

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209482Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 209482

SUPPL #

HFD #

Trade Name Trelegy Ellipta

Generic Name fluticasone furoate, umeclidinium, and vilanterol inhalation powder

Applicant Name GlaxoSmithKline

Approval Date, If Known

### **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)

b) 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:

c) Did the applicant request exclusivity?

YES  NO

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

d) 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# 205625	Arnuity Ellipta (fluticasone furoate) inhalation powder
NDA# 203975	Anoro Ellipta (umeclidinium bromide/vilanterol)
NDA# 204275	Breo Ellipta (fluticasone furoate/vilanterol)
NDA# 205382	Incruse Ellipta (umeclidinium bromide)
NDA# 022051	Flonase Sensimist Allergy Relief

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:

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:

Trial 200109, NDA 205382/S-002

Trial 200110, NDA 205382/S-002

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:

NDA 205382/S-002

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"):

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

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

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

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



Title: Deputy Director, DPARP

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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LEANN D BRODHEAD  
09/18/2017

LYDIA I GILBERT MCCLAIN  
09/18/2017

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 209482 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Trelegy Ellipta Established/Proper Name: fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg Dosage Form: Inhalation Powder		Applicant: GlaxoSmithKline Agent for Applicant (if applicable):
RPM: LeAnn Brodhead		Division: Division of Pulmonary, Allergy, and Rheumatology Products
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)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b> <ul style="list-style-type: none"> <li><input type="checkbox"/> No changes</li> <li><input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)</li> </ul> </li> </ul> Date of check:
<b>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b>		
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>September 18, 2017</u></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
❖ 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 _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<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.

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

- |   |   |
|---|---|
| <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            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

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

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

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

Comments:

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

Action Letters	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) AP, 9/18/17
Labeling	
❖ 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 (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ 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> )	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ 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> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ 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> </ul>	Proprietary Name Granted, 2/14/17 Acknowledgement letter, 12/13/16 Proprietary Name Review, 1/12/17
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: <input type="checkbox"/> None PLR Format Review, 6/12/17 DMEPA: <input type="checkbox"/> None 7/21/17 DMPP/PLT (DRISK): <input type="checkbox"/> None 8/29/17, 8/25/17 OPDP: <input type="checkbox"/> None 8/28/17 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input type="checkbox"/> None 8/29/17 Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting ( <i>indicate date of each review</i> )	Filing Review, 6/12/17
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Completed ( <b>Do not include</b> )
❖ 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>	

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<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 August 23, 2017 _____ If PeRC review not necessary, explain: The pediatric studies requirement for this application has been waived as the indication for the product is chronic obstructive pulmonary disease (COPD) which is an adult-related condition that does not occur in pediatrics. COPD is found on the list of adult-related conditions that qualify for a waiver because studies would be impossible or highly impractical.</li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>❖ Breakthrough Therapy Designation</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></i>)</p>	
<ul style="list-style-type: none"> <li>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	OND RPM communications to applicant: 9/18/17, 9/7/17, 9/5/17, 8/14/17, 8/1/17, 12/2/16 OPQ IR’s: 7/17/17, 7/7/17, 7/5/17, 4/27/17, 4/12/17
<ul style="list-style-type: none"> <li>❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<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 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
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg EOP2 9/18/13, EOP2 CMC 10/21/13 under IND 114873
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	

❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Summary Review 9/18/17
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None Deputy Division Director served as CDTL
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) ( <i>indicate date for each review</i> )	Addendum to primary review 8/24/17, Primary review 8/14/17, filing review 1/6/17
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input 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 checked="" type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Memo regarding financial disclosure, 9/8/17
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> ) <sup>5</sup>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<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
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<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"/> No separate review
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 type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Statistical Memo 9/18/17, Primary review 8/21/17, Filing review 1/10/17

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

<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"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Primary review 8/14/17, Filing review 1/17/17
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review 8/17/17
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Primary review 8/14/17, Filing review 1/13/17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews <sup>6</sup>	
• Tertiary review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
• Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Executive Summary 8/29/17, Drug Substance, 7/25/17 Drug Product, 8/15/17 Process, 8/14/17 Facilities, 8/28/17 CMC filing review 1/10/17, 1/4/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )	<input type="checkbox"/> None

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

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	Per CMC Final Quality Assessment: Request for Categorical Exclusion for Environmental Assessment was included in the submission, based on market forecasts, indications, and dosage information, and estimates. Sponsor stated that the approval of this drug product will not cause the concentration of the drug substance(s) active moiety(ies) to be one part per billion (1 ppb) or greater at the point of entry into the aquatic environment. The claim of categorical exclusion is acceptable, per 21 CFR Part 25.31(b).
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation <b>before issuing approval letter</b> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input checked="" type="checkbox"/> Acceptable, Facilities review 8/28/17 <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
<ul style="list-style-type: none"> <li>❖ For all 505(b)(2) applications:               <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> </li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(Notify CDER OND IO)</i>
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul> </li> </ul>	<input type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ For Breakthrough Therapy (BT) Designated drugs:               <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul> </li> </ul>	<input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
<ul style="list-style-type: none"> <li>❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul> </li> </ul>	<input type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</li> </ul>	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter</li> </ul>	<input type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name</li> </ul>	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ Ensure Pediatric Record is accurate</li> </ul>	<input type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ Send approval email within one business day to CDER-APPROVALS</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Take Action Package (if in paper) down to Document Room for scanning within <b>two business days</b></li> </ul>	

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/s/  
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LEANN D BRODHEAD  
09/19/2017

## Brodhead, LeAnn

---

**From:** Brodhead, LeAnn  
**Sent:** Monday, September 18, 2017 4:45 PM  
**To:** 'Mary Sides'  
**Cc:** Patrick Wire  
**Subject:** NDA 209482 Approval: Trelegy Ellipta  
**Attachments:** NDA 209482 Trelegy Ellipta Approval Letter 091817.pdf  
  
**Importance:** High

Good afternoon Mary-

Please refer to your New Drug Application (NDA) dated November 18, 2016, received November 18, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Trelegy Ellipta (fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg) Inhalation Powder.

We have completed our review of this application, as amended. It is approved, effective on the date of the attached approval letter, for use as recommended in the enclosed agreed-upon labeling text. A courtesy copy of the approval letter is attached for your review and additional information. Should you have any additional questions, please feel free to contact me.

Lastly, please acknowledge receipt of this email. Thank you for your attention to this matter.

Sincerely,

**LeAnn D. Brodhead, PharmD, MPH**  
**LCDR, U.S. Public Health Service**  
**Regulatory Project Manager**  
Food and Drug Administration  
Center for Drug Evaluation and Research/ODEII  
Division of Pulmonary, Allergy, and Rheumatology Products  
10903 New Hampshire Ave., Bldg 22, Room 3315  
Silver Spring, MD 20993  
Phone: 240-402-2605  
Fax: 301-796-9728  
[leann.brodhead@fda.hhs.gov](mailto:leann.brodhead@fda.hhs.gov)

## Brodhead, LeAnn

---

**From:** Mary Sides <mary.v.sides@gsk.com>  
**Sent:** Monday, September 18, 2017 3:51 PM  
**To:** Brodhead, LeAnn  
**Subject:** RE: Trelegy NDA 209482-upcoming action

**Categories:** Red Category

OK you should have it now! Systems working very slow at GSK today.

**Mary Sides**  
**Director, Global Regulatory Affairs**  
US Therapeutic Groups  
RD Chief Regulatory Office

**GSK**  
5 Moore Drive, PO Box 13398, RTP, NC 27709-3398, United States  
**Email** [mary.v.sides@gsk.com](mailto:mary.v.sides@gsk.com)  
**Tel** +1.919.483.6464

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 Please consider the environment before printing this email

---

**From:** Brodhead, LeAnn [<mailto:Leann.Brodhead@fda.hhs.gov>]  
**Sent:** Monday, September 18, 2017 3:23 PM  
**To:** Mary Sides <mary.v.sides@gsk.com>  
**Subject:** RE: Trelegy NDA 209482-upcoming action

**EXTERNAL**

Hi Mary-

You sent me the track changes version. Can you please send me the clean version? Thank you! Still waiting for the materials to come through the gateway.

---

**From:** Mary Sides [<mailto:mary.v.sides@gsk.com>]  
**Sent:** Monday, September 18, 2017 3:05 PM  
**To:** Brodhead, LeAnn  
**Subject:** RE: Trelegy NDA 209482-upcoming action

I just realized I sent you the clean revision. Here is revision marked.

**Mary Sides**  
**Director, Global Regulatory Affairs**

US Therapeutic Groups  
RD Chief Regulatory Office

**GSK**

5 Moore Drive, PO Box 13398, RTP, NC 27709-3398, United States

Email [mary.v.sides@gsk.com](mailto:mary.v.sides@gsk.com)

Tel +1 919 483 6464

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---

**From:** Mary Sides

**Sent:** Monday, September 18, 2017 2:11 PM

**To:** 'Brodhead, LeAnn' <[Leann.Brodhead@fda.hhs.gov](mailto:Leann.Brodhead@fda.hhs.gov)>

**Subject:** RE: Trelegy NDA 209482-upcoming action

Hi LeAnn, as discussed, please find attached the tracked changes version of the proposed labeling. We will submit both a clean and tracked changes version momentarily.

Thanks.

**Mary Sides**

**Director, Global Regulatory Affairs**

US Therapeutic Groups

RD Chief Regulatory Office

**GSK**

5 Moore Drive, PO Box 13398, RTP, NC 27709-3398, United States

Email [mary.v.sides@gsk.com](mailto:mary.v.sides@gsk.com)

Tel +1 919 483 6464

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---

**From:** Brodhead, LeAnn [<mailto:Leann.Brodhead@fda.hhs.gov>]

**Sent:** Monday, September 18, 2017 1:16 PM

**To:** Mary Sides <[mary.v.sides@gsk.com](mailto:mary.v.sides@gsk.com)>

**Cc:** Patrick Wire <[patrick.d.wire@gsk.com](mailto:patrick.d.wire@gsk.com)>

**Subject:** RE: Trelegy NDA 209482-upcoming action

**Importance:** High

EXTERNAL

Good afternoon Mary/Patrick-

Would one of you be able to give me a call to discuss an editorial change that the agency would like to make to the indication statement. Please call [REDACTED] (b) (6). Thank you!

LeAnn

---

**From:** Mary Sides [mailto:mary.v.sides@gsk.com]  
**Sent:** Wednesday, September 13, 2017 1:33 PM  
**To:** Brodhead, LeAnn  
**Cc:** Patrick Wire  
**Subject:** Trelegy NDA 209482-upcoming action

Hi LeAnn. Hope you are well.

I wanted to let you know that I will be going to the UK Friday night and will be there the following week. I intend on working around the clock to support the impending US action from the UK. However, please copy Patrick Wire on the notification so that he or I can acknowledge the letter once received. We look forward to receiving this Monday but if there is any chance it could come on Friday, it would be great to know that in advance as there are numerous things that need to be in place if received late in the day before a weekend.

Take care and many thanks!

**Mary Sides**  
**Director, Global Regulatory Affairs**  
US Therapeutic Groups  
RD Chief Regulatory Office

**GSK**  
5 Moore Drive, PO Box 13398, RTP, NC 27709-3398, United States  
**Email** [mary.v.sides@gsk.com](mailto:mary.v.sides@gsk.com)  
**Tel** +1 919 483 6464

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**Brodhead, LeAnn**

---

**From:** PeRC  
**Sent:** Thursday, September 14, 2017 10:27 AM  
**To:** Brodhead, LeAnn  
**Subject:** RE: Meeting Minutes from August 23, 2017 Meeting

Hi LeAnn-

Please see the comments from PeRC in regards to NDA 209482 Trelegy Ellipta:

**NDA 209482**

**Trelegy Ellipta (fluticasone furoate, umeclidinium, and vilanterol) Inhalation Powder Full Waiver (with Agreed iPSP)**

- Proposed indication: For the long-term, once-daily, maintenance treatment of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
  
- *PeRC Recommendations:*
  - The PeRC agrees with the division to grant this full waiver as agreed upon in the iPSP.

Thanks,

Meshaun Payne, MHCA, BSMT  
Regulatory Health Project Manager  
Division of Pediatric and Maternal Health  
Office of New Drugs  
FDA/CDER/OND/DPMH  
10903 New Hampshire Avenue  
Building 22, Room 6467  
Silver Spring, MD 20993-0002  
301-796-6668  
Email: [Meshaun.Payne@fda.hhs.gov](mailto:Meshaun.Payne@fda.hhs.gov)

---

**From:** lead, LeAnn  
**Sent:** Thursday, September 14, 2017 10:17 AM  
**To:** PeRC  
**Subject:** Meeting Minutes from August 23, 2017 Meeting

Good morning-

I wanted to follow up with PeRC to see if the meeting minutes from the 8/23/17 meeting were available. Thank you!

**LeAnn D. Brodhead, PharmD, MPH**

**LCDR, U.S. Public Health Service**

**Regulatory Project Manager**

Food and Drug Administration

Center for Drug Evaluation and Research/ODEII

Division of Pulmonary, Allergy, and Rheumatology Products

10903 New Hampshire Ave., Bldg 22, Room 3315

Silver Spring, MD 20993

Phone: 240-402-2605

Fax: 301-796-9728

[leann.brodhead@fda.hhs.gov](mailto:leann.brodhead@fda.hhs.gov)

## **Memo Regarding Financial Disclosure**

**Date:** September 8, 2017  
**From:** Sofia Chaudhry, MD Medical Officer  
**Through:** Lydia Gilbert-McClain, MD Deputy Division Director  
**Subject:** Memo Regarding Review of Financial Disclosure Information  
**NDA:** 209482  
**Trade Name:** Trelegy Ellipta  
**Established Name:** Fluticasone furoate/Umeclidinium/Vilanterol  
**Date of Submission:** November 18, 2016  
**PDUFA Goal Date:** September 18, 2017

A review of financial disclosure information for NDA 209482 (Trelegy Ellipta; fluticasone furoate/umeclidinium/vilanterol) is not required. The clinical efficacy, safety data and associated financial disclosure information used to support the review of this NDA application were reviewed under NDA 205382 supplement 2 for Incruse Ellipta (approved February 24, 2016).

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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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SOFIA S CHAUDHRY  
09/08/2017

LYDIA I GILBERT MCCLAIN  
09/08/2017

## Brodhead, LeAnn

---

**From:** Mary Sides <mary.v.sides@gsk.com>  
**nt:** Thursday, September 07, 2017 4:09 PM  
**.o:** Brodhead, LeAnn  
**Subject:** Re: NDA 209482 - Trelegy Ellipta - Labeling Comments/Revisions

Awesome! Thanks!

Sent from my iPhone

> On Sep 7, 2017, at 3:53 PM, Brodhead, LeAnn <LeAnn.Brodhead@fda.hhs.gov> wrote:

>

> EXTERNAL

>

> Good afternoon Mary-

>

> We have completed review of the additional rationale regarding rescue albuterol use provided in your correspondence submitted on Wednesday September 6, 2017. We find the rationale to be acceptable. As a follow up to the labeling comments sent to you on Tuesday Sept 5, 2017, we advise that you keep the following statement in section 14 of the label which reads:

>

> " Across both trials over Weeks 1 to 12, patients treated with umeclidinium + fluticasone furoate/vilanterol on average used less rescue medication compared to patients treated with placebo+ fluticasone furoate/vilanterol."

Please let me know if you have any additional questions and if you are still able to submit a response by tomorrow, September 8, 2017. Thank you!

>

> LeAnn

>

> -----Original Message-----

> From: Mary Sides [mailto:mary.v.sides@gsk.com]

> Sent: Thursday, September 07, 2017 10:42 AM

> To: Brodhead, LeAnn

> Subject: RE: NDA 209482 - Trelegy Ellipta - Labeling Comments/Revisions

>

> OK cool! We are ready to submit tomorrow so can you let me know when we will know?

>

> Mary Sides

> Director, Global Regulatory Affairs

> US Therapeutic Groups

> RD Chief Regulatory Office

>

> GSK

> 5 Moore Drive, PO Box 13398, RTP, NC 27709-3398, United States

> Email mary.v.sides@gsk.com

> Tel +1 919 483 6464

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>

>  
>  
>  
>  
>  
> -----Original Message-----  
> From: Brodhead, LeAnn [mailto:Leann.Brodhead@fda.hhs.gov]  
> Sent: Thursday, September 07, 2017 10:34 AM  
> To: Mary Sides <mary.v.sides@gsk.com>  
> Subject: RE: NDA 209482 - Trelegy Ellipta - Labeling Comments/Revisions  
> Importance: High

>  
> EXTERNAL

>  
> Good morning Mary-

>  
> I wanted to make you aware that the agency has received your submission and are reviewing the follow up information regarding the rescue use statements. While we had requested that you provide a response to the proposed labeling by Friday September 8th, we are now asking that you wait to submit a response until you receive feedback from the Agency regarding the rescue medication labeling statements. Thank you!

>  
> LeAnn

>  
>  
>  
> -----Original Message-----

> From: Mary Sides [mailto:mary.v.sides@gsk.com]  
> Sent: Tuesday, September 05, 2017 4:38 PM  
> To: Brodhead, LeAnn  
> Subject: Re: NDA 209482 - Trelegy Ellipta - Labeling Comments/Revisions

>  
> Thanks received! I should be able to submit by Friday but it may have to be officially through the gateway on Monday but I will check.

>  
> Thanks!

>  
> Sent from my iPhone

>  
>> On Sep 5, 2017, at 3:44 PM, Brodhead, LeAnn <Leann.Brodhead@fda.hhs.gov> wrote:

>>  
>> EXTERNAL

>> Good afternoon Mary-

>>  
>> Your NDA 209482 for TRELEGY ELLIPTA submitted on November 18, 2016, is under review and the labeling review for your application is ongoing.

>>  
>> The enclosed label contains the Division's edits to your proposed Package Insert (PI), Medication Guide (MG) and Instructions For Use (IFU). The Division's proposed insertions are underlined, deletions are in strike-outs. These comments are not all-inclusive and we may have additional comments as we continue our review.

>>  
>> Submit revised labeling incorporating changes shown in the attached marked up labeling as well as update the revision date in the Highlights section of the package insert by the COB September 8, 2017.

>>  
>> Lastly, if you would be so kind as to confirm receipt of this email, it would be greatly appreciated. Thank you!

>>

>> LeAnn D. Brodhead, PharmD, MPH

>> LCDR, U.S. Public Health Service

>> Regulatory Project Manager

· Food and Drug Administration

·> Center for Drug Evaluation and Research/ODEII Division of Pulmonary,

>> Allergy, and Rheumatology Products

>> 10903 New Hampshire Ave., Bldg 22, Room 3315 Silver Spring, MD 20993

>> Phone: 240-402-2605

>> Fax: 301-796-9728

>> leann.brodhead@fda.hhs.gov

>>

>> <NDA 209482 Trelegy Ellipta Draft LABELING 09052017.pdf>

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> GSK monitors email communications sent to and from GSK in order to protect GSK, our employees, customers, suppliers and business partners, from cyber threats and loss of GSK Information. GSK monitoring is conducted with appropriate confidentiality controls and in accordance with local laws and after appropriate consultation.

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NDA 209482



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: September 5, 2017**

<b>To:</b> Mary V. Sides Director, Global Regulatory Affairs	<b>From:</b> LeAnn Brodhead Regulatory Health Project Manager
<b>Company:</b> GlaxoSmithKline	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Email:</b> mary.v.sides@gsk.com	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> (919) 483-6464	<b>Phone number:</b> (240) 402-2605
<b>Subject</b> NDA 209482 – LABELING REVISIONS/GUIDANCE – Trelegy Ellipta	

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**Total no. of pages including cover:** 46

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**Comments:** Please confirm receipt by e-mailing LeAnn Brodhead at leann.brodhead@fda.hhs.gov

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

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Your NDA 209482 for TRELEGY ELLIPTA submitted on November 18, 2016, is under review and the labeling review for your application is ongoing.

The enclosed label contains the Division's edits to your proposed Package Insert (PI), Medication Guide (MG) and Instructions For Use (IFU). The Division's proposed insertions are underlined, deletions are in strike-outs. These comments are not all-inclusive and we may have additional comments as we continue our review.

Submit revised labeling incorporating changes shown in the attached marked up labeling as well as update the revision date in the Highlights section of the package insert by the COB September 8, 2017.

If you have any questions, please contact LeAnn Brodhead, Regulatory Project Manager, at 240-402-2605 or via email: [LeAnn.Brodhead@fda.hhs.gov](mailto:LeAnn.Brodhead@fda.hhs.gov).

Initiated by: L. Gilbert-McClain, 9/5/17

Cleared by: L. Jafari, 9/5/17

Finalized by: L. Brodhead, 9/5/17

Filename: Labeling Revisions

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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LEANN D BRODHEAD  
09/05/2017



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: August 14, 2017**

<b>To:</b> Mary V. Sides Director, Global Regulatory Affairs	<b>From:</b> LeAnn Brodhead Regulatory Health Project Manager
<b>Company:</b> GlaxoSmithKline	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Email:</b> mary.v.sides@gsk.com	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> (919) 483-6464	<b>Phone number:</b> (240) 402-2605
<b>Subject</b> NDA 209482 – LABELING REVISIONS/GUIDANCE – Trelegy Ellipta	

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**Total no. of pages including cover:** 50

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**Comments:** Please confirm receipt by e-mailing LeAnn Brodhead at leann.brodhead@fda.hhs.gov

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

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Your NDA 209482 for TRELEGY ELLIPTA submitted on November 18, 2016, is under review and the labeling review for your application is ongoing.

The enclosed label contains the Division's edits to your proposed package insert (PI). The Division's proposed insertions are underlined, deletions are in strike-outs. These comments are not all-inclusive and we may have additional comments as we continue our review.

Submit revised labeling incorporating changes shown in the attached marked up labeling for the package insert by the COB August 18, 2017.

If you have any questions, please contact LeAnn Brodhead, Regulatory Project Manager, at 240-402-2605 or via email: [LeAnn.Brodhead@fda.hhs.gov](mailto:LeAnn.Brodhead@fda.hhs.gov).

Initiated by: L. Gilbert-McClain, 8/14/17  
Cleared by: L. Jafari, 8/14/17  
Finalized by: L. Brodhead, 8/14/17  
Filename: Labeling Revisions

48 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following  
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/s/  
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LEANN D BRODHEAD  
08/14/2017



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: August 1, 2017**

<b>To:</b> Mary V. Sides Director, Global Regulatory Affairs	<b>From:</b> LeAnn Brodhead Regulatory Health Project Manager
<b>Company:</b> GlaxoSmithKline	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Email:</b> mary.v.sides@gsk.com	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> (919) 483-6464	<b>Phone number:</b> (240) 402-2605
<b>Subject</b> NDA 209482 – GUIDANCE – Revision of Proposed Indication Statement for Trelegy Ellipta	

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

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**Comments:**

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

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Your NDA 209482 for TRELEGY ELLIPTA submitted on November 18, 2016, is under review and the labeling review for your application is ongoing. We are revising your proposed indication statement as follows:

“TRELEGY ELLIPTA is a combination of fluticasone furoate, an inhaled corticosteroid (ICS); umeclidinium, an anticholinergic; and vilanterol, a long acting beta2 adrenergic agonist (LABA), indicated for the long-term, once-daily, maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema who are on a fixed dose combination of fluticasone furoate and vilanterol in whom additional treatment of airflow obstruction with umeclidinium is desired. (1)”

We are sharing this information with you in advance of sending you a complete set of labeling comments to facilitate early discussion on the indication statement. We are amenable to meet (via teleconference) to discuss the indication statement.

If you have any questions, please contact LeAnn Brodhead, Regulatory Project Manager, at 240-402-2605 or via email: [LeAnn.Brodhead@fda.hhs.gov](mailto:LeAnn.Brodhead@fda.hhs.gov).

Initiated by: L. Gilbert-McClain, 8/1/17  
Cleared by: N. Ton for L. Jafari, 8/1/17  
Finalized by: L. Brodhead, 8/1/17  
Filename: Clinical Guidance

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/s/  
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LEANN D BRODHEAD  
08/01/2017

**Brodhead, LeAnn**

---

**From:** Aisida, Bamidele (Florence)  
**nt:** Monday, July 17, 2017 12:26 PM  
**:** 'Sue Holmes'  
**Cc:** Brodhead, LeAnn  
**Subject:** CMC IR NDA 209482 7-19-17

Hello Sue,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by COB July 19 ,2017.

(b) (4)

Please confirm receipt of this IR

Thanks,

*Florence*

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

**From:** Aisida, Bamidele (Florence)  
**To:** "Sue Holmes"  
**Cc:** Brodhead, LeAnn  
**Subject:** RE: CMC IR NDA 209482 7-5-17  
**Date:** Friday, July 07, 2017 1:55:37 PM

---

Hello Sue,

Additional Information request

1. Who is the owner of the design history file and what is the location?
2. Provide a description of the applicant's organizational structure.

Please confirm receipt of this email and respond to this IR by July 11, 2017.

Thanks,

*-Florence*

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

---

**From:** Sue Holmes [mailto:susan.m.holmes@gsk.com]  
**Sent:** Wednesday, July 05, 2017 3:08 PM  
**To:** Aisida, Bamidele (Florence)  
**Cc:** Brodhead, LeAnn  
**Subject:** RE: CMC IR NDA 209482 7-5-17

Hi Florence,

I confirm receipt of this email.

Regards,  
Sue

---

**From:** Aisida, Bamidele (Florence) [mailto:Bamidele.Aisida@fda.hhs.gov]  
**Sent:** Wednesday, July 05, 2017 2:45 PM  
**To:** Sue Holmes <susan.m.holmes@gsk.com>  
**Cc:** Brodhead, LeAnn <Leann.Brodhead@fda.hhs.gov>  
**Subject:** CMC IR NDA 209482 7-5-17

EXTERNAL

Hello Sue,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by July 10 ,2017.

**1. Management Responsibility (21 CFR 820.20)**

Your firm has inadequately addressed the requirement for 21 CFR 820.20, management responsibility.

Please provide a summary of how your firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4). Also, provide a description of the functions and responsibility of each facility involved in the manufacturing of the combination product and its constituent parts.

**2. Purchasing Controls (21 CFR 820.50)**

Your firm has inadequately addressed the requirement for 21 CFR 820.50, purchasing controls.

Please provide a summary of the procedure(s) for purchasing controls. The summary should:

- a. Describe your supplier evaluation process and describe how it will determine type and extent of control you will exercise over suppliers.
- b. Define how you maintain records of acceptable suppliers and how you address the purchasing data approval process.
- c. Explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.

Please explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Provide a description of how you apply the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).

**3. Corrective and Preventive Action (21 CFR 820.100)**

Your firm has inadequately addressed the requirement for 21 CFR 820.100, corrective and preventive actions.

Please summarize the procedure(s) for your Corrective and Preventive Action (CAPA) System. The CAPA system should require:

- a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;
- b. Investigation of nonconformities and their causes;
- c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and

d. Verification or validation of the actions taken.

Please confirm receipt of this email.

*-Florence*

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

**GSK monitors email communications sent to and from GSK in order to protect GSK, our employees, customers, suppliers and business partners, from cyber threats and loss of GSK Information. GSK monitoring is conducted with appropriate confidentiality controls and in accordance with local laws and after appropriate consultation.**

**Brodhead, LeAnn**

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**From:** Aisida, Bamidele (Florence)  
**nt:** Thursday, April 27, 2017 4:05 PM  
**u:** 'Sue Holmes'  
**Cc:** Brodhead, LeAnn  
**Subject:** CMC IR NDA 209482

Hello Ms. Holmes,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by May 11 ,2017.

(b) (4)

Please confirm receipt of this email.

Thanks,

**Florence Aisida, Pharm.D,BCPS**  
Regulatory Business Process Manager  
HHS | FDA | CDER  
Office of Pharmaceutical Quality  
Office of Program and Regulatory Operations  
[Bamidele.aisida@fda.hhs.gov](mailto:Bamidele.aisida@fda.hhs.gov) | 240.402.2691

**From:** [Aisida, Bamidele \(Florence\)](#)  
**To:** ["mary.v.sides@gsk.com"](mailto:mary.v.sides@gsk.com)  
**Cc:** [Brodhead, LeAnn](#)  
**Subject:** CMC IR NDA 209482  
**Date:** Wednesday, April 12, 2017 11:22:32 AM

---

Hello Ms. Sides,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by April 26 ,2017.

1. Revise the statement under description and composition of the drug product in module 3.2.P.1“Each blister contains 100 micrograms of fluticasone furoate, 62.5 micrograms of umeclidinium (as bromide) and 25 micrograms of vilanterol (as trifenate)” so that it clearly indicates what is contained in each of the two distinct blister types within the device.
2. Provide comparative in vitro data (i.e., dose delivery and aerodynamic particle size

(b) (4)

Please confirm receipt of this email.

Thanks,

**Florence Aisida, Pharm.D,BCPS**  
Regulatory Business Process Manager  
HHS | FDA | CDER  
Office of Pharmaceutical Quality  
Office of Program and Regulatory Operations  
[Bamidele.aisida@fda.hhs.gov](mailto:Bamidele.aisida@fda.hhs.gov) | 240.402.2691



NDA 209482

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

GlaxoSmithKline Intellectual Property Development Ltd. England  
c/o GlaxoSmithKline  
Five Moore Drive  
PO Box 13398  
Research Triangle Park, NC 27709-3398

ATTENTION: Mary V. Sides  
Director, Global Regulatory Affairs

Dear Ms. Sides:

Please refer to your New Drug Application (NDA) dated November 18, 2016, received November 18, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Furoate, Umeclidinium, and Vilanterol Inhalation Powder, 100 mcg, 62.5 mcg, and 25 mcg per inhalation.

We also refer to your correspondence, dated and received November 21, 2016, requesting review of your proposed proprietary name, Trelegy Ellipta.

We have completed our review of the proposed proprietary name, Trelegy Ellipta and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your November 21, 2016 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact LeAnn Brodhead, Regulatory Project Manager, in the Office of New Drugs at (240) 402-2605.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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DANIELLE M HARRIS on behalf of TODD D BRIDGES  
02/14/2017



NDA 209482

**PROPRIETARY NAME  
ACKNOWLEDGEMENT**

GlaxoSmithKline Intellectual Property Development Ltd. England  
c/o GlaxoSmithKline  
Five Moore Drive  
PO Box 13398  
Research Triangle Park, NC 27709-3398

ATTENTION: Mary V. Sides  
Director, Global Regulatory Affairs

Dear Ms. Sides:

Please refer to your New Drug Application (NDA) dated November 18, 2016, received November 18, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Furoate, Umeclidinium, and Vilanterol Inhalation Powder, 100 mcg, 62.5 mcg, and 25 mcg.

We acknowledge receipt of your November 21, 2016, correspondence, received November 21, 2016, requesting a review of your proposed proprietary name, TRELEGY ELLIPTA.

If the application is filed, the user fee goal date will be February 19, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, PharmD, RPh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact LeAnn Brodhead, Regulatory Project Manager, in the Office of New Drugs at (240) 402-2605.

Sincerely,

*{See appended electronic signature page}*

Michael Sinks, PharmD, RPh  
Safety Regulatory Project Manager  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TERROLYN THOMAS  
12/13/2016



NDA 209482

**NDA ACKNOWLEDGMENT**

GlaxoSmithKline  
Five Moore Drive  
PO Box 13398  
Research Triangle Park, NC 27709-3398

Attention: Mary V. Sides  
Director, Global Regulatory Affairs

Dear Ms. Sides:

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: Trelegy Ellipta (fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg) Inhalation Powder

Date of Application: November 18, 2016

Date of Receipt: November 18, 2016

Our Reference Number: NDA 209482

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 January 17, 2017, 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

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 LeAnn Brodhead, Regulatory Project Manager, at (240) 402-2605.

Sincerely,

*{See appended electronic signature page}*

LeAnn Brodhead, PharmD, MPH  
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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LEANN D BRODHEAD  
12/02/2016



IND 114873

**MEETING PRELIMINARY COMMENTS**

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 Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GW685698/GSK573719/GW642444 (FF/UMEC/VI) Inhalation Powder.

We also refer to your August 2, 2013 correspondence requesting a Type B meeting (End-of-Phase 2, CMC) to discuss and obtain Agency consensus on the acceptability of the proposed CMC information package supporting the planned Phase 3 clinical studies, and ultimately the filing of the NDA. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting. Our preliminary responses to your meeting questions are enclosed.

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

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

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE:  
Preliminary Meeting Comment



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**PRELIMINARY MEETING COMMENTS**

**Meeting Type:** Type-B  
**Meeting Category:** End-of-Phase 2, CMC

**Meeting Date and Time:** October 21, 2013, 2:30 PM to 3:30 PM (ET)  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1421  
Silver Spring, Maryland 20903

**Application Number:** IND 114873  
**Product Name:** GW685698/GSK573719/GW642444 (FF/UMEC/VI) Inhalation Powder  
**Indication:** Treatment of chronic Obstructive Pulmonary Disease  
**Sponsor/Applicant Name:** GlaxoSmithKline (GSK)

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for October 21, 2013, 2:30 PM to 3:30 PM (ET), 10903 New Hampshire Avenue, Silver Spring, Maryland 20903, between GSK and CDER/FDA. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

## **1.0 BACKGROUND**

GlaxoSmithKline (GSK) submitted a Type B meeting request dated August 2, 2013, discuss and obtain Agency consensus on the acceptability of the proposed CMC information package

supporting the planned Phase 3 clinical studies, and ultimately the filing of the NDA. GSK submitted the briefing package on August 21, 2013. Upon review of the material, the ONDQA provides GSK preliminary responses to the questions.

## **2.0 DISCUSSION**

### **Question 1**

*Does the Agency agree that in vitro APSD data provided for Fluticasone Furoate/Umeclidinium/Vilanterol Inhalation Powder show adequate comparability to the comparator products for Phase 3 clinical studies?*

### **Agency Response to Question 1**

Yes, we agree; however, we note that there are discrepancies between the *in vitro* (b) (4) (b) (4) for FF and VI included in the meeting package submitted on August 21, 2013. Provide an explanation of these discrepancies in the New Drug Application for the FF/UMEC/VI combination drug product.

### **Question 2**

*Does the Agency agree that minor changes to the inhaler which may be needed during Phase 3, i.e. those that do not impact the airflow path and hence the delivery of the drug during patient use, may be handled through GSK's internal change control procedures including risk assessment and do not require an in vitro comparability study to be performed?*

### **Agency Response to Question 2**

Yes, we agree. Low risk changes can be managed through GSK's internal change control procedures.

### **Question 3**

*Does the Agency agree that it is acceptable to implement a change to the composition of materials within the airflow path following the start of Phase 3 through an in vitro comparability study (emitted dose, APSD of the emitted dose and airflow resistance), an assessment of the extractives and leachables profile and safety tests where appropriate?*

### **Agency Response to Question 3**

Yes, we agree but the new material also needs to comply with USP <661> and <87>.

### **Question 4**

*Does the Agency agree that it is appropriate in the NDA for this product to cross reference approved Ellipta inhaler NDA submissions for details on the development of the primary pack,*

*Ellipta inhaler, and secondary pack and that only product specific data are included in m3.2.P2.4. Container Closure System Development?*

**Agency Response to Question 4**

Yes, we agree.

**Question 5**

*In light of airflow resistance data gathered for GSK's approved and pending NDA submissions where airflow resistance in the various products has been demonstrated to be well controlled during the manufacture and assembly processes, does the Agency agree that airflow resistance data are not required to be obtained for Fluticasone Furoate/Umeclidinium/Vilanterol Inhalation Powder for Phase 3 clinical batch release, Phase 3 stability and primary NDA stability studies?*

**Agency Response to Question 5**

Yes, we agree.

**Question 6**

*GSK has recovered normally functioning, partially-used Ellipta inhalers from the clinic for recent NDA submissions, and generated product performance data. As this testing is a function of the inhaler design, does the Agency agree that the database is now adequate and there is no need to obtain additional clinical returns for this product using the Ellipta inhaler?*

**Agency Response to Question 6**

We agree that there is no need to retrieve partially used and normally functioning inhalers for product performance testing.

**Question 7**

*Does the Agency agree to GSK's proposed Phase 3 specification and in particular to have acceptance criteria for FPMass only, with the intent to set acceptance criteria for CPMass and vFPMass in the NDA?*

**Agency Response to Question 7**

Yes, we agree, as long as you collect full APSD profiles for the Phase 3 drug product and provide them in the NDA.

**Question 8**

*GSK considers the chemical stability of the fluticasone furoate strip is well established and further chemical tests do not need to be conducted on this strip during stability studies.*

- a) To support Phase 3 clinical studies*
- b) To support the Fluticasone Furoate/Umeclidinium /Vilanterol Inhalation Powder NDA*

*Does the Agency agree with these proposals?*

**Agency Response to Question 8**

Yes, we agree.

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/s/  
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PRASAD PERI  
10/15/2013  
Signed for Dr. Eric Duffy



IND 114873

**MEETING MINUTES**

Glaxo Group Limited, England d/b/a GlaxoSmithKline  
Five Moore Drive  
P.O. Box 13398  
Research Triangle Park, NC 27709-3398

Attention: Lester Thomas  
Director, Global Regulatory Affairs

Dear Mr. Thomas:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GW685698/GSK573719/GW642444 (fluticasone furoate/umeclidinium/vilanterol) Inhalation Powder.

We also refer to the telecon between representatives of your firm and the FDA on September 18, 2013. The purpose of the meeting was to discuss Phase 3 development plans.

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

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

Sincerely,

*{See appended electronic signature page}*

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

Enclosure:  
Meeting Minutes



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

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** End of Phase 2

**Meeting Date and Time:** September 18, 2013; 1:00 – 2:00 PM

**Application Number:** IND 114873  
**Product Name:** Fluticasone Furoate/Umeclidinium/Vilanterol Inhalation Powder  
**Indication:** Treatment of Chronic Obstructive Pulmonary Disease (COPD)  
**Sponsor Name:** GlaxoSmithKline (GSK)

**Meeting Chair:** Badrul A. Chowdhury, M.D., Ph.D.  
**Meeting Recorder:** Nina Ton, Pharm.D.

**FDA ATTENDEES**

**Invited CDER Participants:**

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)  
Gilbert-McClain, M.D., Deputy Director, DPARP  
Sally Seymour, M.D., Deputy Director for Safety, DPARP  
Susan Limb, M.D., Clinical Team Leader, DPARP  
Jennifer Pippins, M.D. Clinical Reviewer, DPARP  
Marcie Wood, Ph.D., Pharmacology/Toxicology Team Leader, DPARP  
Nina Ton, Pharm.D., Regulatory Project Manager, DPARP  
Satjit Brar, Pharm.D., Ph.D., Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)  
Ping Ji, Ph.D., Clinical Pharmacology Reviewer, DCPII, OCP  
Joan Buenconsejo, Ph.D., Biostatistics Team Leader, Division of Biometrics II, Office of Biostatistics (OB)  
David Hoberman, Ph.D., Biostatistics Reviewer, Division of Biometrics II, OB  
Craig Bertha, Ph.D., Acting Team Leader, Division of New Drug Quality Assessment III, Office of New Drug Quality Assessment (ONDQA)  
Xiaobin Shen, Ph.D., CMC Reviewer, Division of New Drug Quality Assessment III, ONDQA  
Lissa Owens, Pharm.D., Safety Evaluator, Division Of Medication Error Prevention And Analysis, Office Of Surveillance And Epidemiology

**SPONSOR ATTENDEES**

Steve Pascoe, MD, Vice President, Medicines Development Leader  
Nick Locantore, PhD, Manager, Clinical Statistics

Les Thomas, Director, Global Regulatory Affairs  
David Lipson, MD, Physician Project Leader  
Ann Allen, Manager, Clinical Pharmacology Modeling and Simulation  
Helen Barnacle, Clinical Development Director  
Noushin Brealey, MD, Clinical Development Director  
Mauri Fitzgerald, Vice President, Global Regulatory Affairs

## 1. BACKGROUND

GSK submitted an End of Phase 2 meeting request dated June 27, 2013, to the Division of Pulmonary, Allergy, and Rheumatology Products. The purpose of the meeting was to discuss the Phase 3 development plans for the proposed product, fluticasone furoate/umeclidinium/vilanterol Inhalation Powder, for the treatment of patients with chronic obstructive pulmonary disease (COPD). The briefing package was received on August 21, 2013. Upon review of the meeting package, FDA provided preliminary responses to GSK on September 13, 2013. Les Thomas, Director, Global Regulatory Affairs, communicated to the Division via email dated September 16, 2013 that GSK has requested to change the format of the meeting to a teleconference. GSK also requested to focus the meeting discussion to the Introductory Comment, Question 4, and Question 15. GSK accepted FDA's advice on the other questions not discussed during the meeting. The Sponsor's questions are in *italics*, FDA's responses are in normal font, and the meeting discussion is in **bold**.

## 2. DISCUSSION

### Introductory Comment

We have the following general recommendations on the proposed development program for fluticasone furoate/umeclidinium/vilanterol inhalation powder:

- The partial factorial design of the proposed exacerbation trial, Trial CT116855, is intended to demonstrate the benefit of the triple combination product over the two-component products. In order to facilitate the clinical comparisons, the development program should provide *in vitro* and pharmacokinetic data which support the absence of any major pharmaceutical differences between the triple combination product and the comparators. We recommend that you submit these data for review prior to initiating the confirmatory trial.
- Include details on the handling of early withdrawals and missing data in the protocol submission for Trial CT116855.
- We recommend adjudication of deaths in your safety analysis.

### Meeting Discussion

**GSK commented that *in vitro* and PK data will be submitted in the meeting package for the CMC EOP2 meeting. GSK added that the summary for the PK study will be available in mid-November but the study report will not be available for some time. FDA asked that GSK provide the PK synopsis first and submit the study report at a later time. GSK noted that the final protocol for the large study will also be available in late November and asked FDA's timeline for reviewing the protocol. FDA responded that it cannot commit to a timeframe but will coordinate with the team to review and provide feedback.**

**GSK stated that the Sponsor will try to minimize missing data due to early withdrawals by collecting post treatment data with phone follow-up and decoupling premature**

**discontinuation of medication from early study withdrawal. GSK asked FDA to clarify how to handle early withdrawals. FDA advised that GSK continue collecting outcome data such as history of exacerbation, FEV1, rescue medications used, and safety data including deaths and adverse events of special interest (e.g., MI, stroke, pneumonia) after patients discontinue treatment.**

**GSK also confirmed their plan to adjudicate all cases of death.**

**Question 1**

*Given the results of study D30338G, a 13-week combination inhalation toxicology study evaluating FF/UMEC/VI in dogs, and the significant body of information available for each of the individual components, does the Agency agree that no further non-clinical studies are warranted prior to registration?*

**FDA Response**

We agree that the nonclinical program is adequate to support the initiation of longer-term clinical studies with this triple combination in the planned Phase 3 clinical studies and filing of an NDA.

**Meeting Discussion**

**This question was not discussed.**

**Question 2**

*The clinical pharmacology data package describing the FF/UMEC/VI combination product will comprise the FF/UMEC/VI PK studies (CTT116415 and 200587) and the planned FF/UMEC/VI Phase III population PK data. Given the extensive body of data obtained from the completed studies in FF/VI (FF, FF/VI) and UMEC/VI (UMEC, UMEC/VI) programs, does the Agency agree that no additional clinical pharmacology studies are required for the FF/UMEC/VI combination, specifically:*

- *No additional drug-drug interactions (metabolic or transporter-related) studies are required?*
- *No additional PK studies in special populations (e.g. hepatic and renal) are required? and;*
- *No definitive QTc study is required?*

**FDA Response**

Your proposed clinical pharmacology program is dependent on the two bridging studies, CTT116415 and 200587. Pending review of these two studies, your clinical pharmacology program seems acceptable if results from these two studies support the extrapolation to the combination product. Further, we agree that no additional QTc study is required.

**Meeting Discussion**

**This question was not discussed.**

**Question 3**

*Does the Agency agree that the plans to collect PK samples in the proposed Phase III program are adequate to characterize the population PK of FF, UMEC and VI following FF/UMEC/VI administration?*

**FDA Response**

Your sampling schedule seems reasonable.

**Meeting Discussion**

**This question was not discussed.**

**Question 4**

*GSK believes that the proposed single exacerbation study will be sufficient to determine substantial efficacy in support of approval for the proposed indication. GSK proposes to compare FF/UMEC/VI with FF/VI and with UMEC/VI for the primary efficacy endpoints using a threshold of  $p < 0.01$  in order to provide support for the indication. Does the Agency agree?*

**FDA Response**

As described in the Guidance for Industry: *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, there are situations in which a single, well-designed, highly significant trial may support an indication. A single exacerbation trial may be sufficient to support an exacerbation claim for your proposed product provided that the treatment effect observed is clinically meaningful and statistically robust. For example, the efficacy results should be consistent across various subgroups of the patient population.

**Meeting Discussion**

**GSK commented that while they anticipate a win on exacerbation for both comparisons of the triple to the dual products (FF/VI and UMEC/VI), it is possible that the data for the comparison between the triple product and FF/VI might demonstrate encouraging trends, but not statistical significance. GSK asked for the FDA's advice as to how to proactively manage such a situation, and specifically, how to use other supportive evidence to establish efficacy. FDA stated that it would be difficult to compensate for a failure to demonstrate a reduction in exacerbation for the triple combination product compared to FF/VI. One possible approach to managing such a situation would be to demonstrate an effect on an endpoint such as mortality, which is of clear clinical relevance. A demonstration of benefit for a lesser secondary endpoint, such as SGRQ, would likely not be sufficient.**

**Question 5**

*Does the agency agree with the selection of the comparators for the 12 month exacerbation study?*

**FDA Response**

Yes, we agree. Your proposal is reasonable.

**Meeting Discussion**

**This question was not discussed.**

**Question 6**

*The population for the Phase III study will consist of patients who are classified as GOLD Group D according to the GOLD 2013 guidelines and have a documented history of exacerbations in the preceding year. Does the Agency agree with the proposed study population?*

**FDA Response**

Yes, we agree.

**Meeting Discussion**

**This question was not discussed.**

**Question 7**

*Subjects eligible for participation in the Phase III Exacerbation study will enter a 2 week run-in treatment period on their existing COPD medications. Subjects at the end of the run-in period will be randomized to 52 weeks treatment with FF/UMEC/VI, or FF/VI, or UMEC/VI. Does the Division agree with the proposal for the run-in medication and the duration of the run-in?*

**FDA Response**

Your proposal to allow patients to continue their existing COPD medications during the 2-week run-in period is acceptable.

**Meeting Discussion**

**This question was not discussed.**

**Question 8**

*As part of the Phase III program, GSK seeks to understand where an ICS is most likely to be beneficial for COPD patients. There is literature that suggests COPD patients with elevated eosinophil levels may represent a 'responder population' within COPD for ICS therapy. GSK proposes to explore this as a subset analysis of the effect of FF/UMEC/VI versus UMEC/VI in subjects with elevated blood eosinophil levels as a secondary endpoint in the 12 month exacerbation study. Does the Agency have any comments?*

**FDA Response**

The decision of whether or not to conduct these subgroup analyses is at your discretion; however, they will be regarded as exploratory by the Division.

**Meeting Discussion**

**This question was not discussed.**

**Question 9**

*GSK plans to use a single strength FF/UMEC/VI dose, as it emerges from the FF/VI and UMEC/VI registration programs. In this context, we anticipate that the two confirmatory*

*comparisons in the Phase III trial will involve once-daily dosing of 100/62.5/25mcg for FF/UMEC/VI, 100/25mcg for FF/VI and 62.5/25mcg for UMEC/VI. Does the Agency agree?*

**FDA Response**

Your approach to dose selection for the triple combination appears reasonable.

**Meeting Discussion**

**This question was not discussed.**

**Question 10**

*GSK plans to conduct the Phase III exacerbation program as a global multicenter study. We seek Agency agreement on the proposed allocation of subjects from various regions.*

**FDA Response**

Your proposal appears reasonable.

**Meeting Discussion**

**This question was not discussed.**

**Question 11**

*Does the Agency agree that the proposed Phase III study meets the requirements under 21CFR§300.50 for a fixed-dose combination product?*

**FDA Response**

In general, the proposed Phase 3 trial appears reasonable. As previously discussed during the May 7, 2012, Pre-IND meeting for this IND, any potential pharmaceutical differences should be fully characterized prior to initiating Phase 3 trials, as these differences would make it difficult to interpret the contribution of the components to the combination product. Refer to the Introductory Comment.

**Meeting Discussion**

**This question was not discussed.**

**Question 12**

*GSK believes that the safety databases from the FF/VI and UMEC/VI registration programs provide sufficient exposure data to support the initiation of the FF/UMEC/VI Phase III program. Does the Agency agree?*

**FDA Response**

Yes, we agree.

**Meeting Discussion**

**This question was not discussed.**

**Question 13**

*Does the Agency agree that the level of safety monitoring proposed for the FF/UMEC/VI Phase III clinical program is appropriate, based on the existing knowledge of the safety profiles of FF/VI and UMEC/VI?*

**FDA Response**

Yes, we agree.

**Meeting Discussion**

**This question was not discussed.**

**Question 14**

*GSK is planning to provide data for the prospective Phase III program in a format consistent with current CDISC standards. We plan to provide data from the Clinical Pharmacology program in a format consistent with IDSL standards. Does the Agency agree with this proposal?*

**FDA Response**

Yes, we agree.

**Meeting Discussion**

**This question was not discussed.**

**Question 15**

*To make inferences on pre-defined secondary endpoints and control for overall Type I error, the secondary endpoints will be nested under the co-primary efficacy endpoints. GSK proposes to set the significance level at 5% (two-sided) for each step of the hierarchy (including the primary endpoint comparisons) to gatekeep inferences for nested hypotheses. Does the Agency agree with this proposal? Additionally, does the Agency agree with the proposed testing hierarchy and plan for adjustments due to multiple comparisons for the primary and secondary endpoints?*

**FDA Response**

Your plan for adjustments due to multiple comparisons for the primary and secondary endpoints is reasonable. We recommend that the time-to-first moderate/severe exacerbation be moved to the front of the testing hierarchy before the evaluation of lung function and symptoms improvement. We may provide additional comments when we complete our review of the full protocol and the analysis plan.

**Meeting Discussion**

**FDA advised GSK to reorder the hierarchy of the secondary endpoints by placing time to first exacerbation on top, then FEV1 and others. GSK commented that moving time to first exacerbation would make it redundant and close to the primary endpoint. GSK reasoned that moving this secondary endpoint lower in the hierarchy would be more informative. FDA acknowledged GSK's rationale for its choice of order. However, FDA added that changing the order would help address missing data and help rescue in the event the primary endpoint does not win.**

### **Question 16**

*Because the etiology of COPD is most closely associated with cigarette smoking, GSK will propose in our subsequent pediatric plan that the FF/VI/UMEC combination be a candidate for a waiver from pediatric development requirements. While we acknowledge that the final decision on a waiver is a review issue, does the Agency generally agree with this approach?*

### **FDA Response**

Your approach appears to be reasonable.

### **Meeting Discussion**

**This question was not discussed.**

## **3. PREA REQUIREMENTS**

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

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

## **4. DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical

and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

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

#### **5. ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion.

#### **6. ACTION ITEMS**

There were no action items.

#### **7. ATTACHMENTS AND HANDOUTS**

There were no attachments or handouts.

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PHUONG N TON  
10/02/2013