CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204275Orig1s000

CHEMISTRY REVIEW(S)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 204275/000	**Action Goal:**	
S ate:	12-JUL-2012	**District Goal:**	13-MAR-2013
R ory:	12-MAY-2013		
Applicant:	GLAXO GRP LTD	**Brand Name:**	Fluticasone Furoate/Vilanterol Trifenata
	UB6 0NN, UNITED KINGDOM	**Estab. Name:**	
	GREENFORD, MIDDLESEX, , UNITED KINGDOM	**Generic Name:**	
Priority:	1	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	570	001; POWDER, FOR INHALATION; FLUTICASONE FUROATE; 100MG/1INH 001; POWDER, FOR INHALATION; VILANTEROL; 25MCG/1INH	

Application Comment: VILANTEROL TRIFENATATE IS NME. FLUTICASONE FUROATE IS NOT NME. (on 27-JUL-2012 by Y. LIU () 3017961926)

FDA Contacts:	C. BERTHA	Prod Qual Reviewer		3017961646
	Y. LIU	Product Quality PM		3017961926
	A. RAMSEY	Regulatory Project Mgr	(HFD-570)	3017962284
	A. SCHROEDER	Team Leader		3017961749

Overall Recommendation:	ACCEPTABLE	on 09-MAY-2013	by J. WILLIAMS	()	3017964196
	PENDING	on 05-MAR-2013	by EES_PROD		
	PENDING	on 07-AUG-2012	by EES_PROD		
	PENDING	on 07-AUG-2012	by EES_PROD		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9610411 **FEI:** 3003262904

GLAXO OPERATIONS UK LIMITED

PRIORY STREET
WARE, HERTFORDSHIRE, , UNITED KINGDOM

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Establishment Comment: DRUG/DEVICE ASSEMBLY PERFORMED ONSITE. QBD/PI INVESTIGATOR WITH DEVICE EXPERTISE NEEDED. KTM MAY BE WRITTEN FOR THIS INSPECTION. CDER ALSO MAY WANT TO PARTICIPATE ON THE INSPECTION. PLEASE CONTACT VIBHAKAR SHAH AND TARA GOOEN WHEN SCHEDULING. (on 02-NOV-2012 by T. GOOEN (HFD-320) 3017963257)
ALSO PERFORM MICRONISATION STEP OF DRUG SUBSTANCES.
THE DRUG PRODUCT MANUFACTURER ALSO ASSEMBLES THE DEVICE.
(on 23-OCT-2012 by Y. LIU () 3017961926)

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	07-AUG-2012				LIUY
SUBMITTED TO DO	07-AUG-2012	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	03-SEP-2012	Product Specific			BRYKMANR
INSPECTION SCHEDULED	21-MAR-2013		26-APR-2013		IRIVERA
DO RECOMMENDATION	06-MAY-2013			ACCEPTABLE	PHILPYE
AS PER M. FARBMAN, ATL				INSPECTION	
OC RECOMMENDATION	07-MAY-2013			ACCEPTABLE	HEAYNM
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9611205 **FEI:** 3002807079

GLAXO WELLCOME MANUFACTURING PTE LIMITED

2262
JURONG, , SINGAPORE

DMF No: 25906 **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: MANUFACTURING TWO NON-MICONIZED DRUGSUBSTANCES: FLUTICASONE FUROATE AND VILANTEROL TRIFENATATE. (on 27-JUL-2012 by Y. LIU () 3017961926)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				**Reason**	
SUBMITTED TO OC	07-AUG-2012				LIUY
SUBMITTED TO DO	07-AUG-2012	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	11-AUG-2012	Product Specific			PHILPYE
INSPECTION PERFORMED	16-NOV-2012		16-NOV-2012		Julianne.McCullough

This Pre-Approval and GMP inspection of a large non-sterile, chemically synthesized active pharmaceutical ingredient (API) manufacturer was conducted under FACTS assignment #8029829 as requested by HFC-130 (Division of Field Investigations, International Operations Group) for (b) (4) [redacted] NDA 204275 (Fluticasone furoate + Vilanterol). GMP coverage was also afforded to manufacturing of Lamividine which is currently distributed to the US market. This inspection of Glaxo Wellcome Manufacturing Pte. Ltd. (GSK) was performed in ·rdance with Compliance Programs (CP): CP 7356.002FActive Pharmaceutical Ingredient (API) ·ss Inspection and CP 7346.832 - NDA Pre-Approval Inspections for profile class CSN.

·ne previous inspection was completed on 3/9-13/09 and classified NAI. No deficiencies were reported and no FDA 483 was issued.

The current inspection afforded GMP coverage to the Quality, Laboratory, and Production Systems for Lamividine. PAI Inspectional coverage was afforded to all relevant aspects of the Readiness for Manufacturing, Conformance to the Application, and Data Integrity Objectives of the compliance program for NDA [redacted] (b) (4) Readiness for Manufacturing and Conformance to the Application Objectives were covered for NDA 20475 (Fluticasone furoate + Vilanterol). No manufacturing operations were ongoing. The following deficiencies were documented on the List of Inspection Observations (FDA 483) that was issued to the VP & Managing Director at the closeout meeting: 1.) Written procedures for production and process controls are not adequate in that the approved master batch record for chemical synthesis of NDA [redacted] (b) (4) active pharmaceutical ingredient (API) does not include detailed production instructions for the sequence to be followed, ranges of process parameters to be used, critical in-process controls, or time

INSPECTION SCHEDULED	30-NOV-2012		16-NOV-2012		IRIVERA
DO RECOMMENDATION	13-MAR-2013			ACCEPTABLE INSPECTION	PHILPYE
OC RECOMMENDATION	14-MAR-2013			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9610421 **FEI:** 3002807078

GLAXOSMITHKLINE

HARMIRE ROAD
BARNARD CASTLE, COUNTY DURHAM, UNITED KINGDOM DL12 8DT

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

Establishment Comment:

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	07-AUG-2012				LIUY
SUBMITTED TO DO	07-AUG-2012	Product Specific			STOCKM
DO RECOMMENDATION	11-AUG-2012			ACCEPTABLE	BRYKMANR
LAST CDER INSPECTION ENDING 01NOV2010 COVERED THE SAME PROFILE WITH A FINAL CLASSIFICATION OF VAI.				BASED ON FILE REVIEW	
OC RECOMMENDATION	15-AUG-2012			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 1033964 **FEI:** 1033964

GLAXOSMITHKLINE INC

1011 NORTH ARENDELL AVE
ZEBULON, NC 275971217

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE STABILITY TESTER

Establishment Comment:

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				**Reason**	
SUBMITTED TO OC	07-AUG-2012				LIUY
SUBMITTED TO DO	07-AUG-2012	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	17-AUG-2012	Product Specific			JCHANCEY
ASSIGNED INSPECTION TO IB	31-JAN-2013	Product Specific			LTHOMAS
INSPECTION SCHEDULED	22-APR-2013		03-MAY-2013		LTHOMAS
INSPECTION PERFORMED	03-MAY-2013		03-MAY-2013		LTHOMAS
NSPECTION OF THE FIRM WAS CONDUCTED 4/29/13-5/03/13. NO FDA 483 WAS ISSUED, INSPECTION WAS CLASSIFIED NAI, AND THE PROFILE CLASS ADM WAS FOUND ACCEPTABLE.					
DO RECOMMENDATION	08-MAY-2013			ACCEPTABLE	LTHOMAS
AN INSPECTION OF THE FIRM WAS CONDUCTED 4/29/13-5/03/13. NO FDA 483 WAS ISSUED, THE INSPECTION WAS CLASSIFIED NAI, AND THE PROFILE CLASS ADM WAS FOUND ACCEPTABLE.				INSPECTION	
BASED UPON THE INSPECTION RESULTS, THE DISTRICT RECOMMENDS APPROVAL OF THE FIRM FOR ITS LISTED RESPONSIBILITIES IN THE APPLICATION.					
OC RECOMMENDATION	09-MAY-2013			ACCEPTABLE	WILLIAMSJU
				DISTRICT RECOMMENDATION	

Breo® Ellipta® (Fluticasone furoate 100mcg /Vilanterol 25 mcg) Inhalation Powder

NDA 204275
Chemistry, Manufacturing, and Controls
Division Director's Summary Basis of Action

Applicant: Glaxo Group Limited d/b/a GlaxoSmithKline
Five Moore Drive
Research Triangle Park, NC 27709

Indication: BREO ELLIPTA is a combination inhaled corticosteroid/long-acting beta$_2$-adrenergic agonist (ICS/LABA) indicated for long-term, once-daily, maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD).

Presentation: BREO ELLIPTA is supplied as a disposable light grey and pale blue plastic inhaler containing 2 double-foil strips, each with 30 blisters (30 doses). The devise includes a dose counter. The inhaler is packaged within a moisture-protective foil tray with a desiccant and a peelable lid. BREO ELLIPTA is also supplied in an institutional pack and in a physician sample pack containing 2 double-foil strips, each with 14 blisters (doses). They are also packaged within a moisture-protective foil tray with a desiccant and a peelable lid.

EER Status:	Recommendations:	**Acceptable as of May 9, 2013.**
Consults:	EA –	Categorical exclusion provided
	CDRH-	N/A
	Statistics –	N/A
	Methods Validation –	Methods validation was sent but the labs could not reproduce all methods since specific equipment is necessary for blister content. The methods are found acceptable from quality control by the review division but the lab could not comment as a regulatory method since they could not reproduce the methods.
	DMETS-	Acceptable
	Biopharm–	Acceptable
	Microbiology –	Acceptable
	Pharm/toxicology –	Acceptable

Background: This drug product is a replacement for the Advair Diskus series of dry powder inhaler line. The drug product device contains fluticasone furoate and vilanterol for once daily treatment. This new device was called the Gemini Device since there are two strips of blisters within the device each containing 30 doses of fluticasone furoate and vilanterol.

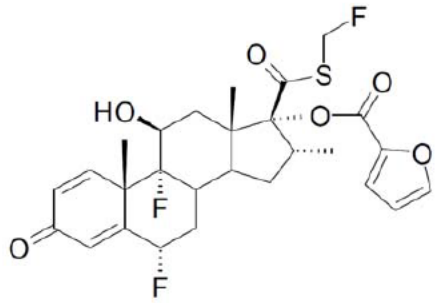
The drug substances and drug product are prepared using a Quality by Design (QbD) Strategy for better assurance of quality from a manufacturer and patient use perspective.

Drug Substances:

Fluticasone Furoate

Reference ID: 3306469

Fluticasone furoate is the active ingredient in the Agency approved Veramyst® nasal spray product under NDA 22-051. The CMC information for fluticasone furoate is stated (b) (4) The modified specifications, batch details, and batch release data are provided. Fluticasone furoate drug substance is controlled for appearance, identification, assay, impurities, residual solvents, water content, residue on ignition, particle size distribution, and foreign particulate matter. All other CMC information is provided by cross-reference to NDA 22-051. The information provided is adequate to support this NDA.



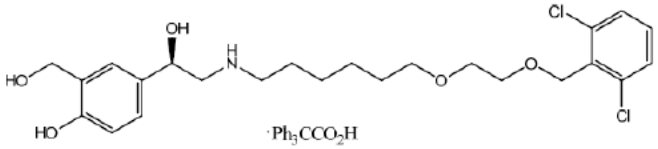
Chemical Name: (6α,11β,16α,17α)-6,9-difluoro-17-{[(fluoro-methyl)thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 2-furancarboxylate
Molecular Formula: $C_{27}H_{29}F_3O_6S$
Molecular Weight: 538.6

Vilanterol trifenatate

The CMC information is referenced to the applicant's DMF 25906. Vilanterol drug substance is controlled for appearance, identification, assay, impurities, enantiomer, residual solvents, water content, residue on ignition, and particle size distribution. The referenced DMF and information is adequate to support this NDA. Both the drug substances are manufactured by GSK in Jurong, Singapore.

Vilanterol trifenatate

Chemical Name: Triphenylacetic acid-4-{(1R)-2-[(6-{2-[2,6-dicholorobenzyl)oxy] ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol (1:1)



Molecular formula: $C_{24}H_{33}Cl_2NO_5 \cdot C_{20}H_{16}O_2$

Molecular Weight: 774.8 (GW642444M, the triphenylacetate salt)

The applicant has also followed Quality by Design (QbD) principles in their development of the manufacturing process for the drug substance and the method that will be used for the

Reference ID: 3306469

determination of drug substance assay and impurities. These approaches included the use of risk-based assessment to identify drug substance quality attributes and process parameters that had potential to impact drug product safety and efficacy. Critical quality attributes (CQAs) of the drug substances were identified and process parameters were categorized as critical or non-critical (CPPs or NCPPs). The applicant performed multivariate experiments and modeled output data to establish links between synthesis process parameters and the quality attributes of intermediates and the final drug substance.

For Fluticasonoe Furoate the PSD was deemed to be a CQA and the influence of PSD ojn the in vitro performance of the drug product was assessed.

For Vilanterol trifenetate the manufacturing process included a description of several CPPs at each stage of manufacturing. Several potentially genotoxic impurities were identified and spiking studies were performed to assess their removal during the manufacturing process. These and several other studies resulted in establishing the control strategy for the drug substance quality control.

Drug Substance: Satisfactory

Drug Product:
The drug product is Breo Ellipta (Fluticasone Furoate/Vilanterol Inhalation Powder) 100/25 mcg. The drug product consists of two strips of double foil blister (b) (4) one containing the fluticasone furoate inhalation powder, the other containing the vilanterol trifenatate inhalation powder, packed together inside the dry powder inhaler device.

The inhaler itself is co-packaged with a desiccant packet inside a hermetically sealed (b) (4) foil tray. Delivery of the dose involves, the opening/turning of the inhalation mouthpiece to make the dose ready followed by oral inhalation by the patient which delivers one dose of aerosolized formulation, consisting of both fluticasone furoate and vilanterol trifenatate inhalation powders, each released from their respective blister foils.

The fluticasone furoate inhalation powder formulation contains only the micronized fluticasone furoate drug substance and lactose monohydrate (b) (4) The formulation is manufactured (b) (4) Each blister contains a nominal amount of (b) (4) formulation (b) (4) The fluticasone furoate inhalation powder of the drug product is controlled for description, identification, assay, impurities, emitted dose content uniformity, aerodynamic particle size distribution, microbiological quality, and foreign particulate matter.

The vilanterol inhalation powder formulation contains the micronized vilanterol trifenatate drug substance, magnesium stearate (b) (4), and lactose monohydrate (b) (4)

Reference ID: 3306469

(b) (4)

Each blister contains a nominal amount of (b) (4) the formulation (b) (4)

The drug product is tested for the following attributes: Description, Identification by UV and HPLC (Vilanterol, Fluticasone furoate), Fluticasone furoate and Vilanterol Content per blister, Impurities, Content Uniformity of Emitted Dose, Aerodynamic Particle Size Distribution, Microbial Limits, and Foreign Particulate Matter.

For the fluticasone/vilanterol inhalation powder product, GSK does not test for degradation products at release and has acceptably justified their approach with the manufacturing processes provided, control strategies, and extensive impurity analyses data. Twenty-four months of real time stability data and up to three months of in use (inhaler stored without the protective tray) stability data have been provided to support a **24 month product expiry**, and additionally, a 6 weeks in use expiry once the protective inhaler is opened.

The drug product is manufactured (including final device assembly) at the Glaxo facility in Ware UK. All manufacturing and testing facilities have an acceptable recommendation from the Office of Compliance as of May 9th, 2013.

Drug Product: Satisfactory.

Labeling:
Product aspects of labeling are acceptable. Immediate container label is attached.

Overall Conclusion:
From a CMC perspective, the application is recommended for approval.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 3306469

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

/s/

ERIC P DUFFY
05/09/2013

NDA 204-275

Breo Ellipta Dry Powder Inhaler

Glaxo Group Limited
d/b/a GlaxoSmithKline

Craig M. Bertha, Ph.D.
Bogdan Kurtyka, Ph.D.
Xiaobin Shen, Ph.D.
Ying Wang, Ph.D.
Division of Pulmonary, Allergy and Rheumatology Drug Products

Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 3

The Executive Summary 8

I. Recommendations 8

A. Recommendation and Conclusion on Approvability 8

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 8

II. Summary of Chemistry Assessments 8

A. Description of the Drug Substances and Drug Product 8

B. Description of How the Drug Product is Intended to be Used 10

C. Basis for Approvability or Not-Approval Recommendation 10

III. Administrative 10

A. Reviewer's Signature 10

B. Endorsement Block 10

C. CC Block 10

Chemistry Assessment 11

I. Review of Responses to Information Request 11

A. Responses Submitted in Amendment 0021 (Dated 22-Mar-2013) 11

B. Responses Submitted in Amendment 0022 (Dated 28-Mar-2013) 11

II. Approved Drug Substance and Drug Product Specifications 13

Chemistry Review Data Sheet

1. NDA 204-275

2. REVIEW #: 1 Amendment

3. REVIEW DATE: 28-Apr-2013

4. REVIEWER: Craig M. Bertha, Ph.D. — Drug Substances, and DMFs of lactose monohydrate, inhaler device, primary packaging (blister lidding and base foil) and container closures.
   Meiyu Shen, Ph.D. — PTIT for DCU (in separate review).
   Xiaobin Shen, Ph.D. — Drug Product.
   Sandra Suarez, Ph.D. — Dissolution contents in P2.
   Ying Wang, Ph.D. — Water content method by Near IR (with consult of Bogdan Kurtyka, Ph.D.).

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment 0021	22-Mar-2013
Amendment 0022	28-Mar-2012

Other amendments older than the last listed do not have CMC related information for review or have been reviewed already.

7. NAME & ADDRESS OF APPLICANT:

Name: Glaxo Group Limited d/b/a GlaxoSmithKline

Reference ID: 3300318

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

Corporate Address
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex, UB6 0NN
United Kingdom

Representative: Patrick D. Wire, Pharm.D.

Telephone: 919-483-7650

Fax: 919-315-0033

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Breo Ellipta
b) Non-Proprietary Name (USAN): Fluticasone furoate / Vilanterol
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4 for fluticasone fuorate; 1 for vilanterol
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NDA 505(b)(1)

10. PHARMACOL. CATEGORY: fluticasone furoate is an inhaled corticosteroid (ICS); vilanterol is a long-acting β2-agonist (LABA)

11. DOSAGE FORM: Inhalation Powder

12. STRENGTH/POTENCY: 100/25 mcg of fluticasone/vilanterol in combination

13. ROUTE OF ADMINISTRATION: Oral Inhalation

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

Reference ID: 3300318

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

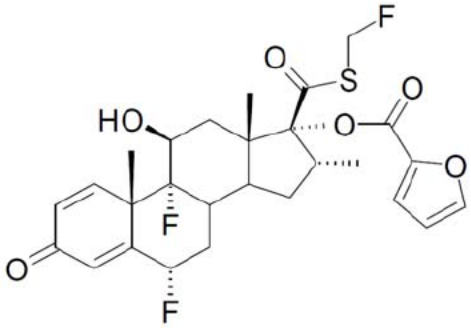
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Fluticasone Furoate

Chemical Name: (6α,11β,16α,17α)-6,9-difluoro-17-{[(fluoro-methyl)thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 2-furancarboxylate

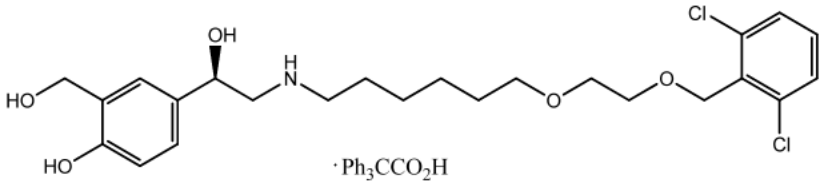


Molecular formula: $C_{27}H_{29}F_3O_6S$

Molecular Weight: 538.6

Vilanterol trifenatate

Chemical Name: Triphenylacetic acid-4-{(1R)-2-[(6-{2-[2,6-dicholorobenzyl)oxy] ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol (1:1)



Molecular formula: $C_{24}H_{33}Cl_2NO_5 \bullet C_{20}H_{16}O_2$

Molecular Weight: 774.8 (GW642444M, the triphenylacetate salt)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	4		(b) (4)	1	adequate	25-SEP-2012	
	3			3			These are the same components used for the applicant's Diskus inhalation powder products
	3			1	adequate	21-Dec-2012	
	3			1	adequate	14-Dec-2012	
	3			1	adequate	25-SEP-2012	
25906	2	GlaxoSmithKline	vilanterol trifenatate	1	adequate	29-NOV-2012	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70,297	FF Inhalation Powder
IND	74,696	VI Inhalation Powder
IND	77,855	FF/VI Inhalation Powder

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Adequate	12-Mar-2013	Dr. Luqi Pei

Reference ID: 3300318

Chemistry Review Data Sheet

Biopharm	Acceptable	13-Mar-2013	Dr. Sandra Suarez
Methods Validation	Acceptable	19-Apr-2013	Dr. John Kauffman
EA	Adequate	—	Dr. Xiaobin Shen
Microbiology	Adequate	27-Nov-2012	Dr. Stephen E. Langille

Reference ID: 3300318

The Chemistry Review for NDA 204-275

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval pending satisfactory EES status.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA.

II. Summary of Chemistry Assessments

A. Description of the Drug Substances and Drug Product

The drug product contains fluticasone furoate and vilanterol trifenatate drug substances.

Fluticasone furoate is the active ingredient in the Agency approved Veramyst® nasal spray product under NDA 22-051. The CMC information for fluticasone furoate is stated (b) (4) The modified specifications, batch details, and batch release data are provided. Fluticasone furoate drug substance is controlled for appearance, identification, assay, impurities, residual solvents, water content, residue on ignition, particle size distribution, and foreign particulate matter. All other CMC information is provided by cross-reference to NDA 22-051. The information provided is adequate to support this NDA.

For vilanterol trifenatate drug substance, all CMC information is referenced to the applicant's DMF 25906. Vilanterol drug substance is controlled for appearance, identification, assay, impurities, enantiomer, residual solvents, water content, residue on ignition, and particle size distribution. The referenced DMF and information provided are adequate to support this NDA.

The drug product is Breo Ellipta (Fluticasone Furoate/Vilanterol Inhalation Powder) 100/25 mcg. The drug product consists of two strips of double foil blister (b) (4), one containing the fluticasone furoate inhalation powder, the other containing the vilanterol trifenatate inhalation powder, packed together inside the dry powder inhaler device.

The inhaler itself is co-packaged with a desiccant packet inside a hermetically sealed (b) (4) foil tray. Delivery of the dose involves, the opening/turning of the inhalation mouthpiece to make the dose ready followed by oral inhalation by the patient which delivers one dose of aerosolized formulation, consisting of both fluticasone furoate and vilanterol trifenatate inhalation powders, each released from their respective blister (b) (4)

The fluticasone furoate inhalation powder formulation contains only the micronized fluticasone furoate drug substance and lactose monohydrate (b) (4) The formulation is manufactured (b) (4) and finally packaging them in the device . Each blister contains a nominal amount of (b) (4) formulation (b) (4) The fluticasone furoate inhalation powder of the drug product is controlled for description, identification, assay, impurities, emitted dose content uniformity, aerodynamic particle size distribution, microbiological quality, and foreign particulate matter.

The vilanterol inhalation powder formulation contains the micronized vilanterol trifenatate drug substance, magnesium stearate (b) (4), and lactose monohydrate (b) (4) Each blister contains a nominal amount of (b) (4) the formulation (b) (4) The vilanterol inhalation powder of the drug product is controlled for description, identification, assay, impurities, emitted dose content uniformity, aerodynamic particle size distribution, microbiological quality, and foreign particulate matter.

For the fluticasone/vilanterol inhalation powder product, GSK does not test for degradation products at release and has acceptably justified their approach with the manufacturing processes provided, control strategies, and extensive impurity analyses data. Twenty-four months of real time stability data and up to three months of in use (inhaler stored without the protective tray) stability data have been provided to support a 24 month product expiry, and additionally, a 6 weeks in use expiry once the protective inhaler is opened.

An overall Establishment Evaluation Recommendation is pending. All Initial Quality Assessment comments have been evaluated and resolved. The analytical method

validations have been completed and deemed acceptable for control and regulatory purposes.

During the review, several information requests were sent to the applicant. Responses to the information requests were evaluated and included at the corresponding sections. Responses received after the archiving of the initial review are evaluated and documented in this amendment.

B. Description of How the Drug Product is Intended to be Used

The product is labeled to be administered as 1 inhalation once daily by the orally inhaled route, for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided information on the chemistry, manufacturing, and controls of the fluticasone furoate/vilanterol inhalation powder product. The product is recommended for approval pending satisfactory EES status based on the following:

- The drug substances specifications provide adequate controls;
- The drug product excipients are of USP/NF grade and acceptable for inhalation use;
- The drug product specifications are supported by provided data and acceptable;
- The drug product container closure systems are acceptable;
- The drug product real time stability data and in use stability data which have been provided support a twenty-four months product expiry and 6 weeks of in use expiry.

III. Administrative

A. Reviewer's Signature

Review is digitally signed in DARRTS.

B. Endorsement Block

ChemistName/Date: Craig Bertha, Xiaobin Shen, Bogdan Kurtyka.
ChemistryTeamLeaderName/Date: Prasad Peri, Eric Duffy
ProjectManagerName/Date: Angela Ramsey, Youbang Liu.

C. CC Block

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/s/

XIAOBIN SHEN
04/28/2013
The NDA is recommended for approval.

BOGDAN KURTYKA
04/29/2013

CRAIG M BERTHA
04/29/2013

PRASAD PERI
04/30/2013
I concur

INSPECTIONAL ASSIGNMENT
(EMAIL TRANSMITTAL)

Date:	April 11, 2013
To:	Division of Medical Products and Tobacco Inspections Office of Regulatory Affairs, HFC-130
Facility:	Glaxo Operations UK Ltd, Priory Street, Ware, Hertfordshire, United Kingdom. FEI #: 3003262904
Drug Name (dosage form, strength/concentration):	Breo Ellipta Dry Powder Inhaler (Fluticasone Furoate/Vilanterol Inhalation Powder) 100/25 mcg
Profile Class:	ADM
A/NDA No.:	NDA 204-275
Chemistry Reviewer	Xiaobin Shen, Ph.D. (xiaobin.shen@fda.hhs.gov; 301-796-1411).
Microbiology Reviewer (if applicable)	Stephen E. Langille, Ph.D. (stephen.langille@fda.hhs.gov)
OC Compliance Officer	Linda Ng, Ph.D., CDER/OC/OMPQ/DGMPA/NDMAB 301-796-1426, (linda.ng@fda.hhs.gov)

CDER has identified specific areas for inspectional focus for drug product manufacturing in connection with NDA 204-275. In accordance with the Drug Process Inspection Compliance Program 7356.002 and Pre-Approval Inspection Program Compliance Program 7346.832, PAIs provide for continuity in our pre-market review of the drug product by focusing on areas in which data are questionable; drug characteristics or sensitivities[1] indicate special scrutiny, the overall manufacturing and control strategy appears lacking; and potential manufacturing weaknesses may exist.

Summary of Product and Manufacturing Process

The Breo Ellipta Dry Powder Inhaler is for long-term once-daily maintenance treatment of airflow

[1] Examples include heat, moisture, oxygen, or light sensitivity, as well as hygroscopicity, polymorphs, particle size, or other physical characteristics

obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema; and to reduce exacerbations of COPD in patients with a history of exacerbations.

This drug product consists of 2 active drug substances: fluticasone furoate that has been approved under NDA 22-051 and vilanterol, a new synthetic molecular entity (NME) described in DMF 25906.

The fluticasone furoate inhalation powder formulation contains micronized fluticasone furoate drug substance and lactose monohydrate (b) (4) The formulation is manufactured (b) (4) Each blister contains a nominal amount of (b) (4) formulation (b) (4)

The vilanterol inhalation powder formulation contains the micronized vilanterol trifenatate drug substance, magnesium stearate (b) (4) and lactose monohydrate (b) (4) Each blister contains a nominal amount of (b) (4) formulation (b) (4)

The drug product consists of two strips of separate foil blister (b) (4) one containing the fluticasone furoate inhalation powder, the other containing the vilanterol trifenatate inhalation powder, packed together inside the dry powder inhaler device. The inhaler itself is packed together with a desiccant packet inside a hermetically sealed (b) (4) foil tray. At time of drug delivery, one actuation (the opening/turning of the inhalation mouthpiece to make the dose ready) and inhalation by the patient delivers one dose of aerosolized formulation, which consists of both fluticasone and vilanterol inhalation powder, each released from one blister of their respectively blister (b) (4)

The stability data proposed is to support 24 month product expiry, and additionally, 6 weeks in use expiry is provided for once the protective inhaler is opened. (b) (4)

I. Chemistry Review

Xiaobin Shen, Ph.D. is the CMC drug product reviewer for this NDA. No PQM was written. However, Dr. Shen shared his 236 page draft review and the items to evaluate in the inspection.

He recommended that investigators evaluate:

(b) (4)

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/s/

LINDA L NG
04/11/2013

TARA R GOOEN
04/11/2013

NDA 204-275

Breo Ellipta Dry Powder Inhaler

Glaxo Group Limited
d/b/a GlaxoSmithKline

Craig M. Bertha, Ph.D.
Bogdan Kurtyka, Ph.D.
Xiaobin Shen, Ph.D.
Ying Wang, Ph.D.
Division of Pulmonary, Allergy and Rheumatology Drug Products

Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 4

The Executive Summary 9

I. Recommendations 9

A. Recommendation and Conclusion on Approvability 9

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 9

II. Summary of Chemistry Assessments 9

A. Description of the Drug Substances and Drug Product 9

B. Description of How the Drug Product is Intended to be Used 11

C. Basis for Approvability or Not-Approval Recommendation 11

III. Administrative 11

A. Reviewer's Signature 11

B. Endorsement Block 11

C. CC Block 12

Chemistry Assessment 13

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data 13

S. DRUG SUBSTANCE (Vilanterol Trifenatate, GSK) 13

P DRUG PRODUCT [Breo Ellipta, Inhalation Powder] 22

3.2.A Appendices 225

R REGIONAL INFORMATION 225

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 228

A. Labeling & Package Insert 228

B. Environmental Assessment Or Claim Of Categorical Exclusion 233

III. Review of Responses to Information Request 233

A. Responses Submitted in Amendment 0008 233

B. Responses Submitted in Amendment 0015 235

C. Responses Submitted in Amendment 0017 235
E. Responses Submitted in Amendment 0019 235

Chemistry Review Data Sheet

1. NDA 204-275

2. REVIEW #: 1

3. REVIEW DATE: 15-Mar-2013

4. REVIEWER: Craig M. Bertha, Ph.D. — Drug Substances, and DMFs of lactose monohydrate, inhaler device, primary packaging (blister lidding and base foil) and container closures.
   Meiyu Shen, Ph.D. — PTIT for DCU (in separate review).
   Xiaobin Shen, Ph.D. — Drug Product.
   Sandra Suarez, Ph.D. — Dissolution contents in P2.
   Ying Wang, Ph.D. — Water content method by Near IR (with consult of Bogdan Kurtyka, Ph.D.).

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	12-Jul-2012
Amendment 0001	13-Aug-2012
Amendment 0007	15-Oct-2012
Amendment 0008	17-Oct-2012
Amendment 0015	14-Dec-2012
Amendment 0017	7-Feb-2013
Amendment 0019	12-Mar-2013

Other amendments older than the last listed do not have CMC related information for review.

Reference ID: 3277456

7. NAME & ADDRESS OF APPLICANT:

Name: Glaxo Group Limited d/b/a GlaxoSmithKline

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

Corporate Address
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex, UB6 0NN
United Kingdom

Representative: Patrick D. Wire, Pharm.D.

Telephone: 919-483-7650

Fax: 919-315-0033

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Breo Ellipta
b) Non-Proprietary Name (USAN): Fluticasone furoate / Vilanterol
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4 for fluticasone fuorate; 1 for vilanterol
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NDA 505(b)(1)

10. PHARMACOL. CATEGORY: fluticasone furoate is an inhaled corticosteroid (ICS); vilanterol is a long-acting β2-agonist (LABA)

11. DOSAGE FORM: Inhalation Powder

12. STRENGTH/POTENCY: 100/25 mcg of fluticasone/vilanterol in combination

13. ROUTE OF ADMINISTRATION: Oral Inhalation

14. Rx/OTC DISPENSED: _X_Rx ___OTC

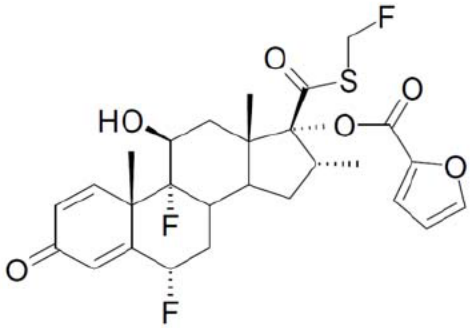
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Fluticasone Furoate

Chemical Name: (6α,11β,16α,17α)-6,9-difluoro-17-{[(fluoro-methyl)thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 2-furancarboxylate

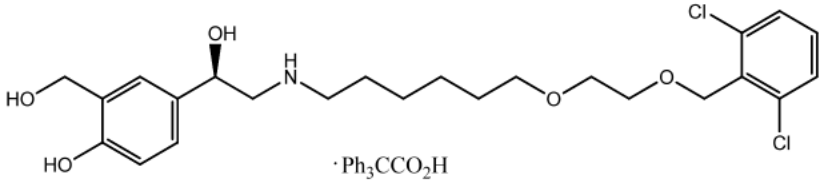


Molecular formula: $C_{27}H_{29}F_3O_6S$

Molecular Weight: 538.6

Vilanterol trifenatate

Chemical Name: Triphenylacetic acid-4-{(1R)-2-[(6-{2-[2,6-dicholorobenzyl)oxy] ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol (1:1)



Molecular formula: $C_{24}H_{33}Cl_2NO_5 \bullet C_{20}H_{16}O_2$

Molecular Weight: 774.8 (GW642444M, the triphenylacetate salt)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	4		(b) (4)	1	adequate	25-SEP-2012	
	3			3			These are the same components used for the applicant's Diskus inhalation powder products
	3			1	adequate	21-Dec-2012	
	3			1	adequate	14-Dec-2012	
	3			1	adequate	25-SEP-2012	
25906	2	GlaxoSmithKline	vilanterol trifenatate	1	adequate	29-NOV-2012	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70,297	FF Inhalation Powder
IND	74,696	VI Inhalation Powder
IND	77,855	FF/VI Inhalation Powder

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Adequate	12-Mar-2013	Dr. Luqi Pei
Biopharm	Acceptable	13-Mar-2013	Dr. Sandra Suarez
Methods Validation	Pending		Dr. John Kauffman
EA	Adequate	—	Dr. Xiaobin Shen
Microbiology	Adequate	27-Nov-2012	Dr. Stephen E. Langille

Reference ID: 3277456

The Chemistry Review for NDA 204-275

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, a recommendation is pending. There are several issues that still need to be resolved, as listed below:

- The drug product manufacturing site is pending inspection.
- GSK has not reached agreement with the Agency regarding the [redacted] (b) (4) APSD testing footnoted in the drug product specifications table.
- GSK has not reached agreement with the Agency regarding the post approval DCU testing sample sizes for the stability studies using the PTIT approach.
- The analytical method validations at the Agency's St. Louis lab has not finished.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA.

II. Summary of Chemistry Assessments

A. Description of the Drug Substances and Drug Product

The drug product contains fluticasone furoate and vilanterol trifenatate drug substances.

Fluticasone furoate is the active ingredient in approved as Veramyst® nasal spray under NDA 22-051. The CMC information for fluticasone furoate is stated [redacted] (b) (4) The modified specifications, batch details, and batch release data are provided. Fluticasone furoate drug substance is controlled for appearance, identification, assay, impurities, residual solvents, water content, residue on ignition, particle size distribution, and foreign particulate matter. All other CMC information is provided by cross-reference to NDA 22-051. The information provided is adequate to support this NDA.

For vilanterol trifenatate drug substance, all CMC information is referenced to the applicant's DMF 25906. Vilanterol drug substance is controlled for appearance, identification, assay, impurities, enantiomer, residual solvents, water content, residue

Reference ID: 3277456

on ignition, and particle size distribution. The referenced DMF and information provided are adequate to support this NDA.

The drug product is Fluticasone Furoate/Vilanterol Inhalation Powder 100/25 mcg. Its commercial name is Breo Ellipta. The drug product consists of two strips of separate foil blister (b) (4) one containing the fluticasone furoate inhalation powder, the other containing the vilanterol trifenatate inhalation powder, packed together inside the dry powder inhaler device. The inhaler itself is packed together with a desiccant packet inside a hermetically sealed (b) (4) foil tray. At time of drug delivery, one actuation (the opening/turning of the inhalation mouthpiece to make the dose ready) and inhalation by the patient delivers one dose of aerosolized formulation, which consists of both fluticasone and vilanterol inhalation powder, each released from one blister of their respectively blister (b) (4)

The fluticasone furoate inhalation powder formulation contains only the micronized fluticasone furoate drug substance and lactose monohydrate (b) (4) The formulation is manufactured (b) (4) . Each blister contains a nominal amount of (b) (4) formulation (b) (4) The fluticasone inhalation powder of the drug product is controlled for description, identification, assay, impurities, emitted dose content uniformity, aerodynamic particle size distribution, microbiological quality, and foreign particulate matter.

The vilanterol inhalation powder formulation contains the micronized vilanterol trifenatate drug substance, magnesium stearate (b) (4), and lactose monohydrate (b) (4) Each blister contains a nominal amount of (b) (4) formulation (b) (4) The vilanterol inhalation powder of the drug product is controlled for description, identification, assay, impurities, emitted dose content uniformity, aerodynamic particle size distribution, microbiological quality, and foreign particulate matter.

For the fluticasone/vilanterol inhalation powder product, GSK does not test for degradation products at release and has acceptably justified their approach with the manufacturing processes provided, control strategies, and extensive impurity analyses data. Twenty-four months of real time stability data and up to three months of in use

(inhaler stored without the protective tray) stability data have been provided to support a 24 month product expiry, and additionally, a 6 weeks in use expiry once the protective inhaler is opened.

All overall Establishment Evaluation Recommendation is pending. All IQA comments have been evaluated and resolved.

During the review, information requests were sent to the applicant. Responses to the information requests are evaluated and included at the corresponding sections. Responses received after the archiving of this review will be evaluated and documented in the review of the future amendment.

B. Description of How the Drug Product is Intended to be Used

The product is to be administered as 1 inhalation once daily by the orally inhaled route only, for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided information on the chemistry, manufacturing, and controls of the fluticasone furoate/vilanterol inhalation powder product. The product is pending a recommendation because of the deficiencies listed below:

- The drug product specifications regarding APSD testing acceptance criteria and DCU testing approach have not reached agreement between GSK and the Agency;

While the following are noted as acceptable:

- The drug substances specifications provide adequate controls;
- The drug product excipients are of USP/NF grade and acceptable for inhalation use;
- The drug product container closure systems are acceptable;
- The drug product real time stability data and in use stability data which have been provided support a twenty-four months product expiry and 6 weeks of in use expiry.

III. Administrative

A. Reviewer's Signature

Review is digitally signed in DARRTS.

B. Endorsement Block

ChemistName/Date: Same date as draft review

Reference ID: 3277456

ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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/s/

XIAOBIN SHEN

03/18/2013

A recommendation is pending for the NDA. The deficiencies are listed at the beginning of the review.

CRAIG M BERTHA

03/18/2013

PRASAD PERI

03/18/2013

I concur. The recommendation would be a Complete Response at this moment until all issues are resolved. A second review will be placed in DARRTS with a final recommendation from ONDQA.

Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

APPLICATION INFORMATION

1. NEW DRUG APPLICATION NUMBER: 204275
   Applicant: Glaxo Group Limited d/b/a GlaxoSmithKline
   CDER Receipt Date: July 12, 2012

2. Drug Name: fluticasone furoate/vilanterol inhalation powder

   Proposed trade name: Breo Ellipta

   "The drug product is a plastic inhaler with a light grey body, a pale blue mouthpiece cover and a dose counter, packed in a foil tray which contains a desiccant packet. The tray is sealed with a peelable lid. The inhaler contains two strips of either 30 or 14 regularly distributed blisters, each containing a white powder. The commercial product (30 blister) and sample pack (14 blister) are available for the treatment of COPD in the following strength combination: 100 microgram fluticasone furoate and 25 microgram of vilanterol (as trifenatate) per inhalation, hereafter referred to as Fluticasone Furoate/Vilanterol Inhalation Powder 100/25 microgram."

3. RECEIVED DATE: 7/12/2012

4. RELATED REVIEW DOCUMENTS:

   a. **Drug Master Files listed on 356h form:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS

Reference ID: 3185071

(b) (4)	IV	(b) (4)		11/14/2011	LOA with this date is listed in DARRTS for this DMF
	III			4/12/2012	DARRTS does show a LOA with this date for (b) (4) Lidding
	III			3/26/12	no LOA listing with this date in DARRTS, check DMF
	III			5/23/2012	no LOA listing with this date in DARRTS, check DMF
	III			12/07/2011	no LOA listing with this date in DARRTS, check DMF
25906	II	GSK	vilanterol trifenatate d.s.	NONE	LOA to be requested – no LOA in the NDA. (NDA does cross reference this DMF); No volumes listed in DARRTS either.

b. Recommended Consults

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	X	☐	A biometrics consult to evaluate the emitted dose content uniformity methods and specifications

Reference ID: 3185071

			may be necessary, since it uses a parametric tolerance interval test. The NDA claims to be following FDA's October 25, 2005 Advisory Committee of Pharmaceutical Science Proposal for Parametric Tolerance Interval Test (PTI Test) Criteria. It is possible that additional information pertaining to this specification and test method needs to be provided. A biometrics consult for stability data and expiration dating period may or may not be necessary: this depends on the review of the stability data.
Clin Pharm	☐	X	
EES	X	☐	EER request submitted 8/07/2012.
Pharm/Tox	☐ maybe	☐	individual specified d.p. impurities are < limits of ICH Q3B [redacted] (b) (4) For the drug substances, the DMFs may be checked by the reviewer to see if there is anything new pertaining to impurities that may need to be evaluated by pharm/tox.
Methods Validation	X	☐	one or two methods to be validated/verified since vilanterol is an NME
EA	☐	X	to be evaluated by reviewer; categorical exclusion has been claimed based on 21 CFR 25.31(b). GSK doesn't know of any extraordinary circumstances.
New Drug Micro	X	☐	evaluate proposal for two tier microbiological quality specification: Tier 1 is a water activity test; Tier 2 is a Microbial Limit Test.
CDRH	X	☐	possibly for aspects of the device (DMF [redacted] (b) (4)) and container closure development section (in P.2), also device assembly (manufacturing process): see 3.2.P.3.3 and see master batch record, executed batch records, etc. in 3.2.R. This also would include a human factors user errors study (3.2.P.2.4.3.3.9.2).

Reference ID: 3185071

Other	☐	☐	

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND	10/30/2003	48,647	Aq. nasal spray, fluticasone furoate(allergic rhinitis)
IND	6/23/2005	70,297	fluticasone furoate DPI (asthma and COPD)
IND	11/08/2007	74,696	vilanterol inhalation powder (asthma and COPD)
IND	5/23/2008	77,855	fluticasone furoate /vilanterol inhalation powder(asthma and COPD)
IND	10/09/2008	(b) (4)	(b) (4)
IND	11/13/2009	(b) (4)	LAMA (GSK573719)/LABA (vilanterol) – (COPD)
NDA	6/28/2006	22,051	Veramyst (fluticasone furoate) Nasal Spray (allergic rhinitis) – a suspension formulation

Note: fluticasone furoate has the code # GW685698;
vilanterol has the code #GW642444.

Reference ID: 3185071

d. <u>Previous Communications with the Applicant to note (if any)</u>:
***Numerous meetings and correspondence are listed in Section 1.6.3 of the NDA, for each single ingredient and for the combination product. Below are listed only some of the recent CMC interactions, mainly for IND 77,855 for the combination drug product (inhalation powder). See NDA for other meetings and correspondence, including, for example, single drug products.**

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
FDA fax	12/1/2011	I 70,297	FDA's written response to CMC questions re: fluticasone furoate
Meeting minutes	9/23/11	I77,855	re: 9/14/11 meeting (pNDA for CMC). These minutes are lengthy (24 questions from the sponsor).
Meeting Minutes	4/27/2009	I77855	EOP2 meeting on 3/31/2009 (CMC), for the FF/VI product for COPD. Note that there was another EOP2 meeting for the other disciplines on the same day.

OVERALL PRODUCT QUALITY CONCLUSIONS AND RECOMMENDATIONS

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
X	☐	1.

Reference ID: 3185071

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
X	☐	1. Modify your drug product specifications [redacted] (b) (4) 2. Separate acceptance criteria are proposed for the Aerodynamic Particle Size Distribution specifications for release and through life. The release specifications may be considered in house specifications; clarify that the regulatory specifications are the "through life" specifications. 3. Provide information pertaining to any different inhaler designs used in clinical studies prior to phase IIb, and provide summary comparative performance data with later designs. 4. Provide a description of the labeling process for your drug product. 5. Update your methods validation section by providing a tabular list of all samples and standards (including the numbers/amounts of each to be included), as well as Material Safety Data Sheets for the standards. 6. Provide 4 samples of the drug product.

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?		
Yes	No	Biopharmaceutics Filing Issues
☐	☐	N.A. – Biopharmaceutics is not involved with this application.

Are there potential biopharmaceutics review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
☐	☐	N.A. – Biopharmaceutics is not involved with this application.

Reference ID: 3185071

Does the submission contain any of the following elements?

	Yes	No	Comments
Botanical Products	☐	☐	
Combination Products	☐	☐	
Nanotechnology	☐	☐	
PET	☐	☐	
QbD Elements	X	☐	NDA does not appear to propose regulatory flexibility
SPOTS	☐	☐	

Is a team review recommended?

Yes	No	Suggested expertise for team
X	☐	Craig Bertha for drug substance, Xiaobin Shen for drug product, and Ying Wang for any modeling information.

CMC Summary:
Critical Issues and Complexities

(This section is formatted to expand as far as needed by author.)

Drug Substance Development:

Drug substance CMC information for fluticasone furoate is cross referenced to NDA 22051 (Veramyst Nasal Spray). [redacted] (b) (4) The particle size distribution for micronized fluticasone furoate drug substance is listed by the applicant as a Critical Quality Attribute (CQA).

Drug substance CMC information for vilanterol trifenatate (a new molecular entity or NME) is cross referenced to DMF 25906. The review of this DMF was entered into DARRTS on 9/4/2012. The reviewer, Dr. Craig Bertha, found this DMF to be inadequate and an IR letter will be sent to the DMF holder. This drug substance (as manufactured for all batches to date) has [redacted] (b) (4)

Reference ID: 3185071

(b) (4)

[redacted]

Drug Product Development:

> "The drug product is a plastic inhaler with a light grey body, a pale blue mouthpiece cover and a dose counter, packed in a foil tray which contains a desiccant packet. The tray is sealed with a peelable lid. The inhaler contains two strips of either 30 or 14 regularly distributed blisters, each containing a white powder." "Each blister on one strip contains a white powder mix of micronized fluticasone furoate (100 mcg) and lactose monohydrate (12.4 mg), and each blister on the other strip contains a white powder mix of micronized vilanterol trifenatate (40 mcg equivalent to 25 mcg of vilanterol), magnesium stearate (125 mcg), and lactose monohydrate (12.34 mg)."

The drug product Quality Target Product Profile (QTPP) is discussed in 2.3.P.2.1. "The formulation and the manufacturing process were selected based on the QTPP, the characteristics of the input materials (drug substances, excipients and container closure system), prior knowledge and product specific understanding based on the development history."

Reference ID: 3185071

6 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Biopharmaceutics Filing Review:
Summary, Critical Issues and Complexities

(This section can expand as far as needed by author.)

Biopharmaceutics is not involved with review of this NDA.

Reference ID: 3185071

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
1.	Is the CMC section organized adequately?	X	☐	☐	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X	☐	☐	
3.	Are all the pages in the CMC section legible?	X	☐	☐	
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	☐	☐	☐	This is a review issue as the information requested in recent meetings for I77855 do not appear to rise to the level of filing issues.

B. FACILITIES*					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
5	Is a single, comprehensive list of all involved facilities available in one location in the application?	X	☐	☐	
6	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**	☐	☐	☐	N.A.

Reference ID: 3185071

7	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	
8	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	

Reference ID: 3185071

9	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x	☐	☐	
1	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	☐	x	☐	"All sites will be ready for Pre-Approval Inspection (PAI) on July 12, 2012, (b) (4) [redacted] As a result of a telephone conference between the applicant and the Agency on 8/29/2012, GSK submitted an amendment dated 8/29/12 (b) (4) [redacted] in the establishment information form [FDA form 356h] (b) (4) [redacted]

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

Reference ID: 3185071

C. ENVIRONMENTAL ASSESMENT					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X	☐	☐	A categorical exclusion has been requested in Section 1.12.14 per 21 CFR Part 25.31(b). The applicant does not have knowledge of extraordinary circumstances.

D. MASTER FILES (DMF/MAF)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		☐	*See table on cover page.* Information is adequate. Originally there was a missing LOA for GSK's DMF 25906 for vilanterol trifenatate drug substance. This was provided at our request to DMF 25906 and to the NDA (submission dated 8/13/12).

Reference ID: 3185071

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
13.	Does the section contain a description of the DS manufacturing process?	☐	X	☐	This information is cross-referenced to GSK's DMF 25906 for vilanterol trifenatate d.s., and to GSK's NDA 22051 for fluticasone furoate. (See Dr. Craig Bertha's just completed review.)
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters?	☐	☐	☐	See #13 above.
15.	Does the section contain information on impurities?	X		☐	There is some information: for fluticasone furoate, specifications (but not methods) are provided in the NDA, and batch test results are provided, along with PSD justification. For vilanterol trifenatate, specifications are provided (but not methods). See also #13 above.
16.	Does the section contain information regarding the characterization of the DS?	☐	X	☐	See #13 above.
17.	Does the section contain controls for the DS?	X	☐	☐	Specifications for each d.s. are provided, but not methods. See #13 above.
18.	Has stability data and analysis been provided for the drug substance?	☐	X	☐	See #13 above.
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	X	☐	☐	A QbD approach is claimed but regulatory flexibility does not seem to be claimed.
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	X	☐	Not found.
21.	Does the section contain container and closure information?	☐	X	☐	See #13 above.

Reference ID: 3185071

F. DRUG PRODUCT (DP)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
22.	Does the section contain quality controls of excipients?	X	☐	☐	Lactose monohydrate and magnesium stearate both comply with USP/NF and they meet additional specifications as well.
23.	Does the section contain information on composition?	X	☐	☐	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?		X	☐	all present except for labeling process
25.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X	☐	☐	
26.	Is there a batch production record and a proposed master batch record?	X	☐	☐	
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X	☐	☐	
28.	Have any biowaivers been requested?	☐	X	☐	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	X	☐	☐	Yes. See also DMF (b) (4) for sub-assemblies and the mouthpiece.
30.	Does the section contain controls of the final drug product?	X	☐	☐	Note that the specification for the following drug product test, content uniformity of emitted dose, is a PTIT method instead of the older zero tolerance method.

Reference ID: 3185071

31.	Has stability data and analysis been provided to support the requested expiration date?	X	☐	☐	The requested expiry dating period is 24 months, based on 18 months of real time stability data on the primary NDA stability batches, and on ICH Q1A (R2). The applicant has not performed a statistical analysis of the stability data for the expiry dating period since 18 month real time stability data are available. A stability update will be submitted 100 days after the original NDA was submitted (the Agency agreed to this at the pNDA meeting for CMC on 9/14/11). This primary stability data includes testing of drug product in the proposed blister strip, in two foil laminate secondary packs (three batches packaged in trays and three batches packaged [redacted] (b) (4)) each with desiccant. These stability batches were produced at production scale at the proposed commercial site with commercial equipment, except that secondary packaging was applied at pilot scale. Whether the stability data are adequate is a review issue. The applicant had proposed not to place the 14 dose sample pack on stability and the Agency concurred (IND 77855, March 2009, EOP2 meeting for asthma): see preliminary comments sent to the applicant on 3/30/2009). Certain test attributes are not proposed for the annual stability protocol: whether the justifications for this are adequate is a review issue.
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	X	☐	☐	Yes, there are some elements of QbD present, but regulatory flexibility does not appear to have been proposed.
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	X	☐	

Reference ID: 3185071

G. [(MV)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
34.	Is there a methods validation package?	☐	X	☐	There is a file named "methods validation package" in R2, but it only very generally references S.4, S.5, P.5 and P.6, as well as making reference to NDA 22051 for the fluticasone furoate reference standard. A tabular list of all samples and standards (including the numbers/amounts of each to be included) should be provided to the NDA, as well as Material Safety Data Sheets for the standards.

H. MICROBIOLOGY					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	☐	X	☐	The drug product is not sterile, however, there is a specification for water activity and for a microbial limit test.

I. LABELING					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
36.	Has the draft package insert been provided?	X	☐	☐	
37.	Have the immediate container and carton labels been provided?	X	☐	☐	
38.	Does section contain tradename and established name?	X	☐	☐	

Reference ID: 3185071

J. FILING CONCLUSION					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
39.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X	☐	☐	
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	☐	☐	X	
41.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X	☐	☐	See the list earlier in this review (in the section entitled: Overall Product Quality Conclusions and Recommendations")

REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

CMC Lead or CMC Reviewer
Branch Chief

{See appended electronic signature page}

Reference ID: 3185071

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

/s/

ALAN C SCHROEDER
09/05/2012

PRASAD PERI
09/06/2012
I concur