observed in patients with COPD, GSK plans to assess the effect of fluticasone furoate (100 and 200mcg QD for 1 year) on the incidence of cataracts in asthmatics, as part of the asthma Phase III program. There are no plans to conduct formal cataract assessments in the COPD trials. Does the Division agree?***

**FDA Response:**

*Again, without additional data from proposed clinical trials, it is premature to comment.*

**Discussion:**

GSK proposed to assess for cataracts as part of their asthma program rather than in COPD patient population where because of a higher background incidence, the assessment for cataracts may be more difficult. The ages studied would be in the same range as that of COPD patients. The Division responded that while the lower incidence of cataracts in the asthma population may provide a “cleaner” study, it may be important to assess for cataract progression which may be better done in COPD patients. The Division recommended that GSK consult with an ophthalmologist to help with the most appropriate study design and patient population.

**Statistical**

**Question 3:**

***Each study is evaluating three doses of Fluticasone Furoate/GW642444 combination. GSK propose to define a hierarchy of statistical tests across the primary and pre-defined secondary endpoints in order to control for multiplicity. Does the Division agree with the defined approach to addressing multiplicity?***

FDA Response:

*When there are multiple studies available and each study has multiple doses, the efficacy evidence will be evaluated collectively from the multiple studies and multiple doses. The error rate of approving an ineffective drug will be controlled if the dose- response relationship is reasonable and results across studies are consistent. The proposed hierarchical testing procedure protects against type I error in a rigid way and may lead to irrational conclusion when the dose- response was guessed incorrectly. In addition, this procedure does not add any value in the selection of the optimal doses, as the optimal doses should be selected based on the effect size, safety concerns, and risk/benefit ratio.*

Discussion:

GSK agreed that the closed testing procedure protects Type I error in a rigid way and may lead to an irrational conclusion. However, they still would like to use the procedure and asked if the Division is in agreement with the proposal. The Division agrees the procedure is acceptable and recommends not to include the comparison between ICS versus placebo in the testing procedure and to include the comparison between the combination versus LABA for trough FEV1. As the sponsor intends to market (b) (4) the combination products, the procedure needs to address this intention.

Question 4:

***Does the Division agree that GSK's data submission plans meet the FDA's expectations, consistent with the new CDISC standards?***

FDA Response:

*The data submission plan looks good in general. We would like to get clarification on how the SDTM datasets are generated. Are the SDTM datasets the same as the raw data management (DM) datasets or generated from the raw data management datasets?*

Discussion:

GSK clarified that the data sets are not the same and that it would require conversions from the raw data management (DM) datasets.

**ATTACHMENTS/HANDOUTS:**

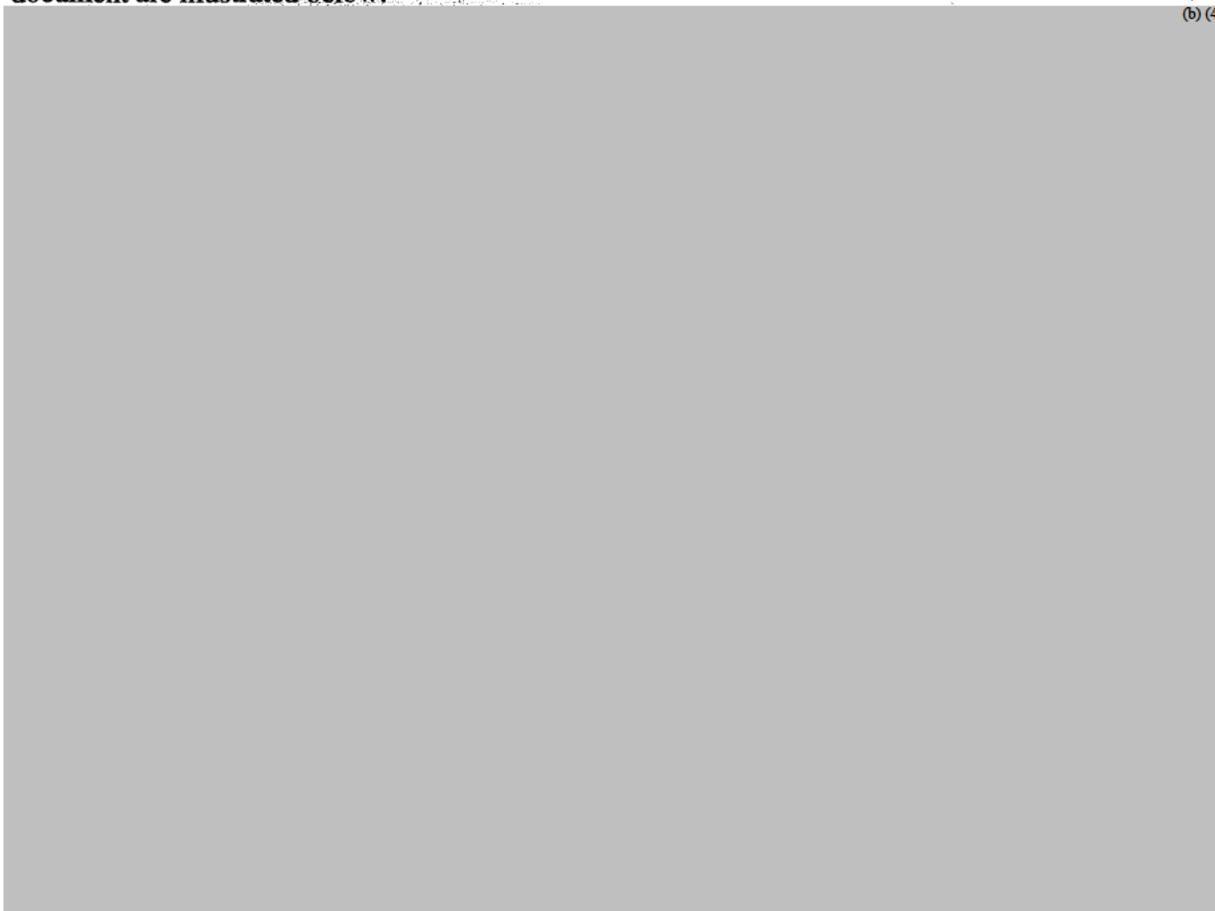
**GSK IND 77,855**

**ALTERNATIVE DESIGNS FOR THE 6-MONTH COMBINATION ICS/LABA STUDIES  
IN COPD**

At the End Of Phase II meeting for the combination product for COPD (June 17, 2009), GSK confirmed its intention to conduct two replicate 12-month exacerbation studies to evaluate 3 separate doses of the ICS/LABA combination (200/25mcg, 100/25mcg and 50/25mcg once daily) compared to the LABA alone (25mcg once daily). These studies will assess efficacy (in

terms of exacerbation rate reduction) and safety (including pneumonia frequency) to identify the lowest effective dose of the combination for COPD patients.

In addition, GSK has proposed two 6-month lung function studies to evaluate the effect of the combination on airflow obstruction in COPD patients. The current designs as per the briefing document are illustrated below:



At the meeting, GSK questioned whether these 6-month lung function studies as currently designed are over-inclusive. Specifically, (b) (4)

(b) (4)

(b) (4), the company is seeking FDA advice (b) (4) in the 6-month studies whilst still supporting an airflow obstruction indication for the combination product.

GSK welcomes the Division's opinion on two alternative designs for the 6-month studies as proposed below:

(b) (4)



Option 1 [redacted] (b) (4) aims to meet the combination regulations for each of the likely combination doses that may be identified as optimal from the 12-month exacerbation studies. [redacted] (b) (4)

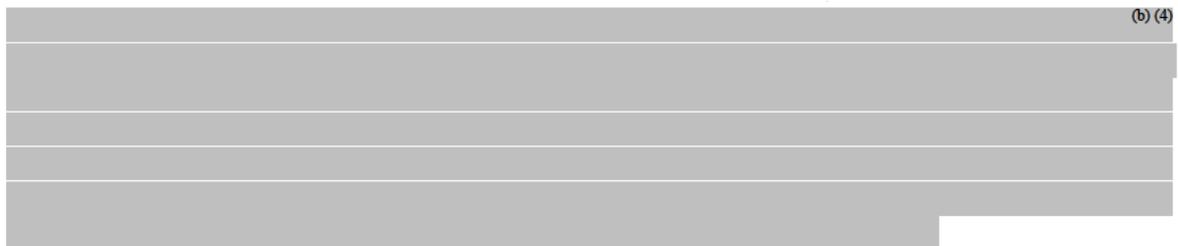


[redacted] GSK explained in the meeting, we believe the replication of ICS effect will be more appropriately assessed in the exacerbation studies that are better suited to assessing the effect of the ICS on more relevant endpoints (exacerbations and pneumonia).

(b) (4)



(b) (4)



GSK believes that Option 1 adequately meets the principles of replication between components and combination and would propose this approach as an alternative to the original designs, and welcomes the FDA's view on this proposal..

**Division Response:**

The Division agrees that the original proposal for Phase 3 studies used to support an indication for airflow obstruction contained some redundancy. After review of the proposed Option 1 and Option 2 proposals outlined above, the Division considers Option 2 as an acceptable alternative to the original proposal with the following caveats:

1. [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]

2. [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]. Thus, it may be important to conduct the Phase 3 program in a fashion, such as a two-tiered approach, that you know the results of the 6-month lung function studies prior to initiation of the exacerbation studies.

3. [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED] Again, the two-tiered approach may be useful in such a scenario.

4. In addition to demonstrating efficacy in the 6-month lung function studies, the dose(s) demonstrated to be efficacious in your exacerbation studies would also be expected to demonstrate effectiveness on FEV1 as a lung function endpoint in those studies.

Linked Applications

Sponsor Name

Drug Name / Subject

-----  
IND 77855

-----  
GLAXO GROUP LTD  
DBA GLAXOSMITHKLINE

-----  
GW685698/GW642444 Inhalation Powder

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

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ANGELA H ROBINSON  
07/10/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 77855

GlaxoSmithKline  
Five Moore Drive  
PO Box 13398

Attention: Lorna Wilson  
Director, US Regulatory Affairs

Dear Ms. Wilson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GW685698/GW64244 Inhalation Powder.

We also refer to the meeting between representatives of your firm and the FDA on March 31, 2009. The purpose of the meeting was to discuss adequacy of safety database to support proceeding to Phase III in Asthma.

A copy of the official minutes of the meeting is attached 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) 796-2284.

Sincerely,

*{See appended electronic signature page}*

Angela Robinson, RN, MSN  
Senior Regulatory Project Manager  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** March 31, 2009  
**TIME:** 12:00- 1:30pm EST  
**LOCATION:** White Oak, Bldg 22, Conference Room 1417  
**APPLICATION:** IND 77855  
**DRUG NAME:** GW685698/GW64244 Inhalation Powder  
**TYPE OF MEETING:** EOP II

**MEETING CHAIR:** Badrul Chowdhury

**MEETING RECORDER:** Angela Robinson

**FDA ATTENDEES:**

**Division of Pulmonary and Allergy Products**

Badrul A. Chowdhury, M.D., Ph.D., Director  
Lydia I. Gilbert-McClain, MD, Deputy Division Director  
Angela Robinson, RN, MSN, Senior Regulatory Project Manager  
Anthony Durmowicz, MD, Clinical Team Leader  
Anya Harry, MD, Clinical Reviewer  
Molly Shea, Acting Pharmacology/Toxicology Team Leader  
Lawrence Sancilio, Ph.D., Pharmacologist/Toxicologist Reviewer  
Prasad Peri, PhD, Pharmaceutical Assessment Lead  
Craig M. Bertha, PhD, CMC Reviewer  
Qian H. Li, Sc.D., Statistical Team Leader  
Dongmei Liu, Statistical Reviewer  
Sally Choe, Ph.D, Clinical Pharmacology Team Leader  
Ying Fan, Ph.D, Clinical Pharmacology Reviewer

**EXTERNAL CONSTITUENT ATTENDEES:**

Brett Haumann, M.D., Respiratory Development  
Elaine Jones, Ph.D., Vice President , Regulatory Affairs  
Darrell Baker, Senior Vice President, Respiratory Development  
Courtney Crim, M.D., Director, Clinical Development  
Kate Knobil, Vice President, Global Clinical  
Lorna Wilson, Director, Regulatory Affairs

**BACKGROUND:**

GlaxoSmithKline submitted a Type B meeting request dated, September 30, 2008 to discuss End-of-Phase II development plans for GW685698/GW64244 Inhalation Powder.

The briefing package was submitted on February 27, 2009. Upon review of the material, the Division responded via fax on March 30, 2009. GlaxoSmithKline request to continue

with face-to-face meeting as scheduled and would like to discuss introductory comments, questions 7, 8, 10, 12, 14, 15, 17, 19 - 22, 23 and additional comments.

The content of the fax is below. Any discussion that occurred during the meeting is captured directly under the relevant response. The sponsor's questions are in ***bold italics***; The Division's response is in *italic*; and discussion is in normal font.

***Introductory Comment:***

*We remind you that regarding the issue of once versus twice daily dosing for your fluticasone furoate/GW642444 combination product (IND# 77,855), at the PIND meeting held on April 29, 2008, we stated, "Our expectation at the End of Phase 2 meeting would be to see a package with convincing data establishing the dosing interval." Because you have not provided any new substantial data to justify a once daily dosing regimen for your combination product since that time, the timing of this End of Phase 2 meeting is premature and the ability to address your questions regarding the proposed Phase 3 program is extremely limited.*

Discussion:

The sponsor stated that they were disappointed with the Division's feedback and felt that during previous discussions with the Division they were lead to believe that the data in their phase II package would be sufficient enough to support QD dosing of LABA. The sponsor stated that they do not have the data the Division requested during the Pre IND meeting on April 29, 2008. The sponsor was not aware that it would prevent them from moving forward to phase III development.

The Division commented that their concern with the proposed clinical trials is that the sponsor is trying to rush to a Phase III program without first showing reasonable support for the dose, and dosing interval. The ideal situation would be to determine the nominal doses that are safe and effective for each individual single ingredient of the combination then combine them to show that each drug contributes to the overall efficacy of the combination product. In the past, other programs have first fully developed each single ingredient product, which made it easier to move forward. The sponsor's current program introduces the potential for greater risk.

The Division clarified that our responses do not prevent the sponsor from moving forward. The Division recommended that the sponsor take the Division's feedback and incorporate any suggestions into the study or if the sponsor is willing to take the risk with the current program they could move forward as proposed; that would be their choice.

The sponsor asked the Division to clarify that the Division would like to 2 studies demonstrating efficacy of the low dose of inhaled corticosteroid. The Division stated they need to provide data to support the replicate efficacy of the low dose corticosteroid in the selected patient population. The Division questioned if the lowest dose of inhaled corticosteroid is not supported with substantial efficacy data then what is the rationale for adding a LABA?

The Division also stated that the sponsor will need to justify the added benefit of the high dose of inhaled corticosteroid over any lower dose(s). The Division stated that these issues are not new.

The sponsor acknowledged and appreciated Division's feedback and will discuss further with their team.

**Question #7**

***Does the Agency agree that the proposed HPA axis study in asthma subjects is adequate to support registration?***

**Response:**

*While your proposed HPA axis study proposal seems reasonable, until we review the actual protocol of the study, we can not comment on the adequacy of the study. Please note that the results of your proposed HPA axis study will not be evaluated based on non-inferiority method you have proposed.*

**Discussion**

The sponsor asked the Division to clarify their response. The Division responded that when analyzing the data you generally won't see an overall significant difference when comparing mean data. The Division recommended looking at all the data and describe the findings and not to claim non-inferiority if there is no effect.

The Division stated that the active control has to show an effect over placebo for the study to be valid. In current program, it is unclear the type of test used and the number of subjects.

**Question #8**

***Does the Agency agree that the available QTc data together with the proposed evaluation of QTc in Phase III and the design of the thorough QTc study will be adequate to support registration of Fluticasone Furoate/GW642444 Inhalation Powder?***

**Response:**

*We recommend that you conduct your thorough QTc study under steady-state condition not after the single dose administration. Additional comments may be forthcoming pending evaluation of the protocol by the QTc Interdisciplinary Review Team (IRT).*

**Discussion:**

The Division stated that IRT would like the sponsor to submit a full protocol. The Division also recommended that the sponsor do a reasonable number of cardiac

assessments in their Phase III program which would address QT effect as well. The Division reminded the sponsor that Phase III QTc requirement still stands for class effect. The sponsor acknowledged Division's feedback.

**Question #10**

***Does the Agency agree the data from the Phase IIb asthma dose ranging study, B2C109575, which was supported by the COPD dose-ranging study, B2C111045 demonstrate that GW642444 is suited to once-daily administration.***

**Response:**

*No, we do not agree. While trough FEV1 and change from baseline weighted mean 24-hour serial FEV1 determinations were statistically significantly improved compared to placebo at doses  $\geq 12.5$  mcg, the data are inadequate to make a final determination regarding the appropriate dosing interval without a comparison of the dose response curves for GW642444 between once and twice daily dosing regimens (see minutes from the teleconference with GSK on January 28, 2008).*

**Discussion:**

Sponsor acknowledged Division's feedback addressed previously in the Introductory Comment. Sponsor recognized that it is their risk to move forward with QD versus BID.

**Question 12**

***Does the Agency agree with the design of the low and mid dose 12-week efficacy studies?***

**Response:**

*While the general design is reasonable it is premature to discuss the study designs in depth until the issue of once vs. twice daily dosing has been adequately addressed. Note that in addition to the combination product demonstrating efficacy, the low (100 mcg) dose of fluticasone furoate should demonstrate substantial efficacy as a stand alone therapy. Also, we recommend the addition of an active comparator arm (at an appropriate dose) in each of the studies.*

**Discussion:**

The sponsor appreciated the Division's detailed expectations and asked the Division to clarify what they meant concerning the addition of an active comparator arm? The Division acknowledged the confusion over the term "active comparator" and stated that they meant a LABA monotherapy arm.

**Question #14**

***Does the Agency agree with the design of the 12-month long-term safety study?***

Response:

*Internal discussions within FDA concerning the safety of LABA-containing products are ongoing. Once they are completed we will be in contact to discuss specific safety requirements, including design of safety studies.*

Discussion:

GSK asked the Division about the LABA safety endpoint. GSK also indicated that there is not a placebo group in the program and asked the Division would a placebo arm be required. The Division responded that this is unknown at this time and will defer comment.

**Question #15**

***Does the Agency agree with the design of the 12-month severe exacerbation study?***

Response:

*See response to previous question.*

Discussion:

No Discussion occurred.

**Question #17**

***Does the Agency agree the size of the database; the length of patient exposure and the proposed safety monitoring provide an adequate safety database to support the asthma NDA?***

Response:

*It is premature to address the adequacy of the proposed safety database while discussions concerning the safety and role of LABAs in the management of asthma are ongoing.*

Discussion:

No discussion occurred.

**Question #19**

***Does the Agency agree with the rationale*** [REDACTED] (b) (4)  
[REDACTED].?

**Response:**

*Your proposal appears reasonable, however the decision regarding waiving* [REDACTED] (b) (4)  
*of pediatric studies is made at the NDA stage.*

**Discussion:**

No discussion occurred.

**Question #20**

***Does the Agency agree with the proposal*** [REDACTED] (b) (4)  
[REDACTED].?

**Response:**

*See the response to the previous question.*

**Discussion:**

No discussion occurred.

**Question #21**

***Does the Agency agree with the proposed Phase IIa and Phase IIb study designs and the proposed doses*** [REDACTED] (b) (4).?

**Response:**

*It is premature to discuss* [REDACTED] (b) (4)  
[REDACTED]

**Discussion:**

The sponsor asked the Division [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]

**Question #22**

***Would the Division provide a preliminary view*** (b) (4)

[Redacted]

?

**Response:**

*See previous responses.*

**Discussion:**

No discussion occurred.

**Question #23**

***For the pivotal efficacy studies, there will be more than one treatment comparison. In addition, GSK plans to use two primary endpoints to assess the effects on lung function: trough FEV<sub>1</sub>, primarily to evaluate the effect of the ICS and weighted mean FEV<sub>1</sub> over 0-24 hours assessed in 50% of subjects, primarily to evaluate the effect of the LABA.***

***To account for multiplicity, a pre-defined step-down closed testing procedure will be utilized for the key treatment comparisons and co-primary lung function endpoints. Does the Agency agree with the multiplicity strategy employed?***

**Response:**

*The relation of the closed testing procedure to the structure of desired claims is not clear. For the approval of a combination product, it is necessary to show contributions of both components, so that the order of testing is irrelevant but harmless. If you contemplate other claims based on partial success in the chain of testing, you should say what they are.*

*Desired labeling claims depending on secondary endpoints should be specified. It is also important to understand that in order for the secondary endpoints to be placed in the label, they need to show consistent results across studies.*

**Discussion:**

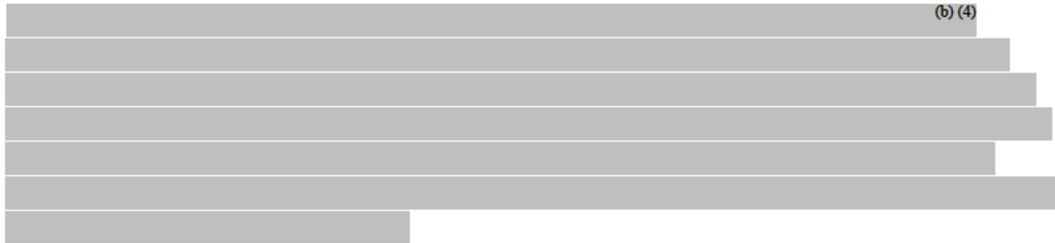
No discussion occurred

**Additional Comments #2:**

[Redacted] (b) (4)

Discussion:

(b) (4)

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**Additional Comments for Question #3**

***Does the agency agree that the proposed plans to study the drug-drug interaction and effect of hepatic impairment will provide appropriate pharmacokinetic data to describe the effects of reduced metabolic clearance and other drug interactions of GW642444M and fluticasone furoate?***

Response:

*No. In addition to what you have proposed, we recommend you studying the effect of P-gp inhibitor (e.g., verapamil) on the fluticasone furoate/GW642444 combination product.*

*Note: Clinical pharmacology proposes to change the preliminary response above to the following.*

*Answer: Based on the results you get from the drug interaction study with ketoconazole, further investigation maybe needed to differentiate the contribution from CYP3A4 and P-gp.*

Discussion:

No discussion occurred.

Linked Applications

Sponsor Name

Drug Name / Subject

IND 77855

GLAXO GROUP LTD  
DBA GLAXOSMITHKLINE

GW685698/GW642444 Inhalation Powder

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/s/

ANGELA H ROBINSON  
04/27/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 77855

GlaxoSmithKline  
Five Moore Drive  
PO Box 13398

Attention: Lorna Wilson  
Director, US Regulatory Affairs

Dear Ms. Wilson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GW685698/GW64244 Inhalation Powder.

We also refer to the meeting between representatives of your firm and the FDA on March 31, 2009. The purpose of the meeting was to discuss adequacy of safety database to support proceeding to Phase III in Asthma.

A copy of the official minutes of the meeting is attached 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) 796-2284.

Sincerely,

*{See appended electronic signature page}*

Angela Robinson, RN, MSN  
Senior Regulatory Project Manager  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** March 31, 2009  
**TIME:** 1:30pm – 2:30 pm EST  
**LOCATION:** White Oak, Bldg 22, Conference Room 1417  
**APPLICATION:** IND 77855  
**DRUG NAME:** GW685698/GW64244 Inhalation Powder  
**TYPE OF MEETING:** EOP II

**MEETING CHAIR:** Prasad Peri

**MEETING RECORDER:** Angela Robinson

**FDA ATTENDEES:** (Title and Office/Division)

**Division of Pulmonary and Allergy Products**

Anthony Durmowicz, MD, Clinical Team Leader  
Angela Robinson, RN, MSN, Senior Regulatory Project Manager  
Prasad Peri, PhD, Pharmaceutical Assessment Lead  
Craig M. Bertha, PhD, CMC Reviewer

**EXTERNAL CONSTITUENT ATTENDEES:**

Sue Holmes, Associate Director, CMC regulatory Affairs  
Jason Creasey, Manager, Extractables and Leechables  
Martyn Vole  
Paul Johnson, Director, Medicine and Process Development  
Brett Haumann, M.D., Respiratory Development  
Darrell Baker, Senior Vice President, Respiratory Development  
Courtney Crim, M.D., Director, Clinical Development  
Kate Knobil, Vice President, Global Clinical  
Lorna Wilson, Director, Regulatory Affairs

**BACKGROUND:**

GlaxoSmithKline submitted a Type B meeting request dated, September 30, 2008 to discuss CMC specific End-of-Phase II development plans for GW685698/GW64244 Inhalation Powder.

The briefing package was submitted on February 27, 2009. Upon review of the material, the Division responded via fax on March 30, 2009. GlaxoSmithKline request to continue with face-to-face meeting as scheduled and would like to discuss FDA's additional comments as well as the responses to questions 2, 10, 11-13 and 15.

The content of the fax is below. Any discussion that occurred during the meeting is captured directly under the relevant response. The sponsor's questions are in ***bold italics***; The Division's response is in *italic*; and discussion is in normal font.

**Question 2:**

[Redacted] (b) (4)

[Redacted] ***Does the Agency agree?***

FDA Response:

*No we do not agree and the proposal is not consistent with current Agency guidance.*

[Redacted] (b) (4)

Discussion:

[Redacted] (b) (4)

**Question 10:**

***Does the Agency agree that this assessment of clinical trial returns can be conducted***

[Redacted] (b) (4)  
[Redacted] ?

FDA Response:

*Without having evaluated the data assessing the performance of routine inhaler returns it is premature to conclude [REDACTED] (b) (4)*

*Regardless of how routine performance assessment is handled [REDACTED] (b) (4) [REDACTED] complaint device returns should always be subjected to performance (emitted dose and ASD) and other pertinent test.*

Discussion:

The sponsor asked the Division to clarify the testing of returned drug product related to complaints. In particular, the sponsor indicated that there may be situations with complaint drug products where they are unable to test the units due to damage.

The Division acknowledged that the complaint will determine the sponsor's actions and the associated tests that should or can be performed. The Division also indicated that we have observed instances for other applications where returned complaint drug product devices were damaged by the patients or tested for performance and were not found to be faulty after all.

Question II:

***Given the results generated by experimental studies to date for Fluticasone Furoate/GW642444 Inhalation Powder, GSK consider [REDACTED] (b) (4)***

***Does the Agency agree with this approach to the study of extractables and leachables for Fluticasone Furoate/GW642444 Inhalation Product?***

FDA response:

*No, we do not agree. We still recommend the characterization and the routine monitoring of the extractables profile of the critical device components is still recommended to monitor for compositional changes that may be due to either changes in input materials or the actual component molding processes.*

Discussion:

The sponsor asked the Division to clarify if their development plans in term of extractables/leachables is appropriate. The sponsor reports no evidence of leachables and stated they expected this will be the case in the future.

The Division acknowledged that the principles outlined in the PQRI Extractables/Leachables<sup>1</sup> report can be followed but that there still needs to be routine testing to assure consistent component composition. The Division recommended that the

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<sup>1</sup> Product Quality Research Institute (PQRI) report of August 2006 entitled *Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products* submitted to the PQRI Drug Product Technical Committee and Steering Committee by the PQRI Leachables and Extractables Working Group.

sponsor see how this issue was addressed for the Advair Diskus product and suggested that the sponsor include a summary of how this routine compositional control will be handled for the device of the current product in the COPD background package.

**Question 12:**

***GSK has outlined the further studies planned for extractable testing of blister and inhaler material batches plus leachable testing on stored drug product. The results of these studies will be provided in the NDA. Can the Agency confirm that this information will satisfy all of the requirements for extractable and leachable studies for the NDA?***

**FDA Response:**

*See the response to question 11 above. Also the mouthpiece of the device should be tested and pass requirements associated with the biological reactivity test of USP<87> and <88>.*

**Discussion:**

GSK questioned whether or not they had to meet the Class V or VI requirements of USP<88> for the mouthpiece. The Division representatives for CMC stated that the pharmacology/toxicology team will be consulted and the answer will be included as a post meeting note in the minutes

Post-Meeting Note: Based on the discussions with PharmTox team, it is agreed that Class VI requirement test for plastics is not needed for the DPI mouthpiece.

**Question 13:**

***Does the Agency agree that the extractable and leachable information provided in the NDA can be conducted***

(b) (4)

?

**FDA Response:**

*No, we do not agree in principle, however, this does not preclude your reference to studies submitted to support other applications that use the same primary and secondary container closure system component. Specifics of such proposals can be discussed with the pertinent review divisions/teams responsible for review of those applications. Also see response to question 11 above.*

Discussion:

The sponsor asked the Division if the blister, excipients, device and package were the same, would that satisfy the requirements.

The Division commented that they were unsure of what the other teams may require for extractables/leachables. Even within the Division, we do not feel comfortable concluding that the studies for leachable can be (b) (4) for the device since it is conceivable that there may be formulation- dependent circumstances that need to be considered.

**Question 15:**

***GSK acknowledges that the appropriateness of the particle size distribution acceptance criteria is a review issue, however can the Agency confirm acceptance of the approach to assess the particle size distribution specification for the commercial product?***

FDA Response:

No, we can not confirm (b) (4)

[Redacted]

Data from Phase III product and primary stability studies should be used to set the APSD acceptance criteria. Refer to additional comment below.

Discussion:

The sponsor asked the Division if blister, excipients, device and package were the same, would that satisfy the requirements.

The Division commented that they are unsure of what other teams may require.

**Question 15 (continues):**

***Is such an approach considered acceptable where a combination of the commercial scale capability, the range used in the clinic and observed on stability is used as the basis for establishing the acceptance criteria?***

FDA response:

We are in general agreement with that type of approach for establishing acceptance criteria.

Discussion:

The Division reiterated (b) (4)

[Redacted] in setting the APSD acceptance criteria for the combination product. However, the Division agrees that it would be acceptable for the applicant to consider APSD data from the development

batches of the combination product when setting the acceptance criteria as long as these were like the planned commercial product.

GSK made the following additional comments:

**APSD [REDACTED] (b) (4) trend**

GSK stated [REDACTED] (b) (4) regarding the [REDACTED] (b) (4) APSD trend, but no specifics were discussed. The Division acknowledged that this issue was solved [REDACTED] (b) (4)

**Patient -unaware Defects and new lid foil [REDACTED] (b) (4) :**

The Division briefly summarized from the prior meeting with GSK on the PUD issue [REDACTED] (b) (4)

[REDACTED]

The Division asked if GSK was still going to pursue improvements [REDACTED] (b) (4) that might increase the robustness of the product with respect to the PUD issue. GSK indicated that they are still following up on this in their development program.

Linked Applications

Sponsor Name

Drug Name / Subject

-----  
IND 77855

-----  
GLAXO GROUP LTD  
DBA GLAXOSMITHKLINE

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GW685698/GW642444 Inhalation Powder

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANGELA H ROBINSON  
04/27/2009

Executive CAC

Date of Meeting: August 21, 2007

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair  
Joseph Contrera, Ph.D., OPS, Member  
Barry Rosloff, Ph.D., DPP, Alternate Member  
Timothy McGovern, Ph.D., DPAP, Team Leader  
Huiqing Hao, Ph.D., DPAP, Presenting Reviewer

Author of Draft: Huiqing Hao, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

The committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogen bioassays, as this does not affect the sponsor's ability to initiate the bioassays. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2006).

IND # 74,696

Drug Name: GW642444

Sponsor: GSK

**Background:**

GW642444 is being developed as the long-acting beta agonist (LABA) component of a once-daily inhaled corticosteroid (ICS)/LABA combination product for treatment of asthma. (b) (4) This combination product and GW642444 monotherapy are also planned for treatment of COPD. The sponsor plans to use doses up to 50 mcg/day for future clinical trials and the anticipated Maximum Recommended Human Dose (MRHS) for marketing is 6.25 mcg/day.

Plasma protein binding was similar across species - 92, 94 and 97% in rats, mice and humans, respectively. GW642444 tested negatively in the Ames assay, rat bone marrow micronucleus assay, in vitro UDS assay and SHE cell assay. Equivocal findings were observed in the mouse lymphoma assay.

**Mouse Carcinogenicity Study Protocol and Dose Selection**

The sponsor proposed a standard 2-year carcinogenicity study in CD-1 mice

(60/sex/dose) at GW642444 doses (b) (4) by nose-only inhalation for 104 weeks with a standard battery of

observations/examinations. Histopathology evaluation will be conducted in all main study animals. 66 mice/sex/group will be included for TK assessment. When survival approaches 25 animals in any treatment group, early termination will be considered. Males and females will be considered separately. The sponsor's dose selection was based on an MTD criterion. [REDACTED] (b) (4)

In a 13-week dose ranging study, a dose of 63,600 mcg/kg resulted in irregular and/or labored breathing and deaths during the first 9 days of dosing. This dose was concluded to have exceeded the MTD. The dose was reduced to 38,200 mcg/kg and resulted in increased body weight gain and microscopic lesions in the nasal turbinates (epithelial degeneration/regeneration, epithelial metaplasia, eosinophilic inclusions), larynx (epithelial squamous metaplasia), liver (decreased hepatocyte cytoplasm rarefaction) and uterus (myometrial hypertrophy) that were not considered dose limiting.

#### Rat Carcinogenicity Study Protocol and Dose Selection

The sponsor proposed a standard 2-year carcinogenicity study in SD rats (60/sex/dose) at GW642444 doses [REDACTED] (b) (4) by nose-only inhalation with a standard battery of observations/examinations. Histopathology evaluation will be conducted in all main study animals. 6 rats/sex/group will be included for TK assessment. When survival approaches 25 animals in any treatment group, early termination will be considered. Males and females will be considered separately. The sponsor's dose selection rationale was based on an MTD criterion [REDACTED] (b) (4)

In a 13-week dose ranging study, the MTD was considered by the reviewer to be 658 mcg/kg. Doses of 10,392 mcg/kg and greater resulted in significant respiratory tract lesions including moderate to marked ulceration of the olfactory and/or respiratory epithelium of the nasal cavity, slight to marked epithelial degeneration/regeneration, olfactory nerve atrophy, and moderate to marked squamous metaplasia. At the lower-mid dose of 658 mcg/kg, lesions were limited to minimal epithelial degeneration/regeneration and minimal to slight laryngeal metaplasia and hyperplasia.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee did not concur with the doses proposed by the sponsor (b) (4)  
[REDACTED]
- The Committee recommended doses of 0, 3000, 10,000, and 30,000 mcg/kg/day by snout-only inhalation, based on an MTD criterion (mortality and clinical signs at 63,600 mcg/kg). The recommended high dose is approximately one-half of the identified lethal dose. The sponsor may add additional lower doses at their discretion.
- The sponsor should contact the agency prior to terminating any groups or changing any doses.

Rat:

- The Committee did not concur with the doses proposed by the sponsor (b) (4)  
[REDACTED]
- The Committee recommended doses of 0, 80, 220, and 650 mcg/kg/day by nose-only inhalation, based on an MTD criterion (severe respiratory tract irritancy and ulceration of the upper airways at doses of 10,392 mcg/kg and higher). The sponsor may add additional lower doses at their discretion.
- The sponsor should contact the agency prior to terminating any groups or changing any doses.

Abigail Jacobs, Ph.D.  
Acting Chair, Executive CAC

cc:\n  
/Division File, DPAP  
/Timothy McGovern, Team leader, DPAP  
/Huiqing Hao, Reviewer, DPAP  
/Philantha, CSO/PM, DPAP  
/ASeifried, OND IO

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LUQI PEI  
02/13/2013

MARCIE L WOOD  
02/14/2013