CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203975Orig1s000

CHEMISTRY REVIEW(S)

Anoro® Ellipta® (umeclidinium 62.5 mcg /Vilanterol 25 mcg) Inhalation Powder

NDA 203975
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: ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist) indicated for long-term, once-daily, maintenance treatment of airflow obstruction (b) (4) with chronic obstructive pulmonary disease (COPD).

Presentation: ANORO ELLIPTA is supplied as a disposable light grey and red plastic inhaler containing 2 double-foil strips, each with 30 blisters (30 doses). The device includes a dose counter. The inhaler is packaged within a moisture-protective foil tray with a desiccant and a peelable lid. ANORO ELLIPTA is also supplied in an institutional pack and in a physician sample pack containing 2 double-foil strips, each with 7 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 December 11, 2013.**
Consults:	EA –	Categorical exclusion provided
	CDRH-	N/A
	Statistics –	N/A
	Methods Validation – the review division	The methods are found acceptable from quality control by
	DMETS	Acceptable
	Biopharm–	Acceptable
	Microbiology –	Acceptable
	Pharm/toxicology –	Acceptable

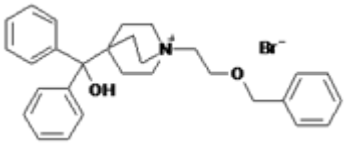
Background: This drug product contains two strips of drug-containing blisters and a device that has been used in a recently-approved NDA, 204275, for fluticasone furoate and vilanterol trifenatate. The drug product device contains umeclidinium bromide and vilanterol trifenatate for once daily treatment.

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:

Umeclidinium Bromide
Umeclidinium bromide is a new molecular entity.

1-[2-(benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide



$C_{29}H_{34}NO_2 \bullet Br$

MW = 508.5

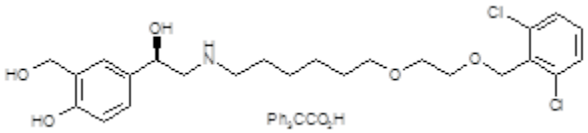
The CMC information is referenced to the applicant's DMF 26339. Umeclidinium bromide drug substance is controlled for appearance, identification, assay, impurities, enantiomer, residual solvents, water content, residue on ignition, and particle size distribution. The referenced DMF and information are adequate to support this NDA. It is manufactured by GSK in Jurong, Singapore.

Vilanterol trifenatate

Vilanterol trifenatate is the active ingredient in the Agency approved NDA 204275 for BREO ELLIPTA. The CMC information is referenced to the applicant's DMF 25906. Vilanterol trifenatate 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 are adequate to support this NDA. The drug substance is manufactured by GSK in Jurong, Singapore.

Vilanerol trifenatate:

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



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

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

For both drug substances 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.

For both drug substances, the PSD was deemed to be a CQA and the influence of PSD on the in vitro performance of the drug product was assessed.

Drug Substance: Satisfactory

Drug Product:
The drug product is ANORO ELLIPTA (Umeclidinium Bromide/Vilanterol Inhalation Powder) 62.525 mcg. The drug product consists of two strips of double foil blister coils, one containing the umeclidinium bromide 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 aluminum 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 umeclidinium bromide and vilanterol trifenatate inhalation powders, each released from their respective blister foils.

The umeclidinium bromide inhalation powder formulation contains the micronized umeclidinium bromide drug substance, magnesium stearate as (b) (4) and lactose monohydrate functioning (b) (4). The magnesium stearate and lactose monohydrate (b) (4)

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

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

GSK does not test for degradation products at release for either inhalation powder and has acceptably justified their approach with the manufacturing processes provided, control strategies, and extensive impurity analyses data. Furthermore there is no testing for specific umeclidinium bromide-related impurities on stability since none have been observed, even under accelerated conditions. Testing for "unspecified impurities" is adequate to control the appearance of umeclidinium bromide-related degradants. 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 tray 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 August 20, 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.

APPEARS THIS WAY ON ORIGINAL

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
12/16/2013

Chemistry Review Cover Sheet

ANORO ELLIPTA
(Umeclidinium bromide and vilanterol trifenatate)

Craig Bertha, Ph.D.
(Drug Substance Review)

Arthur B. Shaw, Ph.D.
(Drug Product Review)

DNDQA III/Branch VIII/DPARP

Table of Contents

Table of Contents **2**

Chemistry Review Data Sheet **4**

The Executive Summary **7**

I. Recommendations 7

A. Recommendation and Conclusion on Approvability 7

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable. 7

II. Summary of Chemistry Assessments 7

A. Description of the Drug Product(s) and Drug Substance(s) 7

1. Drug Substance 7

2. Drug Product 8

B. Description of How the Drug Product is Intended to be Used 9

C. Basis for Approvability or Not-Approval Recommendation 9

III. Administrative 9

S DRUG SUBSTANCE [umeclidinium bromide] ACCEPTABLE See Chem Review #1 10

S DRUG SUBSTANCE [vilanterol trifenatate] ACCEPTABLE See Chem Review #1 10

P DRUG PRODUCT 10

P.1 Description and Composition of the Drug Product 10
P.2 Pharmaceutical Development 10
P.3 Manufacture 12
P.4 Control of Excipients 13
P.5 Control of Drug Product 13
P.6 Reference Standards or Material1 13
P.7 Container Closure System 13
P.8 Stability 13

A APPENDICES N/A 14

R REGIONAL INFORMATION 14

A. Review of Common Technical Document-Quality (CTD-Q) Module 1 **Error! Bookmark not defined.**

A. Carton Label ..... **Error! Bookmark not defined.**

B. Environmental Assessment or Claim of Categorical Exclusion Requested and granted.....**Error! Bookmark not defined.**

C. List of Deficiencies and Comments to Be Communicated to Applicant: None**Error! Bookmark not defi**

Chemistry Review Data Sheet

1. NDA 203795

2. REVIEW #:2

3. REVIEW DATE: November 26, 2013

4. REVIEWER: Arthur B. Shaw, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Document	Document Date
Original	2012-12-14
Filing review	2013-02-15
IR Letter	2013-03-13
Quality Amendment	2013-03-25
Microbiologist's review	2013-04-03
IR Letter	2013-05-16
Quality Amendment	2013-05-31
IR Letter	2013-08-08
Quality Amendment	2013-08-14
Final Draft Labeling	2013-11-15
Quality Amendment	2013-11-18

7. NAME & ADDRESS OF APPLICANT:
Glaxo Group Limited, England d/b/a GlaxoSmithKline
980 Great West Road
Brentford
Middlesex TW89GS
United Kingdom

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Anoro Ellipta (acceptable in Proprietary Name Review, March 19, 2013)
   b) Non-Proprietary Name (USAN): umeclidinium bromide/vilanterol trifenatate
   c) Code Name/#
      umeclidinium bromide GSK573719A
      vilanterol trifenatate GW642444M
   d) Chem. Type/Submission Priority
      - Chem. Type: 1 (umeclidinium bromide). 2 (vilanterol trifenatate)
      - Submission Priority: S

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

10. PHARMACOL. CATEGORY:
    Umeclidinium L Anticholinergic (originally called a "long-acting muscarinic antagonist = LAMA)
    Vilanterol: Long acting beta$_2$ agonist (LABA)

11. DOSAGE FORM: Powder

12. STRENGTH/POTENCY: 62.5 µg/25 µg

13. ROUTE OF ADMINISTRATION: Inhalation

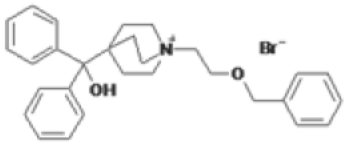
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

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

Umeclidinium bromide:

1-[2-(benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide

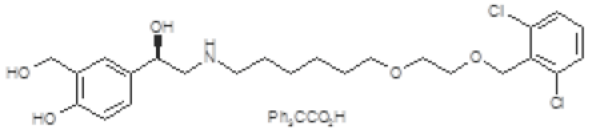


$C_{29}H_{34}NO_2 \bullet Br$

MW = 508.5

Vilanterol trifenatate:

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



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

MW = 774.8

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	Subject	Review Status
25906	Vilanterol Trifenatate (GW642444) as Manufactured in Jurong, Singapore; Hertfordshire, UK for Glaxosmithkline LLC	Acceptable 12/05/2012
26339	Umeclidinium Bromide as Manufactured in Jurong, Singapore; Hertfordshire, UK for Glaxosmithkline LLC	Acceptable 03/29/2013
(b) (4)	[redacted]	Acceptable 12/21/2012

Other DMFs cited in the applications do not need review because there is sufficient information in the NDA. These are:

DMF #	Type	Holder	Item
[redacted]			(b) (4)

(b) (4)

B. Related Documents

IND-074696 GW642444 Inhalation Powder

IND-077855 GW685698/GW642444 Inhalation Powder

IND-104479 GSK573719 Inhalation powder

IND-106616 GSK573719 /GW642444 Inhalation Powder

In addition, GSK has an NDA 204275 (approved 05/10/2013) for fluticasone furoate/vilanterol trifenatate, using the same manufacturing process, blister packaging, inhaler, and secondary packaging.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable		
EA	Categorical Exclusion granted		
Microbiology	Approval	04/03/2013	E. Pfeiler
Statistics	Approval	04/04/2013	M. Shen
Methods Validation	Pending		
Biopharmaceutics review	Acceptable	08/15/2013	S. Suarez

Note: The statistics review was done in support of NDA204275, which uses the same blister and inhaler.
One test method is currently under evaluation by DPA. All other methods have been successfully evaluated. See discussion below under P.5.3 and S.4.3. Howeer the pending evaluation will not hold up approval.

The Chemistry Review for NDA 203975

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved from a CMC point of view.

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

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance

Umeclidinium bromide is a new molecular entity and is designed to be an anticholinergic. It is a white (b) (4) that is slightly soluble in water and in simulated gastric and intestinal fluids. It is present in a (b) (4) with no polymorphs. It is slightly hygroscopic. It is provided in a micronized form. The complete CMC information is provided in DMF 26339, which is held by the applicant, GlaxoSmithKline. The DMF was reviewed by Craig Bertha and found adequate on March 29, 2013. It is very stable, although forced degradation studies have identified potential degradants. The impurities in the drug substance are due to the synthesis. The test methods were found acceptable by the Division of Pharmaceutical Analysis (DPA) in a review dated September 30, 2013.

Vilanterol trifenatate was approved as part of NDA 204275 (5/13/2013). It was, at the time, a new molecular entity and is designed to be a long acting $beta_2$ agonist (LABA). It is a white (b) (4) that is practically insoluble in water and in simulated gastric and intestinal fluids. It is present in a (b) (4) with no polymorphs. It is slightly hygroscopic. It is provided in a micronized form. The complete CMC information is provided in DMF 25906, which is held by the applicant, GlaxoSmithKline. It is quite stable, although degradation products have been identified in the DMF. Most of the impurities in the drug substance are due to the synthesis The DMF was reviewed by Craig Bertha and found adequate on December 5, 2013. The test methods had been found acceptable by DPA in a review to support NDA 204275 dated April 19, 2013

Both drug substances are manufactured by Glaxo Wellcome Private Ltd, in Jurong, Singapore. This site received an acceptable recommendation from the Office of Compliance (May 1, 2013). Both are micronized at Glaxo Operations

UK Ltd, in Ware, UK. This site received an acceptable recommendation from the Office of Compliance (January 15, 2013).

2. Drug Product

The drug product is intended to be delivered to the lungs of patients with Chronic Obstructive Pulmonary Disease (COPD). Building on experience with previously approved dry powder inhalers, the applicant has developed a formulation and delivery system that delivers both drugs simultaneously as dry powders, to be inhaled through a specially designed inhaler, equipped with a dose counter. (b) (4)

Magnesium stearate is added to the (b) (4)

The powders are filled into blister strips (30 count and 7 count) which are assembled into the inhaler. Each inhaler is designed to deliver the contents of each blister in a strip one at a time. Each inhaler is provided in a foil-covered tray to maintain a constant environment for the inhalers during storage. Once the inhaler is removed by the patient it is exposed to the environment. The entire system is designed to deliver a therapeutic dose of drug in the range of (b) (4). Control of the Aerodynamic Particle Size Distribution (APSD) for both drug substances to ensures a therapeutic dose. The labeled strengths of the drug substances are in terms of the free acid and base and the total amount filled in each blister.

The developmental studies identified the Critical Quality Attributes (CQAs) and experiments were designed to assess the effects of the formulation, the manufacturing process and the container closure system on these CQAs. The CQAs include Identity, Blister content, Degradants, Emitted Dose Content Uniformity, APSD, Foreign particulate Matter (FPM) and Microbiological Quality. (b) (4)

The magnesium stearate was found to be necessary (b) (4)

The strips are then assembled into the inhaler, which is then placed in a foil tray with a desiccant (b) (4) and the tray is sealed.

The drug product is very stable, staying within specifications throughout the long-term and accelerated stability studies. The applicant has provided 15 months of long-term stability data to support an expiration date of 24 months. There were no trends in the data so a statistical analysis was not necessary. The applicant proposed that the drug product not be tested for umeclidinium

degradants at release, since the drug substance is very stable and there are no steps in the manufacturing that could cause degradation. This is acceptable. Another feature of the release testing is that some tests are performed on the blister strips, other are performed on the inhalers, and others are performed on the finished product. These are justified by the development data. In addition, the applicant has a two-tier test for microbiological quality. The first tier is a test for water activity. Since water is needed for the growth of most microorganisms a low water activity can be used as a surrogate for actually measuring microbiological contamination. If the sample fails the water activity test, then the standard microbial limits test will be used. This was found acceptable by the Microbiologist's review. In-use studies, in which the inhaler was removed from its secondary packaging, after storage at 25C/60%RH, showed that the drug product was stable out of its secondary packaging for up to three months. This supports the label instructions to discard the inhaler after six weeks out of the secondary packaging.

All sites have an acceptable recommendation from the Office of Compliance (August 20, 2013)

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

The drug product is intended for daily use by patients with patients with Chronic Obstructive Pulmonary Disease (COPD. It is designed to be inhaled through a custom inhaler with minimal patient effort.

C. **Basis for Approvability or Not-Approval Recommendation**
The NDA may be approved based on adequate CMC data to ensure that the drug product delivers the correct therapeutic doses of both drug substances consistently throughout the proposed shell life.

III. Administrative

A. Reviewer's Signature See DARRTS

B. Endorsement Block: See DARRTS

11 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

ARTHUR B SHAW
11/26/2013

ERIC P DUFFY
11/26/2013

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

DATE: 22-AUG-2013

TO: N203975 File

FROM: Craig M. Bertha, Ph.D.
Chemist and Acting CMC Lead
ONDQA, Division III, Branch VIII

THROUGH: Prasad Peri, Ph.D.
Branch Chief
ONDQA, Division III, Branch VIII

SUBJECT: Update on Establishment Evaluation Request for N203975
Umeclidinium/Vilanterol Inhalation Powder; CMC recommendation

SUMMARY:

The Office of Compliance issued an overall recommendation of ACCEPTABLE for the application on 21-AUG-2013. The summary report from the Establishment Evaluation System is attached below.

RECOMMENDATION: Considering the recommendation from the Office of Compliance, the application is **recommended to be approved**.

_____
Craig M. Bertha, Ph.D.
Chemist and Acting CMC Lead

cc:
OND/DPARP/LHann
ONDQA/DIV 3/CBertha/22-AUG-2013
ONDQA/DIV 3/EDuffy
ONDQA/DIV 3/PPeri_____
ONDQA/DIV3/AShaw
ONDQA/DIV 3/YLiu
OND/DPARP/JPippens
OND/DPARP/JSohn
OB/DBII/GLevin

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 203975/000	**Sponsor:**	GLAXO GRP LTD
Org. Code:	570		5 MOORE DR
Priority:	14		RESEARCH TRIANGLE PARK, NC 27709
Stamp Date:	18-DEC-2012	**Brand Name:**	ANORO ELLIPTA
PDUFA Date:	18-DEC-2013	**Estab. Name:**	Umeclidinium Bromide and Vilanterol
Action Goal:		**Generic Name:**	
District Goal:	18-JUL-2013	**Product Number; Dosage Form; Ingredient; Strengths**	

001; POWDER, FOR INHALATION; UMECLIDINIUM BROMIDE; 62.5MCG
001; POWDER, FOR INHALATION; VILANTEROL TRIFENATATE; 25MCG
002; POWDER, FOR INHALATION; UMECLIDINIUM BROMIDE; 125MCG
002; POWDER, FOR INHALATION; VILANTEROL TRIFENATATE; 25MCG

FDA Contacts:	A. SHAW	Prod Qual Reviewer		3017961460
	C. BERTHA	Prod Qual Reviewer		3017961646
	Y. LIU	Product Quality PM		3017961926
	L. HANN	Regulatory Project Mgr	(HFD-570)	3017963367
	ID = 105168	Team Leader		

Overall Recommendation:	ACCEPTABLE	on 21-AUG-2013	by J. WILLIAMS	()	3017964196
	PENDING	on 10-APR-2013	by EES_PROD		
	PENDING	on 10-APR-2013	by EES_PROD		
	PENDING	on 09-APR-2013	by EES_PROD		
	PENDING	on 14-JAN-2013	by EES_PROD		
	PENDING	on 14-JAN-2013	by EES_PROD		
	PENDING	on 14-JAN-2013	by EES_PROD		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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

GLAXO OPERATIONS UK LIMITED
PRIORY STREET

WARE, HERTFORDSHIRE, UNITED KINGDOM

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-AUG-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-JAN-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

GLAXO WELLCOME MANUFACTURING PTE LIMITED
2262

JURONG, , SINGAPORE

DMF No: 25906 **AADA:**

26339

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-MAY-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY 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		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	03-JUN-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** 1033964 **FEI:** 1033964		
	GLAXOSMITHKLINE INC		
	ZEBULON, , UNITED STATES 275971217		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	21-AUG-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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

/s/

CRAIG M BERTHA
08/22/2013

PRASAD PERI
08/23/2013
I concur

Chemistry Review Cover Sheet

ANORO ELLIPTA
(Umeclidinium bromide and vilanterol trifenatate)

Craig Bertha, Ph.D.
(Drug Substance Review)

Arthur B. Shaw, Ph.D.
(Drug Product Review)

DNDQA III/Branch VIII/DPARP

Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 4

The Executive Summary 7

I. Recommendations 7

A. Recommendation and Conclusion on Approvability 7

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable. 7

II. Summary of Chemistry Assessments 7

A. Description of the Drug Product(s) and Drug Substance(s) 7

1. Drug Substance 7

2. Drug Product 8

B. Description of How the Drug Product is Intended to be Used 9

C. Basis for Approvability or Not-Approval Recommendation 9

III. Administrative 9

S DRUG SUBSTANCE [umeclidinium bromide] 10

S.4 Control of Drug Substance [umeclidinium bromide] 10

S.4.1 Specification: [umeclidinium bromide] 10

S.4.4 Batch Analyses: [umeclidinium bromide] 11

S.4.5 Justification of Specification: [umeclidinium bromide] 11

S DRUG SUBSTANCE [vilanterol trifenatate] 11

S.1 General Information [vilanterol trifenatate] 11

S.1.1 Nomenclature [vilanterol trifenatate] 11

S.1.2 Structure [vilanterol trifenatate] 11

S.1.3 General Properties [vilanterol trifenatate] 11

S.2 Manufacture [vilanterol trifenatate] 11

S.2.1 Manufacturers [vilanterol trifenatate] 11

S.2.2 Description of Manufacturing Process and Process Controls [vilanterol trifenatate] 11

S.2.3 11

S.4.1 Specification: [vilanterol trifenatate] 13
S.4.3 Validation of Analytical Procedures: [vilanterol trifenatate] See DMF 25906..... 14
S.4.4 Batch Analyses: [vilanterol trifenatate] 14
S.4.5 Justification of Specification: [vilanterol trifenatate] 14
S.5 Reference Standards or Materials: [vilanterol trifenatate] See DMF 25906 14
S.6. Container Closure [vilanterol trifenatate] See DMF 25906 14
S.7 Stability [vilanterol trifenatate] See DMF 25906 14
P DRUG PRODUCT 15
P.1 Description and Composition of the Drug Product 15
P.2 Pharmaceutical Development 15
P.3 Manufacture 230
P.4 Control of Excipients 243
P.5 Control of Drug Product 248
P.6 Reference Standards or Materials 307
P.7 Container Closure System 307
P.8 Stability 310
A APPENDICES N/A 313
R REGIONAL INFORMATION 313
A. Review of Common Technical Document-Quality (CTD-Q) Module 1 314
A. Labeling & Package Insert: 314
B. Carton Label 316
C. Environmental Assessment or Claim of Categorical Exclusion Requested and granted. 316
D. List of Deficiencies and Comments to Be Communicated to Applicant: None 316

Chemistry Review Data Sheet

1. NDA 203795

2. REVIEW #:1

3. REVIEW DATE: August 16, 2013

4. REVIEWER: Arthur B. Shaw, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Document	Document Date
Original	2012-12-14
Filing review	2013-02-15
IR Letter	2013-03-13
Quality Amendment	2013-03-25
Microbiologist's review	2013-04-03
IR Letter	2013-05-16
Quality Amendment	2013-05-31
IR Letter	2013-08-08
Quality Amendment	2013-08-14

7. NAME & ADDRESS OF APPLICANT:
Glaxo Group Limited, England d/b/a GlaxoSmithKline
980 Great West Road
Brentford
Middlesex TW89GS
United Kingdom

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Proposed: Anoro Ellipta
   b) Non-Proprietary Name (USAN): umeclidinium bromide/vilanterol trifenatate
   c) Code Name/#
   d) Chem. Type/Submission Priority
      - Chem. Type: 1 (umeclidinium bromide). 2 (vilanterol trifenatate)
      - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY:
    Umeclidinium Long acting muscarinic antagonist (LAMA)
    Vilanterol: Long acting $beta_2$ agonist (LABA)

11. DOSAGE FORM: Inhalation Powder

12. STRENGTH/POTENCY: 62.5 µg/25 µg

13. ROUTE OF ADMINISTRATION: Inhalation

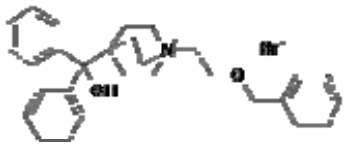
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

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

Umeclidinium bromide:

1-[2-(benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide

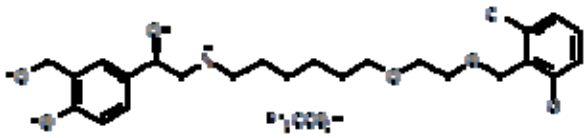


$C_{29}H_{34}NO_2 \bullet Br$

MW = 508.5

Vilatnerol trifenatate:

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



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

MW = 774.8

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

The only two DMFs that require review are the type II DMFs for the drug substances, also held by the applicant.

DMF	Subject	Review Status
25906	Vilanterol Trifenatate	Acceptable 12/05/2012
26339	Umeclidinium Bromide	Acceptable 03/29/2013

The others do not need review because there is sufficient information in the NDA. These are:

DMF #	Type	Holder	Item
(b) (4)			

B. Related Documents

IND-074696 GW642444 Inhalation Powder

IND-077855 GW685698/GW642444 Inhalation Powder

IND-104479 GSK573719 Inhalation powder

IND-106616 GSK573719 /GW642444 Inhalation Powder

In addition, GSK has an NDA 204275 (approved 05/10/2013) for fluticasone furoate/vilanterol trifenatate, using the same manufacturing process, blister packaging, inhaler, and secondary packaging.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
EA	Categorical Exclusion granted		
Microbiology	Approval	04/03/2013	E. Pfeiler
Statistics	Approval	04/04/2013	M. Shen
Methods Validation	Pending		
Biopharmaceutics review	Acceptable	08/15/2013	S. Suarez

Note: The statistics review was done in support of NDA204275, which uses the same blister and inhaler.

The Chemistry Review for NDA 203975

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved from a CMC point of view pending satisfactory CGMP inspections.

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

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance

Umeclidinium bromide is a new molecular entity and is designed to be a long acting muscarinic antagonist (LAMA). It is a white (b) (4) that is slightly soluble in water and in simulated gastric and intestinal fluids. It is present in a (b) (4) with no polymorphs. It is slightly hygroscopic. It is provided in a micronized form. The complete CMC information is provided in DMF 26339, which is held by the applicant, GlaxoSmithKline. The DMF was reviewed by Craig Bertha and found adequate on March 29, 2013. It is very stable, although forced degradation studies have identified potential degradants. The impurities in the drug substance are due to the synthesis.

Vilanterol trifenatate was approved as part of NDA 204275 (5/13/2013). It was, at the time, a new molecular entity and is designed to be a long acting $beta_2$ agonist (LABA). It is a white (b) (4) that is practically insoluble in water and in simulated gastric and intestinal fluids. It is present in a (b) (4) with no polymorphs. It is slightly hygroscopic. It is provided in a micronized form. The complete CMC information is provided in DMF 25906, which is held by the applicant, GlaxoSmithKline. It is quite stable, although degradation products have been identified in the DMF. Most of the impurities in the drug substance are due to the synthesis The DMF was reviewed by Craig Bertha and found adequate on December 5, 2013.

Both drug substances are manufactured by Glaxo Wellcome Private Ltd, in Jurong, Singapore. Both are micronized at Glaxo Operations UK Ltd, in Ware, UK. Both sites have an acceptable recommendation from the office of Compliance.

2. Drug Product

The drug product is intended to be delivered to the lungs of patients with Chronic Obstructive Pulmonary Disease (COPD). Building on experience with previously approved dry powder inhalers, the applicant has developed a formulation and delivery system that delivers both drugs simultaneously as dry powders, to be inhaled through a specially designed inhaler, equipped with a dose counter. (b) (4) he powders are filled into blister strips (30 count and 7 count) which are assembled into the inhaler. Each inhaler is designed to deliver the contents of each blister in a strip one at a time. Each inhaler is provided in a foil-covered tray to maintain a constant environment for the inhalers during storage. Once the inhaler is removed by the patient it is exposed to the environment. The entire system is designed to deliver a therapeutic dose of drug in the range of (b) (4). Control of the Aerodynamic Particle Size Distribution (APSD) for both drug substances to ensures a therapeutic dose. The labeled strengths of the drug substances are in terms of the free acid and base and the total amount filled in each blister.

The developmental studies identified the Critical Quality Attributes (CQAs) and experiments were designed to assess the effects of the formulation, the manufacturing process and the container closure system on these CQAs. The CQAs include Identity, Blister content, Degradants, Emitted Dose Content Uniformity, APSD, Foreign particulate Matter (FPM) and Microbiological Quality. (b) (4)

The magnesium stearate was found to be necessary (b) (4)

The drug product is very stable, staying within specifications throughout the long-term and accelerated stability studies. The applicant has provided 15 months of long-term stability data to support an expiration date of 24 months. There were no trends in the data so a statistical analysis was not necessary. The applicant proposed that the drug product not be tested for umeclidinium degradants at release, since the drug substance is very stable and there are no steps in the manufacturing that could cause degradation. This is acceptable.

Another feature of the release testing is that some tests are performed on the blister strips, other are performed on the inhalers, and others are performed on the finished product. These are justified by the development data. In addition, the applicant has a two-tier test for microbiological quality. The first tier is a test for water activity. Since water is needed for the growth of most microorganisms a low water activity can be used as a surrogate for actually measuring microbiological contamination. If the sample fails the water activity test, then the standard microbial limits test will be used. This was found acceptable by the Microbiologist's review. In-use studies, in which the inhaler was removed from its secondary packaging, after storage at 25C/60%RH, showed that the drug product was stable out of its secondary packaging for up to three months. This supports the label instructions to discard the inhaler after six weeks out of the secondary packaging.

All sites have a satisfactory cGMP status except the stability testing site in Zebulon NC, which is scheduled for inspection.

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

The drug product is intended for daily use by patients with patients with Chronic Obstructive Pulmonary Disease (COPD. It is designed to be inhaled through a custom inhaler with minimal patient effort.

C. **Basis for Approvability or Not-Approval Recommendation**
The NDA may be approved, pending satisfactory inspection results, based on adequate CMC data to ensure that the drug product delivers the correct therapeutic doses of both drug substances constantly throughout the proposed shell life.

III. Administrative

A. Reviewer's Signature See DARRTS

B. Endorsement Block: See DARRTS

307 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

CRAIG M BERTHA
08/20/2013

PRASAD PERI
08/20/2013
I concur

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

APPLICATION INFORMATION

1. NEW DRUG APPLICATION NUMBER: 203975

NME

A QbD approach is claimed for drug product: "The Quality Target Product Profile for UMEC/VI has been defined. Critical Quality Attributes of UMEC/VI have been identified and the control strategy defined, which includes control of the drug substances, excipients, intermediates of the process, container closure system and the manufacturing process of the drug product." [from the cover letter dated 12/18/12, original NDA]

Proposed Indication: maintenance treatment of airflow obstruction in patients with COPD

2. Drug Name: Anoro Ellipta (umeclidinium/vilanterol inhalation powder)

Strengths: 62.5/25 microgram and 125/25 microgram umeclidinium/vilanterol (salt forms are expressed as free cation/free base in the indicated strengths)

3. RECEIVED DATE: December 18, 2012
Applicant: GlaxoSmithKline

4. RELATED REVIEW DOCUMENTS:

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

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
26339	II	GSK	Umeclidinium bromide	11/29/12	LOA should be verified in the DMF. This DMF includes some QbD terminology. Dr. Bertha has reviewed this DMF on 2/12/13 and found it inadequate.
25906	II	GSK	Vilanterol Trifenatate	8/13/12	Last reviewed 11/29/12 by Dr. Bertha and found adequate in support of an inhalation powder. Some QbD terminology is used in the DMF. LOA should be verified in the DMF
[redacted] (b) (4)				11/14/11	LOA should be verified in the DMF
				4/12/12	LOA should be verified in the DMF
				4/12/12	LOA should be verified in the DMF
				3/26/12	LOA should be verified in the DMF
				9/24/12	LOA should be verified in the

					DMF
[redacted] (b) (4)				9/24/12	LOA should be verified in the DMF
				12/7/11	LOA should be verified in the DMF

b. Recommended Consults

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	X	☐	Request for evaluation of PTIT proposal for drug product specification (content uniformity of emitted dose). Reviewer should determine whether a Biometrics consult is needed for stability data/proposed drug product expiry.
Clin Pharm	☐	X	
EES	X	☐	Request submitted to EES on January 14, 2013.
Pharm/Tox	?	☐	To be determined by reviewer whether a consult is needed. Individual, specified drug related impurities appear to be present at levels below the ICH Q3B qualification threshold. However, in the synthesis of umeclidinium bromide, there are [redacted] (b) (4) and if either or both are present in the drug substance, they may need pharm/tox review. This may not be an issue though since the drug dose is very low.
Methods Validation	X	☐	At least one method should be evaluated by the FDA laboratory since the drug product is an NME.
EA	☐	X	To be evaluated by reviewer
New Drug Micro	X	☐	There is a two tier microbial quality specification proposed, involving a water activity test (Tier 1) and a microbial limit test (Tier 2), similar to GSK's proposal for NDA 204275.
CDRH		?	To be determined by the reviewer. It may not be necessary since the device is referenced to DMF

			(b) (4) just as for GSK's NDA 204275.
Other	X	☐	(b) (4)

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

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND 74696	11/08/07		
IND 77855	5/23/08		
IND 104479	7/14/09		
IND 106616	11/13/09		
NDA 204275	7/12/12		

d. Previous Communications with the Applicant to note (if any):
NOTE: Section 1.6 of the NDA lists many communications, including INDs for the monoproducts and other combination products. The list below is significantly abbreviated, focused on IND 106616.

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
UMEC/VI preliminary comments for CMC EOP2 meeting	10/24/10	IND 106,616	
UMEC/VI EOP2 meeting minutes	10/29/10 (meeting date)	IND 106616	no CMC attendees from FDA
UMEC/VI preNDA meeting minutes	1/18/12 (meeting date)	IND 106616	no CMC discussion: we had provided a CMC comment for the NDA however.
FDA fax	6/7/12	IND 106616	clarification for NDA
preliminary comments for CMC preNDA meeting	6/05/12	IND 106,616	

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.

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	

X	☐	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
☐	☐	Not included in this review

Are there potential biopharmaceutics review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
☐	☐	Not included in this review.

Does the submission contain any of the following elements?

	Yes	No	Comments
Botanical Products	☐	X	
Combination Products	X	☐	
Nanotechnology	☐	X	
PET	☐	X	
QbD Elements	X	☐	
SPOTS	☐	X	

Is a team review recommended?

Yes	No	Suggested expertise for team
X	☐	Team review suggested for workload considerations, one CMC reviewer for drug substance section, another CMC reviewer for drug product section.

CMC Summary:
Critical Issues and Complexities

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

Background:

Umeclidinium bromide is a long-acting muscarinic antagonist (LAMA) and vilanterol trifenatate is a long-acting beta2-agonist (LABA)

Both drug substances are NMEs (vilanterol is an NME in N204275, Breo Ellipta)

Indication: maintenance bronchodilator treatment of Chronic Obstructive Pulmonary Disease (COPD), including chronic bronchitis and emphysema.

Device is the same as for GSK's Breo Ellipta (fluticasone furoate/vilanterol inhalation powder).

Drug Product Strengths: 62.5/25 microgram and 125/25 microgram umeclidinium/vilanterol (salt forms are expressed as free cation/free base in the indicated strengths).

The applicant states that in development of this drug product, the principles of ICH Q8, Q9, Q10, Q11 "and other regulatory guidance" were employed.

Drug Substances:

CMC information is referenced in a LOA for the drug substance, umeclidinium bromide, to DMF 26339. The DMF holder/applicant has identified CQAs for the drug substance and CPPs for the manufacturing process. (See the DMF and the QOS in section 2.3.S) This drug substance is a NME (new molecular entity). Studies with X-ray powder diffraction are said to show that the manufacturing process for this drug substance consistently produces [redacted] Both routes are cross referenced to 3.2.S.2.6 of the NDA. A number of drug substance attributes are not considered by the applicant to be CQAs and are not included in the specification (see section 2.3.S.4.5.9). The justifications for these deletions should be evaluated. Total process impurities in the drug substance tend to be low, with batch analysis data showing total impurities for both micronized and unmicronized umeclidinium bromide to be a maximum of [redacted], with most lots significantly less than that. The acceptance criterion for total impurities is much higher, i.e., not greater than [redacted]. The applicant has conducted fate and purging studies to evaluate the amounts of impurities that may be present in the manufacturing process in order to meet the drug substance specification. Impurities that are readily purged and have never been seen in the drug substance above [redacted] w/w are not considered to be CQAs. It is stated that potential genotoxic impurities from the manufacturing process are not present in the drug substance at levels above [redacted], and considering the "extremely low dose of umeclidinium," genotoxic materials are controlled "to considerably lower levels than the TTC." Thus, the applicant has not included any potential genotoxic impurities as CQAs of the drug substance. [see 2.3.S.2.6.3]

CMC information is referenced in a LOA for the other drug substance, vilanterol trifenatate, to DMF 25906. This DMF has been reviewed previously by Dr. Craig Bertha in November, 2012 and found adequate in support of another GSK NDA for an inhalation powder. See the IQA for NDA 204275 and the review of DMF 25906 for additional information about this drug substance. The DMFs are not reviewed in this IQA.

Drug Product:

"*The drug product is a plastic inhaler with a light grey body, a red 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 7 regularly distributed blisters, each containing a white powder. Umeclidinium/Vilanterol Inhalation Powder 62.5/25 microgram is available as 30 and 7 dose packs. Each dose contains 62.5 micrograms of umeclidinium (as bromide) and 25 micrograms of vilanterol (as trifenatate) per inhalation.*

(b) (4)

Figure 7 Exploded View of the Inhaler Showing All Individual Components and the Two Blister Strips

(b) (4)

Note: Image is for illustrative purposes only. Colours do not reflect commercial image.

Note the potential failure addressed for fluticasone furoate/vilanterol inhalation powder, see 3.2.p.2.4 pg. 82-102 of N203975.

NDA 203975 references DMF (b) (4) for the inhaler device; this same DMF was referenced for the device in GSK's NDA 204275 which seems to indicate that this is the same device for both NDAs. This is confirmed by the information below.

The applicant states the following in comparing NDA 203975 (drug product) to their other NDA 204275 (see introduction section of the Quality Overall Summary, 2.3.P): *"Several of the sections are the same/similar to that submitted for Breo Ellipta*

(Fluticasone Furoate/Vilanterol Inhalation Powder, NDA 204275) which is currently under review. These sections include: m3.2.P.3.3. Description of Manufacturing Process and Process Controls…regarding the strip filling and assembly process for vilanterol, m3.2.P.4. Control of Excipients regarding the magnesium stearate excipient, m3.2.P.6. Reference Standards regarding the vilanterol reference standards and m3.2.P.7.Container Closure."

Errors were found to have been made by one analyst in conducting the test for foreign particulate matter (over a period of a number of years). Testing was repeated on samples of drug product stored at later timepoints and these data have been identified and added to the drug product stability tables. The new data are claimed to be within the proposed acceptance criteria. An amendment dated 5/16/12 to IND 106,616 is referenced for a briefing document on this situation, which was investigated. Corrective and preventative actions were identified (per 2.3.P.1.6). It is claimed that there was no impact on patient safety. This information was previously assessed by the Agency.

Following are discussed APSD comparisons of monodrug products as well the proposed combination drug product.

> *"Comparison of APSD for the products used in the Phase III Clinical Studies, Umeclidinium Inhalation Powder (One Umeclidinium blister strip), Vilanterol Inhalation Powder (One Vilanterol blister strip) and Umeclidinium / Vilanterol Inhalation Powder (One Umeclidinium blister strip and one Vilanterol blister strip); are provided in m3.2.P.2.2. Formulation Development, Section 1.1.6.* (b) (4) [redacted] *In addition, for the combination product, the vilanterol is not influenced by the strength of umeclidinium bromide in the drug product."* [from 2.3.P.2.2]

Following are discussed changes to the inhaler between that used for phase III clinical studies, that used for stability batches and that intended for commercial marketing.

> ***"****The intent during development was to ensure that any revisions to the inhaler build did not affect product performance. Thus, it was GSK's intention for there to be minimal changes between the inhaler studied in Phase III clinical studies, primary stability and commercial inhaler. Any design changes have been for compelling reasons only based upon GSK's ongoing assessment of the drug product. These have included:*
>
> *mechanical issues*
> *feedback from patients as part of the ongoing clinical programs*
> *improvements to the commercial inhaler design in order to maintain a robust high volume manufacturing capability.*

A programme of work was undertaken to understand the consequences of any such changes to the inhaler and impact upon DPCQAs prior to their implementation. The programme has included an assessment of the effect on the in-vitro product performance of the changes by testing the airflow resistance, the aerodynamic particle size distribution and emitted dose of the product. The data presented demonstrate that the performance of the commercial inhaler is fully representative of the inhaler studied in Phase III clinical studies, as detailed in m3.2.P.2.4. Container Closure System Development, Section 5." [from 2.3.P.2.4.4]

The following is a brief listing of some QbD elements in the drug product section of the application:

Quality Target Product Profile (QTPP)

Drug Product CQAs

Drug Product CPPs

Relationship Matrix: Relationships (strong vs. weak) were determined between input material or unit operation, and drug product CQA. This was achieved by the Failure Modes and Effects Analysis (FMEA) and/or prior knowledge.

These relationships were also determined for each micronized drug substance and each excipient.

A summary of the control strategy is provided, to show when a DP CQA is impacted by a CPP or a CQA. The control strategy "is based on the previous knowledge, extensive process understanding gained during the development of the drug product, and the use of a Quality Risk Management Approach.

Certain aspects of possible regulatory flexibility are noted below (with kind input from Dr. Chatterjee).

It is proposed to not test the drug product impurities (degradants) at release. Based on the applicant's justification and based on team discussion of this point with management for N204275 (also GSK), it was decided to accept this proposal, therefore it may be similarly acceptable for NDA 203975.

The impurities test appears as part of the drug product specifications with a footnote indicating that it is not tested at release.

Other aspects suggestive of regulatory flexibility include the following: (b) (4) (b) (4) (b) (4)) and some relatively wide drug product

manufacturing process parameters [redacted] (b) (4)

A number of tests are not part of the drug product specification (see 2.3.P.5.6.11), and these include [redacted] (b) (4)

The following information pertains to drug product controls:

The applicant has proposed an approach to address certain APSD failures (with retesting), as well as mass balance criteria and mass balance retesting.

A PTIT approach is proposed for emitted dose content uniformity.

Microbiological quality involves a two tier/two test approach (water activity is tested under Tier 1, microbial limits are tested under Tier 2).

The identification test for each active ingredient may be performed on the blister strip prior to the assembly stage of manufacture. This applies to certain other tests as well, e.g., content uniformity of the blisters, [redacted] (b) (4) microbial limit test.

A second identification test (for both actives together) may be performed on the inhaler prior to the packing stage of manufacture. This applies to certain other tests as well, e.g., content uniformity of emitted dose, APSD, foreign particulate matter.

The applicant has proposed a manufacturing overage [redacted] (b) (4) for umeclidinium and up to [redacted] (b) (4) for vilanterol), and their justification for this should be evaluated.

Description of Facility Related Risks or Complexities (i.e. foreign sites, large number of sites involved, etc.)
See EES for complete list of facilities related to this application.
Three facilities are in foreign sites (UK, Singapore).

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?	☐	☐	X	Comments provided prior to the NDA submission are judged to be review issues for the NDA, not filing issues and CMC information in the NDA will be evaluated by the reviewers.

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.**	☐	☐	X	

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	☐	☐	DMF numbers are separately provided; they are not included on the Form 356h list of establishments.
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	☐	☐	

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	☐	☐	
10	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X	☐	☐	

* 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.

C. ENVIRONMENTAL ASSESMENT					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
11	Has an environmental assessment report or categorical exclusion been provided?	X	☐	☐	See 1.12.14. 21 CFR Part 25.31(b) is referenced, and the applicant does not have knowledge of any 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.*

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	☐	☐	Yes, by reference to the drug substance DMFs. This pertains to DMF 26339; adequate information is assumed for DMF 25906 because it has been recently reviewed and found to be adequate.
14	Does the section contain identification and controls of critical steps and intermediates of the DS (in process parameters?	X	☐	☐	See comment for #13 above
15	Does the section contain information on impurities?	X	☐	☐	See comment for #13 above
16	Does the section contain information regarding the characterization of the DS?	X	☐	☐	See comment for #13 above
17	Does the section contain controls for the DS?	X	☐	☐	See comment for #13 above. The NDA itself contains the specification sheet for the drug substances.
18	Has stability data and analysis been provided for the drug substance?	X	☐	☐	See comment for #13 above
19	Does the application contain Quality by Design (QbD) information regarding the DS?	X	☐	☐	some QbD elements.
20	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	X	☐	none found so far
21	Does the section contain container and closure information?	X	☐	☐	Yes, by reference to the drug substance DMFs. This pertains to DMF 26339; adequate information is assumed for DMF 25906 because it has been recently reviewed and found to be adequate.

F. DRUG PRODUCT (DP)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
22	Does the section contain quality controls of excipients?	X	☐	☐	USP tests plus additional attributes.
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	☐	☐	It does not appear, at first look, that labeling is described as part of the manufacturing process. The reviewer should determine whether the manufacturing process description in 3.2.P.3.3 is sufficiently complete (besides the missing labeling process). Section 3.2.R contains executed batch records and master batch records.
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	☐	☐	It is stated that there are no intermediate products in manufacture of the drug product.
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	☐	☐	It is indicated (P.2.2) that early clinical formulations used (b) (4) but this was later replaced with magnesium stearate. This applies to both umeclidinium and to vilanterol trifenatate formulations. It is noted also that (b) (4) until the new inhaler became available. Some dose ranging studies and other clinical studies were conducted with two strip inhaler devices using placebo in the second strip. Early clinical studies used (b) (4) which was later replaced by vilanterol trifenatate. The drug product formulations used in phase III clinical studies appear to be comparable to the formulations proposed for marketing (in addition there were other product strengths made); this assumes no change in the properties of the active and inactive ingredients. All phase III clinical studies used protective packaging including (b) (4) desiccant packet. The phase III formulations were evaluated as (b) (4) The phase III clinical study formulations, primary stability batches and drug product intended for marketing are said to have (b) (4). Some improvements have been made to the inhaler and secondary pack after phase III studies had been initiated; these are discussed in sections P.2.4, and 3.3.8, and 4.2.5. These improvements were apparently made to resolve issues that had been identified during studies of the device. Details of the drug product changes during development and their data comparisons are review issues.
28	Have any biowaivers been requested?	☐	X	☐	

29	Does the section contain description of to-be-marketed container/closure system and presentations?	X	☐	☐	Note that the device was reviewed in DMF (b) (4) by Dr. Bertha and found adequate on 12/20/2012. There is information about the device in the NDA too, and information about the secondary packaging (foil laminate tray and lid, and desiccant packets).
30	Does the section contain controls of the final drug product?	X	☐	☐	Note that footnote m, Table 1, section P.5.1 (for each strength of product) contains an approach to address certain APSD failures (with retesting), as well as mass balance criteria and mass balance retesting. Impurities are tested on stability but not at release. A PTIT approach is proposed for emitted dose content uniformity. Microbiological quality involves a two tier/two test approach (water activity is tested under Tier 1, microbial limits are tested under Tier 2). Methods and method validations are described. Method descriptions contain basic data but appear to be abbreviated.
31	Has stability data and analysis been provided to support the requested expiration date?	X	☐	☐	The primary stability data (three batches for each product strength) are provided for 12 months at 25°C/60%RH. These stability batches are production scale batches manufactured at the proposed commercial site (Ware, UK). A statistical analysis of these data are provided to support the proposed shelf life (b) (4) Evaluation of the data is a review issue. The applicant has also provided 12 months of stability data at 30°C/75% RH (rather than at 25°C/75%RH for one third of shelf life to test the (b) (4) packaging, as per the draft MDI/DPI guidance) and 6 months stability data at 40°C/75%RH. An in use period of 6 weeks is proposed once the inhaler is removed from the protective packaging. Six weeks of supportive stability data (in use) are provided for the 7 dose format product. Certain tests are not performed at each stability time point.

32	Does the application contain Quality by Design (QbD) information regarding the DP?	X	☐	☐	There are some QbD elements. Certain aspects of regulatory flexibility are noted below (with kind input from Dr. Chatterjee). The drug product impurities (degradants) are proposed to not be tested at release. Based on the applicant's justification and based on team discussion of this point with management for N204275 (also GSK), it was decided to accept this proposal, therefore it should be similarly acceptable for NDA 203975. The impurities test appears as part of the drug product specifications with a footnote indicating that it is not tested at release. Other aspects suggestive of regulatory flexibility include the following: (b) (4) and some relatively wide drug product manufacturing process parameters (b) (4) in section P.3.3.1.3.3 on page 7, where the (b) (4)
33	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	X	☐	none found

G. METHODS VALIDATION (MV)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
34	Is there a methods validation package?	X	☐	☐	

H. MICROBIOLOGY					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
35	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	☐	☐	X	

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

NDA #203975: Received Date: Dec. 18, 2012

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	☐	☐	

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.	☐	☐	☐	
41	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X	☐	☐	See earlier in this review.

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
02/14/2013
Initial Quality Assessment (IQA)

PRASAD PERI
02/15/2013
I concur