CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205625Orig1s000

CHEMISTRY REVIEW(S)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 205625/000
Type: 570
Priority: 5
Stamp Date: 22-OCT-2013
PDUFA Date: 22-AUG-2014
Action Goal:
District Goal: 23-JUN-2014

Sponsor: GLAXOSMITHKLINE
1250 COLLEGE RD UP 4410
COLLEGEVILLE, PA 194260989
Brand Name: FLUTICASONE FUROATE GW685698
Estab. Name:
Generic Name: FLUTICASONE FUROATE GW685698
Product Number; Dosage Form; Ingredient; Strengths
001; POWDER, FOR INHALATION; FLUTICASONE FUROATE; 100MCG
002; POWDER, FOR INHALATION; FLUTICASONE FUROATE; 200MCG

FDA Contacts:				
	E. JAO	Prod Qual Reviewer		3017961684
	S. LANGILLE	Micro Reviewer	(HFD-805)	3017961557
	Y. LIU	Product Quality PM		3017961926
	P. TON	Regulatory Project Mgr		3017961648
	C. BERTHA	Team Leader		3017961646

Overall Recommendation:	ACCEPTABLE	on 23-DEC-2013	by T. SHARP	()	3017963208
	PENDING	on 07-NOV-2013	by EES_PROD		

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
GLAXO (b) (4) (b) (4)
[redacted]
DUNS: **AADA:**
Responsibilities: 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: 23-DEC-2013
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4)		
	GLAXO (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	08-NOV-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4)		
	GLAXOSMITHKLINE (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	08-NOV-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4)		
	GLAXOSMITHKLINE INC		
DMF No:	(b) (4)	**AADA:**	
Responsibilities:	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	23-DEC-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/

MARY GRACE LUBAO
08/29/2014

NDA 205625

Fluticasone Furoate Inhalation Powder

Glaxo Group Limited d/b/a GlaxoSmithKline

Edwin Jao, Ph.D.
Division of Pulmonary, Allergy, and Rheumatology Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 205625

2. REVIEW #: 1

3. REVIEW DATE: July 18, 2014

4. REVIEWER: Edwin Jao, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	10/22/2013
Amendment	4/25/2014

7. NAME & ADDRESS OF APPLICANT:

Name: Glaxo Group Limited d/b/a GlaxoSmithKline

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

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

Representative: Patrick D. Wire, Pharm. D.

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4) and (b) (4)
b) Non Proprietary Name (USAN): Fluticasone furoate 100 mcg inhalation powder and Fluticasone furoate 200 mcg inhalation powder
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
Chem. Type: 4
Submission Priority: S

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

10. PHARMACOL. CATEGORY: inhaled corticosteroid

11. DOSAGE FORM: Inhalation Powder

12. STRENGTH/POTENCY: 100 mcg and 200 mcg of fluticasone furoate

13. ROUTE OF ADMINISTRATION: Oral Inhalation

14. Rx/OTC DISPENSED: X Rx ____OTC___

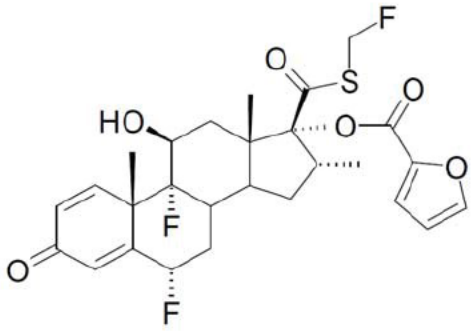
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

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



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

Molecular Weight: 538.6

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)b) (4)	4	(b) (4)	(b) (4)	3	adequate		
	3			3	adequate		(b) (4)

(b) (4)	3	(b) (4)	(b) (4)	3	adequate		(b) (4)
(b) (4)	3	(b) (4)	(b) (4)	3	adequate		
(b) (4)	3	(b) (4)	(b) (4)	3	adequate		

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70,297	FF Inhalation Powder

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	12/23/2013	T. Sharp
Pharm/Tox	Not sent		No individual impurity/degradant is controlled at above ICH Q3(B) level, and the genotoxic impurity (b) (4) controlled such that its daily exposure is NMT (b) (4) for the 200 mcg strength.
Method Validation	Not sent		All analytical methods for the drug product are the same as those used for the approved Breo Ellipta.
EA	acceptable	7/18/2014	Edwin Jao
Microbiology	approval	6/20/2014	Dr. Stephen E. Langille

The Chemistry Review for NDA 205625

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is recommended for approval.

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

NA.

II. Summary of Chemistry Assessments

A. Description of the Drug Substances and Drug Product

The drug substance fluticasone furoate in this NDA is also one of the active ingredients in the applicant's recently approved drug product Breo Ellipta (the combination drug product, NDA 204275). The CMC information for fluticasone furoate is (b) (4) the approved NDA 204275. The specifications and batch release data are provided. The impurity controls are equally adequate for both 100 mcg and 200 mcg strengths of the drug product, since the highest possible daily exposure of individual impurity would be 200 mcg x (b) (4)% = (b) (4) mcg for (b) (4) (the highest acceptance criterion for identified impurity), which is less than the threshold for toxicological concern of (b) (4). All drug substance batches met the proposed specification. See NDA 204725 review by Dr. Xiaobin Shen for detailed description and discussion of the drug substance fluticasone furoate.

The drug product is Fluticasone Furoate Inhalation Powder 100 mcg and 200 mcg. The proposed commercial name is Trade name (b) (4) The drug product consists of single strip of (b) (4) blister (b) (4) containing either 30 blister (trade) or 14 blisters (institution and sample) of fluticasone furoate/lactose inhalation powder. The inhaler is packed together with a desiccant packet inside a (b) (4) aluminum foil tray. At time of drug administration, one actuation (the opening/turning of the inhalation mouthpiece to make the dose ready) and inhalation by the patient deliver one dose of aerosolized formulation released from one blister (100 mcg or 200 mcg). The drug product Trade name (b) (4) uses the same inhaler as the approved Breo Ellipta, except that only a single blister strip (b) (4) instead of two is enclosed within the device during manufacturing.

Executive Summary Section

The fluticasone furoate inhalation powder formulation contains only the micronized fluticasone furoate drug substance and lactose monohydrate, the latter functioning as (b) (4) . (b) (4) Each blister contains a nominal amount of 12.5 mg formulation (an up to (b) (4) manufacturing overage (not over fill) is used to ensure that the targeted blister fill is achieved). The formulation and manufacturing for the drug product are (b) (4) and the fluticasone furoate portion of the approved combination drug product. The revised acceptance criteria for DCU and APSD reflect the (b) (4) The proposed specification for the 200 mcg strength drug product provides adequate assurance for the quality (assay and impurity controls) and performance as well as (b) (4) (DCU and APSD). The analytical methods used for release and stability are (b) (4) for the approved combination drug product. All registration batches of the drug product met the proposed specification, and are consistent with the clinical batches in terms of quality and performance. Twenty four months of long term stability data, and 3 months of in-use stability data ate provided and were satisfactory. Some data points were observed to be slightly out of specification (OOS) during the stability studies (e.g., DCU and the coarse particle fraction of APSD). These OOS data points seem to be isolated events, and are not expected have significant clinical implications. All the tested attributes either do not display significant trending during stability or the trend lines are not expected to exceed the specification at the proposed shelf life of 30 months. The proposed shelf life of 30 months with 6 weeks of in-use period is granted. The post approval stability protocol and commitments are provided and are acceptable. The proposed labeling and container labels meet the requirements listed in 21CFR201 and are acceptable.

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

The product is to be administered as 1 inhalation once daily (either 100 mcg or 200 mcg) by the orally inhaled route only, and is indicated for maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older.

C. Basis for Approvability or Not-Approval Recommendation

NA.

III. Administrative

A. Reviewer's Signature

Edwin Jao, PhD
Review is digitally signed in DARRTS.

B. Endorsement Block

Craig Bertha, Ph D, Acting CMC lead, Division III, Branch VIII, ONDQA

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C. CC Block

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

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

/s/

EDWIN JAO
07/17/2014

CRAIG M BERTHA
07/18/2014
Signing for Dr. Eric Duffy

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications
NDA #: 205625 Received Date: 22-OCT-2013

APPLICATION INFORMATION

1. NEW DRUG APPLICATION NUMBER: N205625

Fluticasone Furoate (FF) is a steroid that has already been approved in combination with vilanterol for the inhalation powder (or dry powder inhaler or DPI) drug product of NDA 204275 (approved 10-MAY-2013) for long-term treatment of chronic obstructive pulmonary disease (COPD). The current FF DPI in 100 and 200 mcg/actuation strengths is proposed for the treatment of asthma in patients of 12 years of

(b) (4)

both

2. Drug Name: Fluticasone Furoate Inhalation Powder

3. RECEIVED DATE: 22-OCT-2013 (Applicant: Glaxo Group Ltd. (doing business as GlaxoSmithKline or GSK)

4. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM	LOA DATE	COMMENTS
(b) (4)	4	(b) (4)	(b) (4)	13-FEB-2013	Verify LOA in file; Last reviewed 25-
(b) (4)	3	(b) (4)		12-APR-2012	(b) (4)
(b) (4)	3	(b) (4)		17-DEC-2012	(b) (4)

					(b) (4)
(b) (4)	3	(b) (4)	(b) (4) (b) (4)	24-SEP-2012	
	3	(b) (4)	(b) (4)	18-MAR-2013	

b. Recommended Consults

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	☐	X	The Parametric Tolerance Interval Test (PTIT) requirements are the same as what was approved for NDA 204275. Request evaluation of stability data if trends in parameters will limit expiry, but unlikely considering the stability data observed for NDA 204275 (i.e., consult likely unnecessary).
Clin Pharm	☐	X	
EES	X	☐	Sub by ONDQA PM on 07-NOV-2013
Pharm/Tox	☐	X	Note, (b) (4) in the drug product, thus with a 200 mcg osure is limited to (b) (4) /day or less.
Methods Validation	☐	X	Left to reviewer discretion if any drug product methods are questionable and warrant assessment by the Agency laboratory.
EA	☐	X	Applicant claims environmental introduction concentration allows exclusion as per 21 CFR 25.31(b); reviewer can evaluate if any data are needed to support claim
New Drug Micro	☐	X	Two tier microbial quality specification proposed with water activity testing (tier 1) and a microbial limit testing (tier 2) (appears similar to what was approved in N204275). The microbiology team has been notified

			regarding the NDA.
CDRH	☐	X	Device is the same as approved for N204275
Other	X	☐	Reviewer may need consult for Near IR method for determination of water activity if it differs from that for approved N204275

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

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND	30-OCT-2003	48647	For Allergic Rhinitis
IND	**23-JUN-2005**	**70297**	**For Asthma**
IND	23-MAY-2008	77855	For Asthma and COPD
IND	(b) (4)	(b) (4)	For Asthma
NDA	28-JUN-2006	22051	For Allergic Rhinitis

d. Previous Communications with the Applicant to note (see module 1.6.3 for complete detail):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
Meeting minutes	11-FEB-2013	IND 70297	Pre-NDA meeting (DPARP)
Meeting minutes	08-APR-2013	IND 70297	CMC Pre-NDA meeting
Meeting minutes	16-MAR-2013	IND 70297	EOP2 meeting

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	

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?		
Yes	No	Biopharmaceutics Filing Issues
☐	☐	To be separately assessed by the biopharmaceutics team

Are there potential biopharmaceutics review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
☐	☐	See above

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	

CMC Summary:
Critical Issues and Complexities

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

Background: The drug substance is fluticasone furoate (FF), which is a corticosteroid to be used for the inhalation treatment of asthma in patients of 12 years or older. It is to be administered QD. The specification for the FF [redacted] approved N204275 (Breo Ellipta). The device is the Ellipta™, which, based on the trademark and information in [redacted] referenced Drug Master File [redacted] is the same device that is also used for the drug products of the approved N204275 (Breo Ellipta) and for N203975 [redacted] Ellipta, currently under review). The Ellipta™ device can contain two separate blister strips of pre-metered formulations, but for the N205625 drug product, only a single blister strip is being used for the commercial presentation of the drug product, as this is not a combination drug product.

The drug product is a pre-metered inhalation powder that includes a light gray and orange plastic inhaler, and it also includes a numerical dose counter. The pre-metered drug formulation is contained in a continuous blister strip of either 30 (commercial) or 14 (institutional) dosage units. The filled device is protected with a foil [redacted] tray with lid, that also contains a [redacted] desiccant unit. There are two strengths of the drug product, with each pre-metered blister containing either 100 or 200 mcg of fluticasone furoate drug substance with a lactose monohydrate [redacted]. The drug product formulation is shown below:

Start of Applicant Material

Table 1 Composition of Fluticasone Furoate Inhalation Powder

Inhalation Powder Strength	100 mcg	200 mcg	Function	Reference to Standard
Component	**Quantity (Per 12.5 mg Blister[1])**			
Fluticasone furoate micronised[2]	100 mcg	200 mcg	Active	GlaxoSmithKline[3]
Lactose monohydrate	[redacted]		[redacted]	JP, Ph. Eur and USP/NF[4]

Notes: mcg = microgram.
1. A manufacturing overage of up to [redacted] may be included in the final product.
2. The quantity of drug may be [redacted]
3. Details of the specification of the active ingredient are provided in m3.2.S.4.1. Specification.
4. Excipient complies with JP, Ph. Eur. and USP/NF and additional tests to ensure the quality for inhaled use. Details of the specification are provided in m3.2.P.4.1. Specification.

End of Applicant Material

The inhaler device used for the drug product is shown (exploded view) in the figure reproduced below (note that colors do not match the commercial version in Fig. 7).

Start of Applicant Material

Figure 7 Exploded View of the Inhaler Showing all Individual Components and Blister Strip

(b) (4)

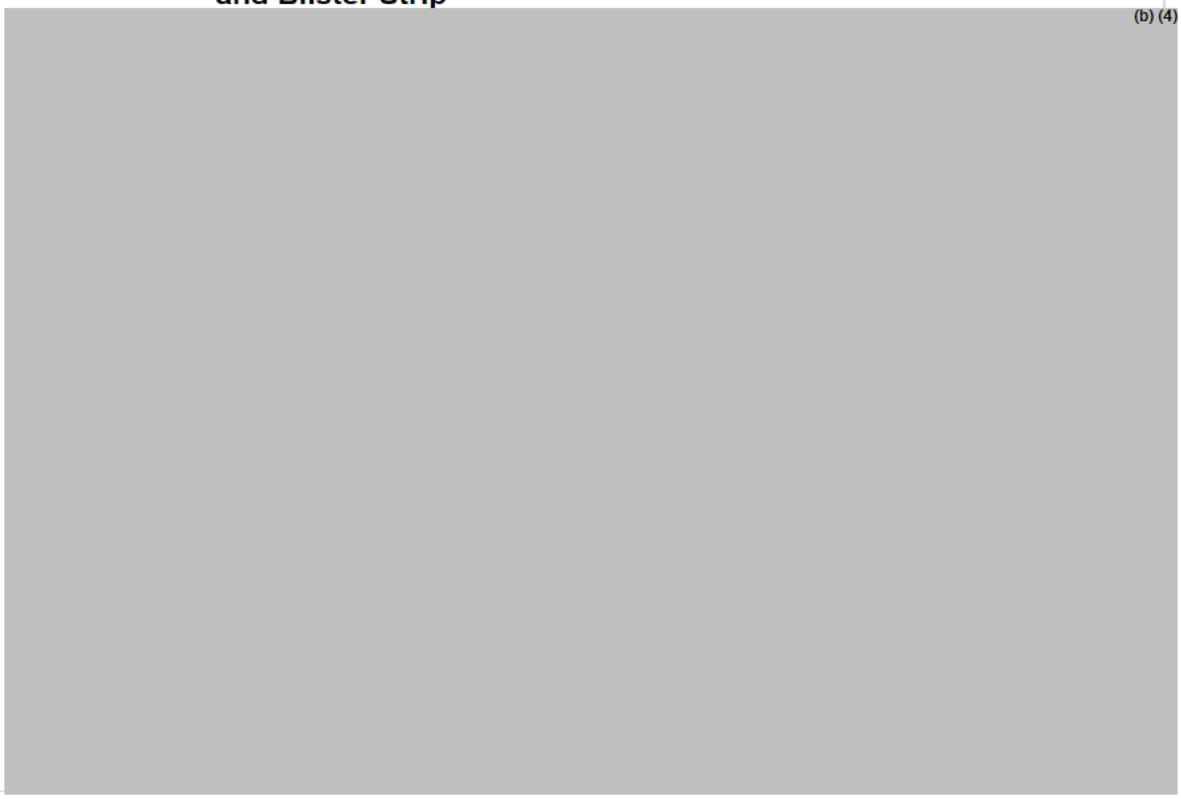

Figure 4 External View of the Inhaler

Note:
Image of a 30 dose inhaler is provided for illustrative purposes only.

End of Applicant Material

The applicant claims to have used Quality by Design principles in the development of their drug product, but little or no regulatory flexibility is being sought relative to previously approved inhalation powder drug products. GSK indicates that they have "incorporated knowledge gained during the development of Fluticasone Furoate/Vilanterol Inhalation Powder" of N204275.

Critical Issues and Complexities:

- As discussed at the CMC pre-NDA meeting, the applicant has not used the FF monotherapy product with two-blister strips (one a placebo strip), to support the proposed APSD acceptance criteria. However, for the low strength, they do propose to base the fine particle mass acceptance criterion range on (b) (4) A statistical approach alone is used to derive APSD acceptance criteria for the higher strength product. No (b) (4) is proposed for APSD testing, as the applicant had done for previous applications using the Ellipta device. To help evaluate the APSD and other related specification acceptance criteria, it is recommended that the reviewer compare what is proposed to what was approved for the related drug product of N204275.

- The applicant has used FF inhalation powder drug product with single strip (as to be marketed) but also with a second placebo strip, to produce a product with a better *in vitro* performance match to the combination drug product of NDA

204275. An evaluation (see review of 02-NOV-2011) of the comparative *in vitro* performance data provided in the 16-MAY-2011, amendment for IND 70297 had concluded that the single versus the two strip FF monotherapy products were sufficiently comparable in terms of the APSD fine particle mass (FPM). However, additional data in the 28-AUG-2012, meeting package did demonstrate that there were *in vitro* aerodynamic particle size distribution (APSD) differences when comparing the single-strip (to-be-marketed) and the two-strip (not to-be-marketed) monotherapy drug products (e.g., up to (b) (4) differences in fine particle mass and up to (b) (4) higher exposure for the single strip configuration). Note that the clinical/clinical pharmacology teams are aware of these differences (this issue was addressed at the pre-NDA meeting of 11-FEB-2013).

Considering the *in vitro* differences between the single and two strip FF monotherapy versions, the applicant was informed that it would (b) (4) However, the Agency agreed with the remainder of the proposal, i.e., to base the APSD acceptance criteria on batches that are representative of the proposed commercial product stored under long term stability conditions.

- Error's made by an analyst for several years in the testing for foreign particulate matter have resulted in the invalidation of some of the drug product stability data, which is captured in footnotes in the stability data tables. Data from later time points are substituted in some cases. The applicant claims that the "data generated are satisfactory and the conclusions drawn from FP Matter data are unaltered."

- There have been some changes made to the inhaler from Phase III to that intended for commercial marketing. These are outlined and said to be supported with data in P.2.4. Because the final device to be commercialized is approved, albeit in a two-strip presentation with different cap color, for N204275, these changes are largely of academic interest only for this application. Refer to the CMC reviews of N204275 for related evaluation.

- The applicant proposes a parametric tolerance interval test (PTIT) approach for the assessment of content uniformity of the emitted dose (i.e., delivered dose uniformity or DDU). The biometrics team will not need to be consulted as this approach does not differ from that with which we approved under N204275.

- The specification requirement for microbiology quality for the drug product is unique in that it proposes a two-tiered approach that uses hybrid testing, i.e., water activity testing for the first tier and standard microbial limits testing for the second tier (as approved for N204275).

- The specification for the drug product does not require the testing for drug-related

impurities at release (analogous to what was approved for N204275).

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.

Biopharmaceutics Filing Review:
Summary, Critical Issues and Complexities

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

Note: A separate filing review may be provided by the biopharmaceutics team.

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?	☐	☐		All pages examined for production of this IQA were legible
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X	☐	☐	The adequacy of the provided data will be determined during review

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	☐	☐	See module 1.1.2 of Sequence # 0000
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	☐	☐	Note that the associated continuation sheet includes a GSK R&D site at [redacted] (b) (4) that was responsible for collection of the primary stability data for the drug product and the micronized FF. This site is not intended to be used for these functions once commercial production takes place. Dr. E. Duffy has indicated in an electronic mail message of 07-NOV-2013, that this site does not need to be included in the EER.
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	☐	☐	See comment above in 7.

9	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	
1	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X	☐	☐	

* 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	☐	☐	It is left to the reviewer to decide whether or not supportive information or data are needed to support the request for categorical exclusion under 21 CFR 25.31(b); Applicant also claims that they know of no extraordinary circumstances regarding the EA.

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.* The reviewer should check for updates and amendments for DMFs already reviewed for CCS components in support of GSK's other applications that also have drug products using the Ellipta® device and associated protective packaging.

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	☐	However, this information is referenced to the applicant's NDA 22051.
14.	Does the section contain identification and controls of critical steps and intermediates of the DS (in process parameters?	☐	☐	☐	See comment for 13 above
15.	Does the section contain information on impurities?	☐	☐	☐	See comment for 13 above
16.	Does the section contain information regarding the characterization of the DS?	☐	☐	☐	See comment for 13 above
17.	Does the section contain controls for the DS?	☐	☐	☐	See comment for 13 above; the NDA contains the specification sheet for the drug substance, as well as batch analyses data.
18.	Has stability data and analysis been provided for the drug substance?	☐	☐	☐	See comment for 13 above
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	☐	☐	☐	See comment for 13 above
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	☐	☐	See comment for 13 above
21.	Does the section contain container and closure information?	☐	☐	☐	See comment for 13 above

F. DRUG PRODUCT (DP)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
22.	Does the section contain quality controls of excipients?	X	☐	☐	
23.	Does the section contain information on composition?	X	☐	☐	The reviewer should be aware that the applicant is using an (b) (4) overage of the formulation blend to "compensate for drug losses during blister filling." A justification for the overage is covered in P.2.3.
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X	☐	☐	
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	☐	☐	Refer to P.3.4 for control of critical steps; there are no intermediate products associated with the drug product manufacture
26.	Is there a batch production record and a proposed master batch record?	X	☐	☐	See 3.2.R
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X	☐	☐	There is limited description of earlier formulations of the drug product having been considered (see Tables 12 & 13 in P.2.2). Clinical studies used a two strip version of the drug product that contained a placebo second strip (in an attempt to more closely match the *in vitro* performance in terms of FF delivery, when compared to the combination drug product of NDA 204275, FF and vilanterol inhalation powder). The commercial drug product will not contain the second (placebo) strip (see section on critical issues and complexity above for more details).
28.	Have any biowaivers been requested?	☐	X	☐	

29.	Does the section contain description of to-be-marketed container/closure system and presentations?	X	☐	☐	Also see DMF (b) (4) for the (b) (4) (b) (4)
30.	Does the section contain controls of the final drug product?	X	☐	☐	The reviewer can assess the drug product control relative to what was approved for N204275 to assure consistency, particularly for unique features (e.g., PTIT for DDU, APSD retesting proposal, two tier/method microbiology testing, no impurities testing at release); note that NDAs 203975 and 205382 are also currently under review and use the Ellipta® drug product device and associated protective packaging.
31.	Has stability data and analysis been provided to support the requested expiration date?	X	☐	☐	Twenty-four months of long term (25°C/60%RH) stability data are provided for three batches manufactured at the commercial site (b) (4) using a "representative commercial process." The scale was (b) (4) and (b) (4) kg (said to be "typical"), but packaging into the protective packages was said to be pilot scale "representative of production scale." The inhaler used for these batches was that to be used commercially after approval. No statistical analyses have been performed and the applicant proposes a 30 month shelf-life. Three months of in-use stability data were collected on new and aged drug product (in-use period is 30 days). A six-week in-use period is requested.
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	X	☐	☐	The applicant's QbD approach is outlined in P.2.1. The only "regulatory flexibility" that is observed is the absence of testing of the drug product for impurities at release (same approach as for approved N204275). QbD principles were also applied in the method development (see P.5.3). No design spaces are proposed.
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	X	☐	

G. METHODS VALIDATION (MV)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
34.	Is there a methods validation package?	X	☐	☐	See 3.2.R

H. MICROBIOLOGY					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	☐	☐	X	Product is not sterile

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.	☐	☐	X	Describe filing issues here or on additional sheets
41.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	☐	X	☐	Describe potential review issues here or on additional sheets

REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

Craig M. Bertha, Ph.D., Acting CMC Lead
Eric Duffy, Ph.D., Division Director

{See appended electronic signature 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
11/25/2013

ERIC P DUFFY
11/26/2013