CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209482Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 209482
Review #1

Drug Name/Dosage Form	Fluticasone furoate (FF), umeclidinium (UMEC), vilanterol (VI) inhalation powder
Strength	100/62.5/25 mcg FF/UMEC/VI per actuation
Route of Administration	oral inhalation
Rx/OTC Dispensed	Rx
Applicant	GlaxoSmithKline Intellectual Property Development Ltd. England
US agent, if applicable	Mary V. Sides

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	*18-NOV-2016*	*all*
Amendment	*24-APR-2017*	*drug product*
Amendment	*25-MAY-2017*	*process*
Amendment	*07-JUL-2017*	*facilities*
Amendment	*11-JUL-2017*	*facilities*
Amendment	*19-JUL-2017*	*drug product*
Amendment	*17-AUG-2017*	*drug product*

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Larry Perez	NDBII/DNDAPI
Drug Product	Venkat Pavuluri	NDPBIV/DNDPII
Process	Brian Rogers	PABIV/DPAII
Microbiology	Brian Rogers	PABIV/DPAII
Facility	Daniel DeCiero	DIA
Biopharmaceutics	Ge Bai	BBIII/DB
Regulatory Business Process Manager	Florence Aisida	RBPMBI/DRBPMI
Application Technical Lead	Craig M. Bertha	NDPBIV/DNDPII
Laboratory (OTR)		
ORA Lead	Caryn McNab/Michael Tollon	PQIB/DPQP
Environmental Analysis (EA)		

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	III		(b) (4)	N/A		Sufficient information in NDA
	III			N/A		Sufficient information in NDA
	IV			N/A		Sufficient information in NDA
	III			Adequate	21-DEC-2012	No amendments since last review
	III			N/A		Sufficient information in NDA
25906	II	GlaxoSmithKline	Vilanterol	Adequate	03-APR-2017	
26339	II	GlaxoSmithKline	umeclidinium	Adequate	03-APR-2017	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70297	FF inhalation powder
IND	77855	FF/VI inhalation powder
IND	104479	UMEC inhalation powder
IND	106616	UMEC/VI inhalation powder
IND	112510	FF/UMEC inhalation powder
IND	114873	FF/UMEC/VI inhalation powder

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

Based on the reviews and recommendations from the drug substance, drug product, process, and facilities teams outlined in the review below, an overall recommendation of **approval** is forwarded to the clinical Division, DPARP.

II. Summary of Quality Assessments

A. Product Overview

The current application seeks approval for a fixed-dose triple combination drug product, an inhalation powder, for the long-term maintenance treatment of chronic obstructive pulmonary disease (COPD).

Proposed Indication(s) including Intended Patient Population	COPD
Duration of Treatment	Chronic
Maximum Daily Dose	100/62.5/25 mcg FF/UMEC/VI per unit dose
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Fluticasone furoate (FF) is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. FF is marketed in the U.S. in a nasal spray for allergy symptom relief, in an inhalation powder for treatment of asthma, and in combination with vilanterol trifenatate (VI) in an inhalation powder for treatment of asthma and chronic obstructive pulmonary disease (COPD). FF possesses nine stereogenic centers with the (6*S*,8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*R*,17*R*) configuration, is manufactured as a white (b) (4) by Glaxo Wellcome in Jurong, Singapore, and is micronized in Hertfordshire, United Kingdom.

Umeclidinium bromide (UMEC) is a quaternary ammonium bromide salt with anticholinergic activity. UMEC is marketed in the U.S. in an inhalation powder and in combination with VI in an inhalation powder, both for treatment of COPD. The drug substance umeclidinium bromide is an achiral compound with no stereogenic centers. UMEC is manufactured as a white (b) (4) by Glaxo Wellcome in Jurong, Singapore, and is micronized in Hertfordshire, United Kingdom.

Vilanterol trifenatate (VI) is a [redacted] (b) (4) with bronchodilation activity. VI is a selective long-acting beta2-adrenergic agonist with inherent 24-hour activity for once daily treatment of COPD and asthma. VI possesses one stereogenic center with the (1*R*) configuration, is manufactured as a white [redacted] (b) (4) by Glaxo Wellcome in Jurong, Singapore, and is micronized in Hertfordshire, United Kingdom.

Information on the drug substance fluticasone furoate is cross-referenced with NDA022051 and with NDA204275. Information on the drug substances umeclidinium bromide and vilanterol trifenatate is cross-referenced with DMFs 26339 and 25906, respectively. For these three drug substances, additional information on Specification, Batch Analysis, and Justification of Specification is included in this NDA application.

For NDA209482, GlaxoSmithKline Intellectual Property Development Ltd England has provided sufficient information in regards to identity, strength, purity and quality to ensure consistent manufacturing of the three drug substances, fluticasone furoate, umeclidinium bromide and vilanterol trifenatate. Based upon the assessment of the drug substance data for each of these drug substances in this application, a recommendation of approval is made for each of the drug substances as formulated in the drug product Fluticasone Furoate/Umeclidinium/ Vilanterol Inhalation Powder.

TRELEGY™ ELLIPTA® (fluticasone furoate, umeclidinium, and vilanterol inhalation powder) is an inhalation powder or dry powder inhaler, containing two strips of either 30 or 14 regularly distributed blisters in a plastic inhaler device, each containing a white powder; one blister containing Fluticasone Furoate 100 micrograms, and the other containing Umeclidinium, and Vilanterol in pre-metered amounts of 62.5 and 25 micrograms respectively. Each inhalation of the product provides a delivered dose of 92/55/22 micrograms of fluticasone furoate/umeclidinium/vilanterol. The plastic inhaler with a light grey body, a beige mouthpiece cover, and a dose counter is packaged into a foil tray containing a [redacted] (b) (4) desiccant packet and sealed with a peelable foil laminate lid.

Clinical batch release data together with the data from primary stability batches at initial and up to 18 months at long-term and 12 months at intermediate storage conditions, manufactured at the commercial manufacturing site, are supportive of a **shelf-life of 24 months** for drug product. No statistical evaluation of the stability data was presented in the submission.

The processes for [redacted] (b) (4) the individual blister strips are very similar to that approved in previous inhalation powder applications using the Ellipta device. The difference between the previous processes and that proposed in the dual component formulation (UMEC/VI) is supported with sufficient data and is not a substantial risk to the drug product quality. The container closure system including the double foil blister laminate, inhaler, desiccant and tray is the same as that in the approved Ellipta products; with the exception of the inhaler mouthpiece cover color, which is product specific. No changes in the assembly of the container were proposed.

Following review of the inspection documentation and application documents, the manufacturing facilities for NDA 209482 are considered **acceptable**. Note, however, that a post approval inspection is required for the design firm for the device per ICC1600811:

GlaxoSmithKline Intellectual Property Development Ltd. England
980 Great West Road
Brentford, Middlesex,
United Kingdom., TW8 9GS
(FEI# 3003451948)

OPQ recommends that the application be **approved.**

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

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

LABELING NDA-209482

IQA Review Guide Reference

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Included
Dosage form, route of administration	Included
Controlled drug substance symbol (if applicable)	Not Applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Included

Section 2 Dosage and Administration

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Not Applicable

2. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Meets the requirements
Strengths: in metric system	
Active moiety expression of strength with equivalence statement (if applicable)	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Disposable light grey and beige plastic inhaler containing 2 foil blister strips

3. *Section 11 Description*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Meets the requirement
Dosage form and route of administration	(b) (4) Device Description to be changed to: TRELEGY ELLIPTA is a light grey and beige plastic inhaler containing 2 double-foil blister strips. The statement "In adult subjects with very severe COPD (FEV1/FVC [forced vital capacity] less than 70% and FEV1 less than 30% predicted), mean peak inspiratory flow through the ELLIPTA inhaler was 65.8 L/min (range: 43.5 to 94.1 L/min), (b) (4)
Active moiety expression of strength with equivalence statement (if applicable)	Meets the requirement
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Meets the requirements
Statement of being sterile (if applicable)	Not Applicable
Pharmacological/ therapeutic class	
Chemical name, structural formula, molecular weight	Adequate
If radioactive, statement of important nuclear characteristics.	Not Applicable
Other important chemical or physical properties (such as pKa or pH)	Adequate

4. ***Section 16 How Supplied/Storage and Handling***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Meets the requirement
Available units (e.g., bottles of 100 tablets)	Meets the requirement for individual (Trade and Institutional) packs.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Meets the requirement
Special handling (e.g., protect from light)	Store in a dry place away from direct heat or sunlight. TRELEGY ELLIPTA should be stored inside the unopened moisture-protective foil tray and only removed from the tray immediately before initial use. Discard TRELEGY ELLIPTA 6 weeks after opening the foil tray or when the counter reads "0" (after all blisters have been used), whichever comes first.
Storage conditions	Meets the requirements.
Manufacturer/distributor name (21 CFR 201.1(h)(5))	

Reviewer's Assessment of Package Insert: Inadequate.

The section, 11. DESCRIPTION, require changes as suggest above. Dosage form and route of administration information is missing.

Refer the "List of Deficiencies" at the end of the document.

II. Labels:

1. *Container and Carton Labels*

Container label (Trade pack)

(b) (4)

2. *Carton Label*

(b) (4)

Item	Information provided in the container label(s) (including the tray lid)	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Meets the requirements	Meets the requirements
Dosage strength	Relevant information included	Relevant information included
Net contents	Relevant information included	Relevant information included
"Rx only" displayed prominently on the main panel	Meets the requirement	Meets the requirement
NDC number (21 CFR 207.35(b)(3)(i))	Yes	Yes
Lot number and expiration date (21 CFR 201.17)	Space identified for printing Lot number and Exp. Date on the inhaler back label and tray lid	Space identified on the front panel for printing Lot number and Exp. Date
Storage conditions	Information provided, Adequate	Information provided, Adequate
Bar code (21CFR 201.25)	Bar code included on trade and institutional packs (Sample Not for Sale on the Sample packs)	Bar code included on trade and institutional packs (Sample Not for Sale on the Sample packs)
Name of manufacturer/distributor	Relevant information included	Relevant information included
And others, if space is available	Includes: Discard the Inhaler 6 weeks after opening the moisture protective foil tray or when the counter reads "0" (after all blisters have been used), whichever comes first. "For Oral Inhalation Only" on immediate container and tray lid. On the immediate container (inhaler) label there is space for recording the Tray opened and Discard (6 weeks) dates.	Includes: Discard the Inhaler 6 weeks after opening the moisture protective foil tray or when the counter reads "0" (after all blisters have been used), whichever comes first. "For Oral Inhalation Only" . Instructions for Using TRELEGY™ ELLIPTA®, in both text and figures. Box containing "Federal Law Requires the Dispensing of TRELEGY ELLIPTA with the Medication Guide Inside the Carton.

Reviewer's Assessment of Labels: Adequate

The labeling information on immediate container (inhaler) labels was placed on two sides differentiating the trade, institutional and sample packs. The lid of the tray also has similar information as the immediate container labels and complies with the regulatory requirements.

The text on the outer carton also comply with the relevance regulatory requirements from the CMC perspective

List of Deficiencies:

In the Prescribing Information, Section 11. DESCRIPTION, require changes as suggest below. Dosage form and route of administration information is missing., require changes as suggest below.

1. Revise the statement "[redacted] (b) (4) To ""TRELEGY ELLIPTA is an inhalation powder drug product for delivery of a combination of fluticasone furoate (an ICS), umeclidinium (an anticholinergic) and vilanterol (a LABA) to patients by oral inhalation".

2. Revise Device Description to "TRELEGY ELLIPTA is a light grey and beige plastic inhaler containing 2 ***double***-foil blister strips".

Overall Assessment and Recommendation: The Container and Carton labels comply with the regulatory requirement from CMC perspective. However, the Prescribing Information requires revisions as indicated above. Inclusion of the statement "In adult subjects with very severe COPD (FEV1/FVC [forced vital capacity] less than 70% and FEV1 less than 30% predicted), mean peak inspiratory flow through the ELLIPTA inhaler was 65.8 L/min (range: 43.5 to 94.1 L/min), suggesting that the inhalation efforts achieved by patients with severely compromised lung function are sufficient to use the inhaler." In section11. Prescribing Information needs further evaluation by the Clinical Team.

Primary Labeling Reviewer Name and Date: **Venkateswara R. Pavuluri, Ph. D.; R. Ph.**
09-AUG-2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Julia C. Pinto, Ph. D.

Venkateswara Pavuluri

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Julia Pinto

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Attachment – Final Risk Assessment

DP attribute/ CQA	Factors that can impact the CQA[1]	O[2]	S[2,3]	D[2]	FMECA RPN #	Comment & considerations
Identity	• Identity of micronized fluticasone furoate (FF), umeclidinium (UMEC) and vilanterol (VI) • Solid state forms of FF, UMEC, and VI	2	3	2	12	• Identity and the solid state forms of FF, UMEC, and VI are confirmed by testing of the input drug substance by Infrared Spectroscopy • Identity testing for FF, UMEC, and VI is done for the formulated drug product (UV spectrum and HPLC retention time) • (b) (4)
Emitted Dose	• Variable API concentrations (b) (4)	2	3	4	24	(b) (4)

[1] Based on underlying assumption that patients use the device as intended (human factors beyond scope of CMC evaluation)

[2] O = Probability of Occurrence; S = Severity of Effect; D = Detectability

[3] Severity of effect can only be estimated; input from clinical or pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs; beyond the scope of a CMC risk assessment

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Attachment – Final Risk Assessment

Aerodynamic Particle Size Distribution (APSD) of the emitted dose	• Refer to all factors above for emitted dose • Particle size distribution of input APIs • Composition of device air flow path components	2	3	4	24	• See associated comments above for all relevant factors that can affect emitted dose, which are equally applicable to the APSD of the emitted dose • APSD tested at release/stability, but small sample size • Applicant tests the mouthpiece and manifold components of the device for extractable consistency with FT-IR (surrogate for detection of changes in the composition of these important device components that might impact drug delivery)
Drug-related impurities	(b) (4)	2	3	3	18	(b) (4)
Foreign particulate matter		2	3	3	18	

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Attachment – Final Risk Assessment

						(b) (4)
Leachables	(b) (4)	1	3	5	15	• Dry powder inhalers are generally not prone to expose patients to leachables upon use (this is not generally a CQA for these types of drug products); no testing for leachables is proposed
Microbiological quality		1	3	4	12	(b) (4)

Craig
Bertha

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

DATE: 10-JAN-2017

TO: N209482 File for Trelegy Ellipta Inhalation Powder

FROM: Craig M. Bertha, CMC Lead
OPQ/ONDP/DNDPII/Branch IV

SUBJECT: Background regarding product strip configurations and *in vitro* performance comparability for GlaxoSmithKline drugs that use the Ellipta device

The applicant has four approved inhalation powder drug products that use the Ellipta device with various drug combinations (fluticasone furoate or FF; vilanterol or VI, umeclidinium or UMEC):

Proprietary Name	IND	NDA (approval date)
Breo Ellipta (FF/VI)	IND 77855	NDA 204275 (10-MAY-2013)
Anoro Ellipta (UMEC/VI)	IND 106616	NDA 203975 (18-DEC-2013)
Incruse Ellipta (UMEC)	IND 104479	NDA 205382 (30-APR-2014)
Arnuity Ellipta (FF)	IND 70297	NDA 205625 (20-AUG-2014)
Trelegy Ellipta (FF/UMEC/VI)	**IND 114873**	**NDA 209482 (pending)**

Ellipta (see figure below) is an inhalation powder device that can have one or two foil-foil blister strips containing (b) (4) formulations that are delivered simultaneously when the patient inhales from the mouthpiece.

(b) (4)

The four approved products and the proposed Trelegy Ellipta (triple drug combination) have various configurations in terms of the formulations and strips used (i.e., one or two). In order to satisfy the combination drug product rule (21CFR300.50) for Breo, Anoro, and **Trelegy**, the clinical studies included monotherapy and dual comparator drug products (listed in *italics* in the table below). For Breo, the monotherapy comparators used in phase III included placebo second strips to more closely match the combination drug product. This was not the case for phase III studies for Anoro, however, where single strip comparators were used.

Drug Product/phase III comparators	**First strip (API in mcg)**	**Second strip (API in mcg)**
Breo Ellipta, FF/VI (N204275)[1]	100 or 200 FF/L[2]	25 VI/L/MgSt[2]
FF mono comparator for Breo[1,3]	*100 or 200 FF/L*	*L/MgSt*
VI mono comparator for Breo[1]	*L*	*25 VI/L/MgSt*
Anoro Ellipta (203975)[4]	62.5 UMEC/L/MgSt	25 VI/L/MgSt
UMEC mono comparator for Anoro[4]	*62.5 UMEC/L/MgSt*	*None*
VI mono comparator for Anoro[4]	*None*	*25 VI/L/MgSt*
Incruse Ellipta (N205382)	62.5 UMEC/L/MgSt	None
Arnuity Ellipta (N205625)	100 or 200 FF/L	None
Trelegy Ellipta (N209482)[5,6]	100 FF/L	62.5 UMEC/25 VI/L/MgSt
FF/VI dual comparator for Trelegy[5,6]	*100 FF/L*	*25 VI/L/MgSt*
UMEC/VI dual comparator for Trelegy[5]	*62.5 UMEC/L/MgSt*	*25 VI/L/MgSt*
UMEC mono comparator for Trelegy[6]	*62.5 UMEC/L/MgSt*	*None*

Craig M. Bertha -S

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Craig M. Bertha, CMC Lead

cc:
OPQ/ONDP/DNDPII/Branch IV/CBertha/10-JAN-2017
OPQ/ONDP/DNDPII/Branch IV/JPinto
OPQ/OPRO/FAisida
OND/DPARP/LBroadhead
OND/DPARP/SChaudhry
OND/DPARP/BChowdhury
OND/DPARP/LGilbert-McClain
OCP/DCPII/BSaluja

[1] *In vitro* dose performance of monotherapy drug products considered comparable to combination drug product (see 29-APR-2008, and 14-SEP-2011, meeting minutes I77855)
[2] Key: L for lactose; MgSt for magnesium stearate
[3] *In vitro* comparability demonstrated for FF monotherapy drug product with two strips versus one strip (see 01-DEC-2011, written responses I70297)
[4] *In vitro* dose performance differences noted when UMEC monotherapy drug product with one versus two strips (i.e., latter including "placebo" strip) were compared (see 24-OCT-2010, meeting minutes I106616); GSK then planned to bridge two versus one strip UMEC monotherapy with a pharmacodynamic study (see 18-JAN-2012, meeting minutes I106616)
[5] *In vitro* comparability demonstrated for FF/UMEC/VI Trelegy versus the FF/VI and UMEC/VI dual comparators (see 27-FEB-2014, written response I114873)
[6] *In vitro* comparability demonstrated for FF/UMEC/VI "closed" versus "open" (FF/VI + UMEC) triple combinations (see 08-JUN-2016, meeting minutes I114873)

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 209482	**Submission Type: 505(b)(1)**	**Established/Proper Name: fluticasone furoate (FF), umeclidinium (UMEC), vilanterol (VI)[1]**
Applicant: GlaxoSmithKline Group, Ltd.	**Letter Date: 18-NOV-2016**	**Dosage Form: inhalation powder**
Chemical Type: 5	**Stamp Date: 18-NOV-2016**	**Strengths: 100 mcg FF/62.5 mcg UMEC/25 mcg VI/metered actuation**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?		X	N/A

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[2]	☐	☒	
2.	Botanical[2]	☐	☒	
3.	Naturally-derived Product	☐	☒	
4.	Narrow Therapeutic Index Drug	☐	☒	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☐	☒	
8.	Transdermal[2]	☐	☒	
9.	Pediatric form/dose[2]	☐	☒	
10.	Locally acting drug[2]	☒	☐	

[1] Note that for this triple combination inhalation powder drug product for chronic obstructive pulmonary disease (COPD), the umeclidinium (UMEC) is in the formulation as a quaternary ammonium salt, umeclidinium bromide and vilanterol (VI) is also a salt in the formulation, vilanterol trifenatate.

[2] Contact Office of Testing and Research for review team considerations

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FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
11.	Lyophilized product[2]	☐	☒	
12.	First generic[2]	☐	☒	
13.	Solid dispersion product[2]	☐	☒	
14.	Oral disintegrating tablet[2]	☐	☒	
15.	Modified release product[2]	☐	☒	
16.	Liposome product[2]	☐	☒	
17.	Biosimilar product[2]	☐	☒	
18.	Combination Product _____	☐	☒	Although drug product consists of a device and associated formulation, by the strict definition of 21 CFR 3.2(e)(1), this does not seem to be a true combination product because neither the device nor the formulation alone would be regulated separately for use without the other.
19.	Other_____	☒	☐	Four previous drug products from GSK are approved that use the Ellipta device (NDAs 205625, 205382, 204275, 203975; see attachment 1); current drug product comes in one strength combination but with two dose counts, 14 and 30 blisters for one actuation per day

Regulatory Considerations				
20.	USAN Names Assigned	☒	☐	
21.	End of Phase II/Pre-NDA Agreements	☒	☐	For I114873, a CMC-only EoP2 meeting was held 21-OCT-2013: • *In vitro* aerodynamic particle size distribution (APSD) data and measured systemic PK data were inconsistent • Agency agreed that "minor" inhaler changes could be handled by GSK's internal change control procedures; Agency agreed to allowing device composition changes supported by *in vitro* comparability data • Agency agreed that information supporting the Ellipta device and protective packaging could be provided by cross-reference to approved applications using these components • No air-flow resistance data would be necessary considering that the device is used as part of other approved inhalation powder drug products • Agency agreed that there was no need for GSK to test routine partially-used drug product units from the clinical studies (a typical requirement for inhalation drug products) • Provision of chemical stability data for the

					FF strip deemed unnecessary (note FF strip is already approved for use in Breo® Ellipta®) EoP2 meeting of 23-FEB-2016: • The Agency indicated that based on the *in vitro* drug aerodynamic particle size distribution data provided, which compares the triple combination (FF/VI/UMEC) to the double combinations (FF and VI from FF/VI and UMEC from FF/UMEC), that it agreed that for these comparisons, GSK had demonstrated sufficient pharmaceutical equivalence (also see the related response to question 1 for the 24-MAY-2016, type C meeting regarding "open" and "closed" triple combinations) • The Agency agreed that GSK could provide data in the NDA to justify the absence of testing for foreign particulate matter and the microscopic evaluation of the formulation for the primary stability samples
22.	SPOTS (Special Products On-line Tracking System)		☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☐	Unknown
24.	Comparability Protocol(s)[3]		☐	☒	
25.	Other_____		☒	☐	This application is the first for a triple combination inhalation powder drug product
Quality Considerations					
26.	Drug Substance Overage		☒	☐	(b) (4)
27.	Design Space	Formulation	☐	☒	
28.		Process	☒	☐	(b) (4)
29.		Analytical Methods	☐	☒	
30.		Other	☐	☒	

[3] Contact Post Marketing Assessment staff for review team considerations

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31.	Real Time Release Testing (RTRT)		☐	☒	
32.	Parametric Release in lieu of Sterility Testing		☐	☒	Drug product is not sterile
33.	Alternative Microbiological Test Methods		☐	☐	To be determined by process review team
34.	Process Analytical Technology[2]		☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☒	☐	
36.		Excipients	☒	☐	
37.		Microbial	☒	☐	(b) (4)
38.	Unique analytical methodology[2]		☐	☒	
39.	Excipients of Human or Animal Origin		☒	☐	Lactose (b) (4)
40.	Novel Excipients		☐	☒	
41.	Nanomaterials[2]		☐	☒	
42.	Hold Times Exceeding 30 Days		☒	☐	(b) (4)
43.	Genotoxic Impurities or Structural Alerts		☒	☐	Although there are likely many structural alert functions in the APIs and related compounds (e.g., FF contains a Michael acceptor in the A ring), this is of academic interest only as these three drug substances are already approved for use in other GSK inhalation drug products
44.	Continuous Manufacturing		☐	☒	
45.	Other unique manufacturing process[2]		☐	☒	Not considering that there are 4 other products that use the Ellipta device that have been approved
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☐	N/A – drug is for topical application and action in the lung
47.	New delivery system or dosage form[2]		☐	☒	The Ellipta® device is already approved as a part of four other GSK inhalation powder drug products
48.	Novel BE study designs		☐	☐	To be evaluated by the clinical pharmacology group
49.	New product design[2]		☐	☒	
50.	Other_____		☐	☐	

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	Applicant requests a categorical exclusion as per 21 CFR 25.31(b)
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices	☒	☐	☐	• Most of the information and data to support the three APIs is provided by reference to other applications and DMFs • The application provides 18 months of long-term data for three registration stability batches of the

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C. FILING CONSIDERATIONS					
	○ Facilities and Equipment ○ Adventitious Agents Safety Evaluation ○ Novel Excipients ❑ Regional Information ○ Executed Batch Records ○ Method Validation Package ○ Comparability Protocols				triple combination drug product (at production scale from the commercial site; see P.8.3, table 1) • The application includes "summary" batch records for the three registration stability batches as well as a master batch record (compliant with the 314.50 regulation for a 505(b)(1) application) • A separate methods validation package is not included, but there is a list of available samples that can be provided to the Agency laboratory if method assessment is deemed necessary during review (see R.2)
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? 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? 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)	☒	☐	☐	Four sites listed on 356h: • Glaxo Operations UK Ltd. (FEI 3003262904) • Glaxo Wellcome Manufacturing Pte Ltd. (FEI 3002807079) • Glaxo Operations UK Ltd. (FEI 3002807078) • GlaxoSmithKline R&D Ltd. (FEI 3004036283)
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	☒	☐	☐	
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☒	☐	☐	There are two type II DMFs from GSK for the vilanterol trifenatate and umeclidinium bromide drug substances (DMFs 25906 and 26339, respectively)
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a	☒	☐	☐	Most information for the three APIs is provided by reference to previous GSK applications and the DMFs cited in box 5

C. FILING CONSIDERATIONS					
	review? ❑ general information ❑ manufacture o Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment				above; additional API information is also included in module 3 (specifications, batch analyses, and justification of specifications)
	DRUG PRODUCT INFORMATION				
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to	☐	☒	☐	• Applicant indicates in P.5.6 that the clinical batches manufactured for the phase 3 clinical studies are representative of the proposed commercial drug product • A complete description of product lots and their uses during development could is located in P.5.4 • The drug product is not sterile • A single excipient is used, lactose monohydrate and this meets both compendial and additional criteria imposed by the applicant • The "Registration batches" were produced at the intended commercial manufacturing site

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C. FILING CONSIDERATIONS					
	support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product ○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System ○ Include data outlined in container closure guidance document ❑ Stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				• P.3.5 includes data on 14 batches of drug product intended to confirm that the manufacturing process yields drug product of consistent quality • See box 2 above with regard to the methods validation package • The majority of the details of the CMC information for the device is provided by reference to (b) (4) [redacted] • A full 18 months of long term stability data has been collected for three (3) batches of the drug product prepared a full production scale at the intended commercial production site in Ware, UK • Lactose monohydrate (b) (4) [redacted] • See box 2 above regarding the regional information
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☒	☐	☐	BA/BE data will be reviewed by Office of Clinical Pharmacology
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	☐	☐	☒	The to-be-marketed product is the same product used in the pivotal clinical studies. There is one drug product manufacturing site in UK
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☒	☐	

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C. FILING CONSIDERATIONS					
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☐	☒	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	☒	☐	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	See box 2 above
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	☐	☐	☒	
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: o LAL instead of rabbit pyrogen o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples	☐	☐	☒	

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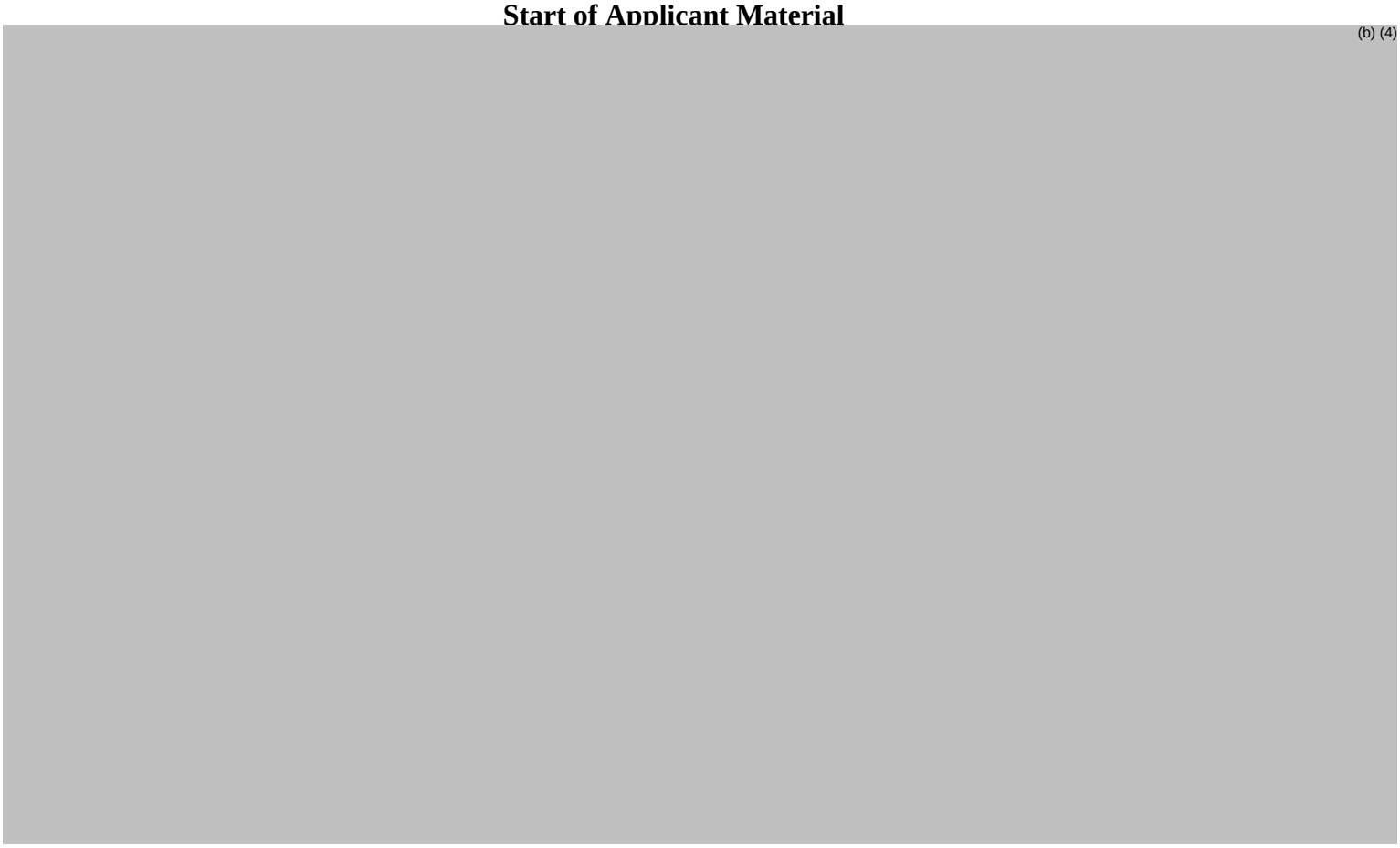
FILING REVIEW Attachment 1 – Ellipta® Device

Start of Applicant Material

(b) (4)



End of Applicant Material

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FILING REVIEW Attachment 2 – Risk Assessment

DP attribute/ CQA	Factors that can impact the CQA[4]	O[5]	S[5, 6]	D[5]	FMECA RPN #	Comment & considerations
Identity	• Identity of micronized fluticasone furoate (FF), umeclidinium (UMEC) and vilanterol (VI) • Solid state forms of FF, UMEC, and VI	2	3	2	12	• Identity and the solid state forms of FF, UMEC, and VI are confirmed by testing of the input drug substance by Infrared Spectroscopy • Identity testing for FF, UMEC, and VI is done for the formulated drug product (UV spectrum and HPLC retention time) • (b) (4)
Emitted Dose	(b) (4)	3	3	4	36	(b) (4)

[4] Based on underlying assumption that patients use the device as intended (human factors beyond scope of CMC evaluation).
[5] O = Probability of Occurrence; S = Severity of Effect; D = Detectability
[6] Severity of effect can only be estimated; input from clinical or pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs; beyond the scope of a CMC risk assessment.

	(b) (4)					(b) (4)
Aerodynamic Particle Size Distribution (APSD) of the emitted dose	• Refer to all factors above for emitted dose • Particle size distribution of input APIs • Composition of device	3	3	4	36	• See associated comments above for all relevant factors that can affect emitted dose, which are equally applicable to the APSD of the emitted dose • APSD tested at release/stability, but small sample size • Applicant tests the mouthpiece and manifold components of the device for extractable consistency with FT-IR (surrogate for

	air flow path components					detection of changes in the composition of these important device components that might impact drug delivery)
Drug-related impurities	(b) (4)	2	3	3	18	(b) (4)
Foreign particulate matter	(b) (4)	3	3	4	36	(b) (4)

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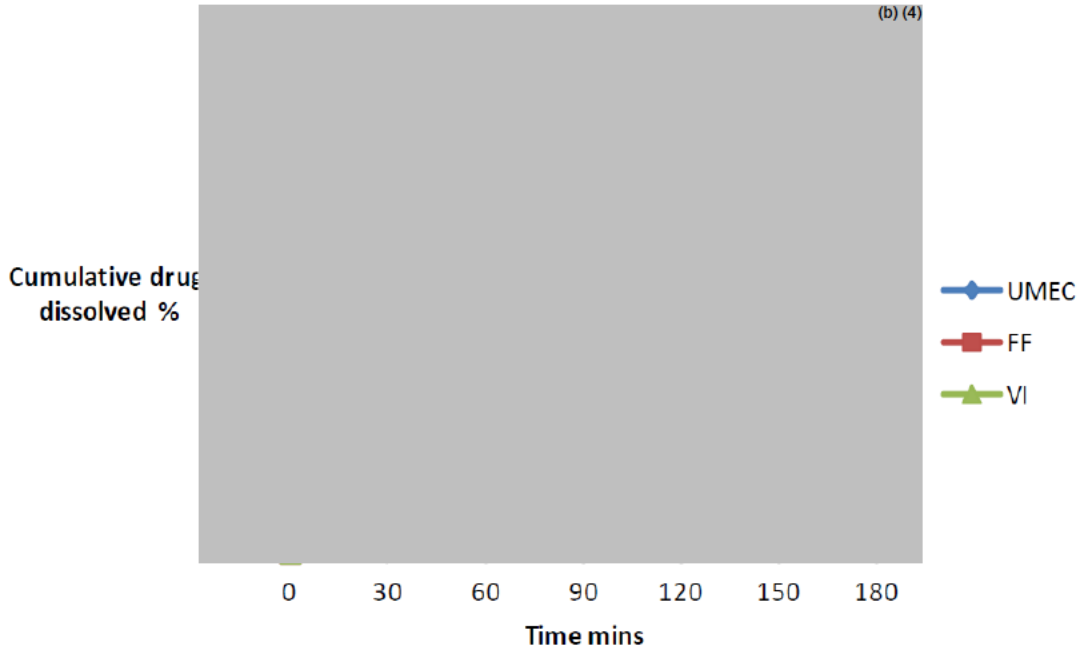
FILING REVIEW Attachment 2 – Risk Assessment

						(b) (4)
Leachables	(b) (4)	1	3	5	15	• Dry powder inhalers are generally not prone to expose patients to leachables upon use (this is not generally a CQA for these types of drug products); no testing for leachables is proposed
Microbiological quality		1	3	4	12	(b) (4)

In-Vitro Dissolution is not a drug product release specification. During formulation development stage, the Applicant studied the in-vitro dissolution characteristics of the drug product by using a flow cell with simulated lung fluid as dissolution medium. HPLC was used to analyze the dissolved drug substance. The dissolution profiles of the three drug substance are shown in the figure below. The dissolution rates observed are consistent with those previously presented for fluticasone furoate, umeclidinium, and vilanterol in the approved GSK's Ellipta products. The details of the dissolution method can be found in Section 3.1 of \\cdsesub1\evsprod\nda209482\0000\m3\32-body-data\32p-drug-prod\ff-ub-vi-inhalation-powder\32p2-pharm-dev\pharmaceutical-development-p22.pdf

Figure 17 Dissolution Profile of Fluticasone Furoate, Umeclidinium and Vilanterol in Fluticasone Furoate/Umeclidinium/Vilanterol Inhalation Powder



Craig M. Bertha, ATL (DNDPII, CMC Lead for DPARP)

Ge Bai, Biopharmaceutics Reviewer

Craig
Bertha

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