CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205434Orig1s000

CHEMISTRY REVIEW(S)

M E M O R A N D U M

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

DATE: July 24, 2014
FROM: Nina Ni, Ph.D., Review Chemist, Branch IV, DNDQA II/ONDQA
THROUGH: Danae Christodoulou, Ph.D., Acting Branch Chief, Branch VII, DNDQA III/ONDQA
SUBJECT: Addendum to CMC Review #1 for NDA 205434
TO: NDA 205434

In my CMC Review #1, dated 06/13/2014, this NDA was recommended for approval pending on the following issue:

- The overall recommendation regarding manufacturing sites from the Office of Compliance was pending.

Recently, the Office of Compliance has issued an overall "Acceptable" recommendation in the EES (establishment evaluation system), see the attachment. Since the pending issue has been resolved on 07/17/2014, this NDA is recommended for approval.

Attachment: EER reports

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 205434/000	**Sponsor:**	GLAXOSMITHKLINE CONS
Org. Code:	560		1500 LITTLETON RD
Priority:	8		PARSIPPANY, NJ 070543884
Stamp Date:	23-SEP-2013	**Brand Name:**	FLONASE ALLERGY RELIEF (FLUTICASONE PROP
PDUFA Date:	23-JUL-2014	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	24-MAY-2014	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; SPRAY, METERED; FLUTICASONE PROPIONATE; .05MG	

FDA Contacts:	N. NI	Prod Qual Reviewer	3017965296
	R. MCKNIGHT	Product Quality PM	3017961765
	J. LEE	Regulatory Project Mgr	3017963599
	S. DE	Team Leader	3017961664

Overall Recommendation:	ACCEPTABLE	on 17-JUL-2014	by E. DOBBIN	()	2404024266
	PENDING	on 21-FEB-2014	by EES_PROD		
	PENDING	on 07-NOV-2013	by EES_PROD		
	PENDING	on 24-OCT-2013	by EES_PROD		
	PENDING	on 23-OCT-2013	by EES_PROD		

Establishment:	**CFN:** 9610411 **FEI:** 3003262904		
	GLAXO OPERATIONS UK LIMITED PRIORY STREET		
	WARE, HERTFORDSHIRE, UNITED KINGDOM		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE (b) (4)		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	28-OCT-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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

GLAXO WELLCOME MANUFACTURING PTE LIMITED
1 PIONEER, SECTOR 1

SINGAPORE, , SINGAPORE

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 28-OCT-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

GLAXOSMITHKLINE
HARMIRE ROAD

BARNARD CASTLE, , UNITED KINGDOM

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STABILITY TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-OCT-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** **FEI:** 3003215057

GLAXOSMITHKLINE
COBDEN STREET

MONTROSE, , UNITED KINGDOM

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-FEB-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 9615283 **FEI:** 3002807086 GLAXOSMITHKLINE INC 7333 MISSISSAUGA NORTH ROAD MISSISSAUGA, ONTARIO, CANADA		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	25-FEB-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** 9611905 **FEI:** 3002807436 GLAXOWELLCOME PRODUCTION 23 RUE LAVOISIER B.P. 118 EVREUX, , FRANCE		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE (b) (4)		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	17-JUL-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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/s/

NINA NI
07/24/2014

SWAPAN K DE
07/24/2014

NDA 205434

FLONASE® Allergy Relief
(fluticasone propionate) Nasal Spray

GlaxoSmithKline Consumer Healthcare

Nina Ni, Ph. D.
Office of New Drug Quality Assessment
Division II, Branch IV

For the Division of
Nonprescription Clinical Evaluation

CHEMISTRY REVIEW #1

Table of Contents

Chemistry Review Data Sheet

1. NDA 205434

2. REVIEW #: 1

3. REVIEW DATE: 13-Jun-2014

4. REVIEWER: Nina Ni

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
Rx NDA 20121	20-Nov-1991

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	23-Sept-2013
Amendment 0005	07-Jan-2014
Amendment 0007	17-Jan-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	GlaxoSmithKline Consumer Healthcare
Address:	1500 Littleton Rd. Parsippany, NJ 07054
Representative:	Gregory D. Smith
Telephone:	973-889-2540

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Flonase® Allergy Relief
Non-Proprietary Name (USAN): Fluticasone Propionate
Chem Type: Type 8 – Partial Rx to OTC Switch
Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: Corticosteroid with anti-inflammatory activity

11. DOSAGE FORM: Nasal Spray

12. STRENGTH/POTENCY: 50 µg/actuation

13. ROUTE OF ADMINISTRATION: Intranasal

14. Rx/OTC DISPENSED: ___Rx _X_OTC

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

_____SPOTS product – Form Completed

__X___Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

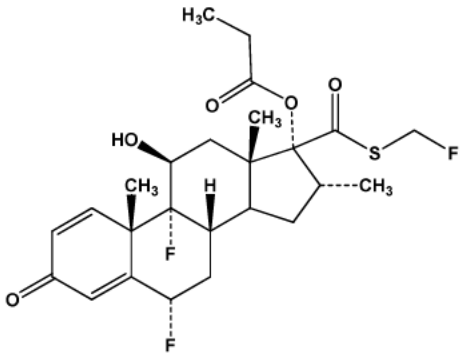
_____NANO product – Form Completed (See Appendix A.4)

__X___Not a NANO product

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

Chemical Name: S-(fluoromethyl)6α,9-difluoro-11β-17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate

Structural Formula:



Molecular Formula: $C_{25}H_{31}F_3O_5S$

Molecular Weight: 500.6 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	III		(b) (4)	1&4	Adequate	7/16/2009	Reviewed by Z. Ling
	III			4	Adequate	NA	NA
	III			1&4	Adequate	06/24/2013	Reviewed by Y. Lin
	III			1&4	Adequate	10/30/2013	Reviewed by E. Englund
	III			1&4	Adequate	07/30/2010	Reviewed by C. Bertha
	III			1&4	Adequate	10/30/2013	Reviewed by E. Englund
	III			1&4	Adequate	10/03/2011	Reviewed by C. Bertha

[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
NDA	20121	Flonase® Nasal Spray

18. STATUS

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Microbiology	Approval	05/30/2014	John Metcalfe, Ph.D.
EES	Pending		
Biopharm	N/A		
Methods Validation	Not required. No novel methods.		
Toxicology/Clinical	N/A		
EA	Conducted by CMC reviewer. Granting the categorical exclusion as per 21 CFR 25.31(b).	03/12/2014	Nina Ni, Ph.D.

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X_ Yes ____ No If no, explain reason(s) below:

20. EES INFORMATION

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**

Manufacturer	Glaxo Wellcome Manufacturing Pte Ltd 1 Pioneer Sector 1 Jurong, Singapore 628413	FEI: 3002807079 CFN: 9611205	Accepted based on profile 28-Oct-2013
Manufacturer	GlaxoSmithKline Cobden St. Montrose, UK	FEI: 3003215057	Accepted based on profile 21-Feb-2013
(b) (4)	Glaxo Wellcome Production Zone Industrielle No. 2 23 Rue Lavoisier, France 27091	FEI: 3002807436 CFN: 9611905	Inspected on 04/07/14 to 04/11/14
	Glaxo Wellcome Operations Priory Street Ware, Hertfordshire, UK SG12 0DJ	FEI: 3003262904 CFN: 9610411	Accepted based on profile 28-Oct-2013
Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
Manufacturing, Quality Control and Product Release Testing, Primary Packaging, Labeling, Secondary Packaging	GlaxoSmithKline, Inc. 7333 Mississauga North Road Mississauga, Ontario Canada L5N 6L4	FEI: 3002807086 CFN: 9615283	Accepted based on profile 19-Feb-2014
Stability Tester	Glaxo Operations UK Ltd. Harmire Road Barnard Castle, Durham UK DL12 8DT	FEI: 3003722390 merged into 3002807078	Accepted based on profile 24-Oct-2013

Chemistry Review for NDA 205434

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has not made an overall "Acceptable" recommendation for the facilities involved in this NDA.

The labeling is under review by DMEPA and the Clinical Division of Nonprescription Clinical Evaluation. CMC information provided in the labeling is consistent with the information provided in the NDA.

From CMC perspective, this NDA is recommended for approval pending cGMP recommendation. A final recommendation will be made after OC issues an overall cGMP recommendation.

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)

NDA 205434 was submitted for a partial switch from prescription (Rx) to over the counter (OTC) use. Thus, the original Rx NDA 20121 as well as its CMC supplements and annual reports, which are reviewed and found satisfactory up to date, are referenced for the CMC section of this NDA.

(1) Drug Substance

The drug substance fluticasone propionate used to manufacture the proposed OTC product Flonase® Allergy Relief in this application is unchanged from that used for the approved Rx Flonase® Nasal Spray.

Information for the drug substance is cross referenced to the Applicant's approved Flonase Nasal Spray NDA 20121, which are reviewed and found satisfactory up to date.

(2) Drug Product

The proposed OTC Flonase Allergy Relief Nasal Spray, 50 µg is exactly the same in components and composition as the approved Rx Flonase Nasal Spray, 50 µg, with spray configurations of (b) (4), 60, (b) (4), 120, and (b) (4) actuations. The spray configurations for the approved Rx drug product marketed in US are 50 actuations for the physician sample and 120 actuations for commercial use. The Flonase Allergy Relief Nasal Spray, 50 µg is a white, (b) (4), aqueous suspension of (b) (5) fluticasone propionate (b) (4) for topical administration to the nasal mucosa by means of a metering, atomizing spray pump.

All stability batches were manufactured using the proposed commercial manufacturing process at the intended commercial manufacturing site. The

stability data indicate that the drug product physically and chemically stable with no significant change when stored at 30°C for up to 18 months (b) (4) All tested attributes are within the specification. The stability data support the proposed expiration dating period of (b) (4) 24 months for the other actuation configurations when stored at 4 to 30 C (39 to 86°F). The proposed shelf life and storage condition for 60, (b) (4), 120, (b) (4) actuation configurations in (b) (4) bottles are identical to the approved Rx product. (b) (4)

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

Flonase Allergy Relief Nasal Spray, 50 µg for topical administration to the nasal mucosa by means of a metering, atomizing spray pump.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments ultimately provided adequate information on the chemistry, manufacturing, and controls to assure identity, strength, purity, and quality of the drug product, Flonase Allergy Relief Nasal Spray, 50 µg. The CMC deficiencies communicated to the applicant during the review have been resolved satisfactorily.

An acceptable cGMP recommendation by the Office of Compliance has not been made yet up to date.

The labeling is under review by DMEPA and the Clinical Division of Nonprescription Clinical Evaluation. CMC information provided in the labeling is consistent with the information provided in the NDA.

From CMC perspective, this NDA is recommended for approval pending cGMP recommendation. A final recommendation will be made after OC issues an overall cGMP recommendation.

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/s/

NINA NI
06/13/2014

DANAE D CHRISTODOULOU
06/13/2014
I concur with the reviewer's conclusion and recommendation

Lee, Jung E (OND)

ɔm:	ees_admin@fda.gov
ɹent:	Thursday, July 17, 2014 1:12 PM
To:	Godwin, Francis; Lee, Jung E (OND); Salganik, Maria*; Spain, Nancy *; Ni, Nina; McKnight, Rebecca; De, Swapan K; Kyada, Yogesh*
Subject:	Overall OC Recommendation NDA 205434/000 Decision: ACCEPTABLE, Decision Date: 07/17/2014, Re-evaluation Date: 09/25/2015
Follow Up Flag:	Follow up
Flag Status:	Flagged
Categories:	Print

This is a system generated email message to notify you that the
Overall Compliance Recommendation has been made for the above Application.

For general questions about how to use EES in your work, send
an email to EESQUESTIONS (EESQUESTIONS@cder.fda.gov).
To contact the EES technical staff, send an email to
CDER EES Help (EESHELP@fda.hhs.gov). Thank you.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

ation:	NDA 205434/000	**Sponsor:**	GLAXOSMITHKLINE CONS
ode:	560		1500 LITTLETON RD
Priority:	8		PARSIPPANY, NJ 070543884
Stamp Date:	23-SEP-2013	**Brand Name:**	FLONASE ALLERGY RELIEF (FLUTICASONE PROP
PDUFA Date:	23-JUL-2014	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	24-MAY-2014	**Product Number; Dosage Form; Ingredient; Strengths**	001; SPRAY, METERED; FLUTICASONE PROPIONATE; .05MG

FDA Contacts:	N. NI	Prod Qual Reviewer	3017965296
	R. MCKNIGHT	Product Quality PM	3017961765
	J. LEE	Regulatory Project Mgr	3017963599
	S. DE	Team Leader	3017961664

Overall Recommendation:	ACCEPTABLE	on 17-JUL-2014	by E. DOBBIN	()	2404024266
	PENDING	on 21-FEB-2014	by EES_PROD		
	PENDING	on 07-NOV-2013	by EES_PROD		
	PENDING	on 24-OCT-2013	by EES_PROD		
	PENDING	on 23-OCT-2013	by EES_PROD		

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

GLAXO OPERATIONS UK LIMITED
PRIORY STREET

WARE, HERTFORDSHIRE, UNITED KINGDOM

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE (b) (4)

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 28-OCT-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 9611205 **FEI:** 3002807079		
	GLAXO WELLCOME MANUFACTURING PTE LIMITED 1 PIONEER, SECTOR 1		
	SINGAPORE, , SINGAPORE		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	28-OCT-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** 9610421 **FEI:** 3002807078		
	GLAXOSMITHKLINE HARMIRE ROAD		
	BARNARD CASTLE, , UNITED KINGDOM		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-OCT-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** **FEI:** 3003215057		
	GLAXOSMITHKLINE COBDEN STREET		
	MONTROSE, , UNITED KINGDOM		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	25-FEB-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

'shment: **CFN:** 9615283 **FEI:** 3002807086

GLAXOSMITHKLINE INC
7333 MISSISSAUGA NORTH ROAD

MISSISSAUGA, ONTARIO, CANADA

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-FEB-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 9611905 **FEI:** 3002807436

GLAXOWELLCOME PRODUCTION
23 RUE LAVOISIER B.P. 118

EVREUX, , FRANCE

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE (b) (4)

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-JUL-2014

'on: ACCEPTABLE

n: DISTRICT RECOMMENDATION

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre-Marketing Applications (Original)

I. Review Cover Sheet
II. Application Detail
III. Filing Checklist
IV. Manufacturing Summary
V. Overall Conclusions and Recommendations

I. Review Cover Sheet

1. OMPQ Reviewer: Juandria Williams/Robert H. Wittorf

2. NDA/BLA Number: **NDA 205434**
   Submission Date: **September 23, 2013**
   21st C. Review Goal Date: **TBD**
   PDUFA Goal Date: **July 23, 2014**

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Flonase® Allergy Relief
Established or Non-Proprietary Name (USAN) and strength:	Fluticasone Propionate Nasal Spray, 50 mcg
Dosage Form:	Spray, metered

4. SUBMISSION PROPERTIES:

Review Priority :	STANDARD
Applicant Name:	GlaxoSmithKline Consumer Healthcare
Responsible Organization (OND Division):	DNCE

II. Application Detail

1. INDICATION: For the relief of the nasal and ocular symptoms associated with allergic (b) (4) rhinitis (b) (4) years and older.
2. ROUTE OF ADMINISTRATION: Intranasal
3. STRENGTH/POTENCY: 50 mcg
4. Rx/OTC DISPENSED: ☐Rx xOTC
5. ELECTRONIC SUBMISSION (yes/no)? Yes
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		x		
2.	Breakthrough Therapy Designation		x		
3.	Orphan Drug Designation		x		
4.	Unapproved New Drug		x		
5.	Medically Necessary Determination		x		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		x		
7.	Rolling Submission		x		
8.	Drug/device combination product with consult		x		
9.	Complex manufacturing		x		
10.	Other (e.g., expedited for an unlisted reason)		x		

III. FILING CHECKLIST

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

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	**Yes**	**No**	**Comment**
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	x		DS and DP sites in 356h; DP sites also listed in 3.2.P.2.1
12.	Do all sites indicate they are ready to be inspected (on 356h)?	x		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	x		DP: 3.2.P.2.1 and 356h DS: listed in 356h
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	x		DP: 3.2.P.2.1; and 356h DS: 356h
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #?	x		
	2. Do comments in EES indicate a request to participate on inspection(s)?		x	
	3. Is this first application by the applicant?		x	

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
16.	Have any Comparability Protocols been requested?		x	

IMA CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
17.	Does this application fit one of the EES Product Specific Categories?		x	
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion?	x		
	Have all EERs been updated with final PAI recommendation?	x		
19.	**From a CGMP/facilities perspective, is the application fileable?** If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	x		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements? No

Nanotechnology	RTRT Proposal	PAT	Drug/Device Combo
☐	☐	☐	☐

PET	Design Space	Continuous Mfg	Naturally derived API
☐	☐	☐	☐

Other (explain):

Manufacturing Highlights

The subject NDA provides for a change in the marketing status of the indication for the relief the nasal and ocular symptoms associated with allergic (b) (4) rhinitis (b) (4) (b) (4) for Flonase Nasal Spray from Rx (as provided for in NDA 20121) to over-the-counter (OTC).

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		x	DS process (b) (4) approved for Rx under NDA 20121

The drug substance used to manufacture the proposed OTC finished product is the same as that for the approved and marketed Rx Flonase Nasal spray under NDA 20121.

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		x	DP process (b) (4) approved for Rx under NDA 20121

Per Section 3.2.P.3.3 "Description of Manufacturing Process and Process Controls" The drug product is manufactured (b) (4) No critical issues with respect to the manufacturing of the drug product are noted. In 2002, an inspection (Facility FEI#3002807078, GlaxoSmithKline, Inc.) (b) (4) was conducted and appropriate corrective actions were implemented. The inspection was classified as NAI.

3. Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues.

The facilities used to manufacture the finished product remain unchanged. A review of facility inspectional history and product was conducted. No facility-related risks were identified at the time of this review.

4. Drug Product Facility Inspectional History that could impact the manufacturing of this product

The drug product site was reviewed for inspectional trends, product specific issues, and manufacturing processes. As noted above, a 2002 on-site inspection was conducted for the drug product manufacturer under NDA 20121, which was classified NAI. No additional facility inspectional history that could impact the drug product is noted. All sites are currently approved under NDA 20121 for Rx version of the drug product.

Additional information not covered above

No additional information

Manufacturing Facilities Chart (generated from 602A DARRTS report and OMPQ macro):

Establishment Name	EER Creation Date	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Inspection History, Dates, Classifications	PAI Recommendation	Most Recent Milestone	Most Recent EER Compliance Status	Comment
GLAXO WELLCOME MANUFACTURING PTE LIMITED	10/24/2013	3002807079	ROW	SGP	Manufacturing	CSN	11/12-16/2012 VAI	28-Oct-2013 Based on Profile	OC RECOMMENDATION	AC	EER Re-eval: 16-Nov-2015
GLAXOWELLCOME PRODUCTION	10/24/2013	3002807436	WEU	FRA	Manufacturing (b) (4), Testing	CSN	3/16-19/2012 NAI	28-Oct-2013 GMP	ASSIGNED INSPECTION TO (b) (4)	PN	In DO Mailbox for CSN profile (not covered in 2012, last covered in 2009)- ADM, TCM, and POW covered in 2012
GLAXOSMITHKLINE	11/7/2013	3003215057	WEU	GBR	Manufacturing	CSN	05/27-31/2013 VAI	07-Nov-2013 Based on Profile	OC RECOMMENDATION	AC	EER Re-eval: 31-May-2016
GLAXO OPERATIONS UK LIMITED	10/24/2013	3003262904	WEU	GBR	Manufacturing (b) (4), Testing	CSN	4/17-25/2013 VAI	28-Oct-2013 Based on Profile	OC RECOMMENDATION	AC	EER Re-eval: 16-Nov-2015
GLAXOSMITHKLINE	10/2/2013	3002807078	WEU	GBR	Stability Testing	CTL	4/292012-5/9/2012 VAI	24-Oct-2013 Based on Profile	OC RECOMMENDATION	AC	EER Re-eval: 09-May-2016 Merged FEI: 3003722390
GLAXOSMITHKLINE INC	10/2/2013	3002807086	AME	CAN	Manufacturing (DP), Release Testing, Packaging	LIQ	9/19/2012-2/05/2013 NAI	24-Oct-2013 GMP	UNDER REVIEW	PN	Previously inspected in September 2013 but only 1 of 7 profiles was updated even though (b) (4) coverage was claimed

For each EER, indicate PAI recommendation on the Manufacturing Facilities Chart above (e.g., PS, GMP, 10 Day, AC based on file review). This is the recommendation that will be entered into EES.

V. Overall Conclusions and Recommendations

Is the application fileable? Yes

Based on Section IV, is a KTM warranted for any PAI? No

Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? No

Comments for 74 Day Letter

1.
2.
3.

REVIEW AND APPROVAL

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

/s/

ROBERT H WITTORF
12/20/2013

MAHESH R RAMANADHAM
12/20/2013

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 205-434
2. DATES AND GOALS:

Letter Date: 09/23/2013	Submission Received Date : 09/23/2013
PDUFA Goal Date: 07/23/2014	

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Flonase Allergy Relief
Established or Non-Proprietary Name (USAN):	Fluticasone propionate aqueous nasal spray, 50 mcg/metered spray
Dosage Form:	Nasal spray
Route of Administration	Intranasal
Strength/Potency	50 mcg/metered spray
Rx/OTC Dispensed:	OTC

4. INDICATION: Temporarily relieves these symptoms due to hay fever, other respiratory allergies, (b) (4) nasal congestion, runny nose, sneezing, itchy nose, itchy, watery eyes.

5. DRUG SUBSTANCE STRUCTURAL FORMULA:

   S-(fluoromethyl)6α,9α-difluro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate,17-propionate

6. NAME OF APPLICANT (as indicated on Form 356h):

   GlaxoSmithKline Consumer Healthcare
   1500 Littleton Road
   Parsipanny, NJ 07054

7. SUBMISSION PROPERTIES:

Review Priority:	Standard
Submission Classification (Chemical Classification Code):	Type 8- Partial Rx to OTC Switch
Application Type:	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	Division of Nonprescription Clinical Evaluation (DNCE)

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	X		
Clinical Pharmacology	X		
Establishment Evaluation Request (EER)	X		
Pharmacology/Toxicology	X		
Methods Validation	X		
Environmental Assessment	X		
CDRH		X	
Other		X	

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes
CMC Filing Issues:
1. None

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? No
CMC Comments for 74-Day Letter:
1. Provide a Letter of Authorization (LoA) to the Drug Master File (DMF (b) (4)) supporting the dust cap. 2. Submit updated stability data including updated stability summary for the NDA batches. 3. Submit stability data to support your proposed storage statement "Store between 4° and 30°C (39° and 86°F)".

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes No
Biopharmaceutics Filing Issues:
1. N/A

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes No
Biopharmaceutics Comments for 74-Day Letter:
1.

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes No
Microbiology Filing Issues:
See Microbiology Filing Review for details and for any potential Microbiology review issues. (Microbiology filing review is pending at this time).

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	

Is a team review recommended?	No
Suggested expertise for team:	

Summary of Critical Issues and Complexities

Drug Product:

- Changes between the approved Rx and proposed OTC drug product are included in Module 2 which should be evaluated in-depth.
- (b) (4)
- The applicant proposed that product label will have the storage statement "Store between 4^{o} and 30^{o}C (39° and 86°F)". (b) (4)
- Has adequate justification been provided for the microbial limits test in the release specification of the drug product? Microbiological Attributes section 3.2.P.2.5 is included and needs a consult review by a microbiologist.
- It is noted that stability data for only (b) (4), 2 batches for 60 spray count, 1 batch each for 120 (b) (4) spray count configuration is bracketed by the 60 and 120 spray configurations. Is the submitted 12-month stability data (b) (4) for the drug product enough to

support the proposed 24-month shelf-life of the drug products for all configurations (b) (4) 60, (b) (4), 120 (b) (4)?

Initial Quality Assessment

Summary:

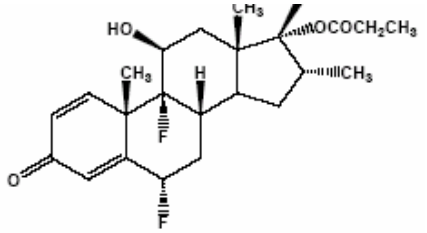
This is a CTD formatted NDA application for Flonase® (fluticasone propionate nasal spray, 50 mcg) submitted as a 505(b)(1) NDA with reference to previously approved Rx NDA for Flonase (NDA 20-121). *Flonase Allergy Relief* Nasal Spray, 50 mcg is exactly the same in composition as the approved Rx Flonase® Nasal Spray, 50 mcg. It is a white, (b) (4) suspension of (b) (4) fluticasone propionate (b) (4)) for topical administration to the nasal mucosa by means of a metering, atomizing spray pump.

Flonase was originally approved in 1994 for the management of the nasal symptoms of seasonal (SAR) and perennial (PAR) allergic rhinitis in adults and adolescents 12 years of age and older. However, Rx Flonase approval was expanded later to include pediatric patients (4 years of age and older) and patients with perennial non-allergic rhinitis (PNAR). GSK CH is seeking approval for the use of OTC *Flonase Allergy Relief* for the temporary relief of the following symptoms due hay fever, other respiratory allergies (b) (4) nasal congestion, runny nose, sneezing, itchy nose, and itchy, watery eyes.

Flonase is currently sold as a nonprescription treatment for allergies in 13 countries (UK, New Zealand, Ireland, Denmark, Finland, Sweden, China, Latvia, Estonia, South Africa, Singapore and Slovenia.

Drug Substance:

The Drug substance, Fluticasone Propionate used to manufacture the proposed OTC finished product, *Flonase Allergy Relief* Nasal Spray, 50 mcg is identical with the drug substance used for the approved and marketed Rx Flonase® Nasal Spray NDA 20-121. Therefore, drug substance section is cross referenced to the approved Rx Flonase® Nasal Spray NDA 20-121 as agreed in the Pre-NDA meeting. To facilitate review, the applicant has provided a table (Section 2.3.S) to locate appropriate (updated) information. Chemical Structure and formula is shown below (taken from NDA 21-121)



Fluticasone propionate
Molecular formula: $C_{25}H_{31}F_3O_5S$
Molecular weight: 500.57
CAS Registry Numbers: 80474-14-2; 90566-53-3 (fluticasone base).

Specification for Fluticasone Propionate (b) (4) **)**
Taken from NDA 20-121

(b) (4)

(b) (4)

Drug Product:

The OTC *Flonase Allergy Relief* Nasal Spray, 50 mcg is identical in composition as the approved Rx Flonase® Nasal Spray, 50 mcg. There is no change to the drug product composition, manufacturing process, site of manufacture or the process controls. In addition, it will be dispensed using the same metered-dose spray pump as the Rx product. Proposed OTC Flonase Allergy Relief Nasal Spray drug product will be different from the Rx product regarding container closure system. (b) (4)

The appearance of OTC drug product dust cover will be (b) (4) green with a debossed logo instead of Rx product dust cover which is (b) (4) green without a logo.

(b) (4)

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

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

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**	**Comment**
1.	Is the CMC section organized adequately?	X		Refers to NDA 20-121
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?		X	Refers to NDA 20-121
3.	Are all the pages in the CMC section legible?	X		Refers to NDA 20-121
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		Refers to NDA 20-121

B. FACILITIES*				
*	**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.**			
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		Refers to NDA 20-121; Section 1.1.2
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			N/A

	Parameter	Yes	No	Comment
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		Section 1.1.2
8.	Are drug product 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		5 manufacturing facilities are entered to the EES system for inspection.

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory 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		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		Justification is included in Module 1.12.14

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?		X	Refers to NDA 20-121
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		X	Refers to NDA 20-121
14.	Does the section contain information regarding the characterization of the DS?		X	Refers to NDA 20-121
15.	Does the section contain controls for the DS?		X	Refers to NDA 20-121
16.	Has stability data and analysis been provided for the drug substance?		X	Refers to NDA 20-121
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		Refers to NDA 20-121
20.	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		Refers to NDA 20-121
21.	Is there a batch production record and a proposed master batch record?	X		Refers to NDA 20-121
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		Refers to NDA 20-121
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?		X	
25.	Does the section contain controls of the final drug product?	X		Refers to NDA 20-121
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	X		

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?		X	Refers to NDA 20-121

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	X		Refers to NDA 20-121

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		Refers to NDA 20-121

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (5)	III		(b) (5)	07/12/2013	
	III			07/03/2013	
	III			04/30/2013	
	III			04/30/2013	
				04/30/2013	
				04/30/2013	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		

33.	Have the immediate container and carton labels been provided?	X		

{When applicable, paste the Biopharmaceutics Filing Checklist table here. Whether a Biopharmaceutics Filing Checklist table is added here or not, delete this note.}

ONDQA Initial Quality Assessment (IQA) and Filing Review
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This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page}
Swapan K De, Ph.D.
CMC-Lead
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment

{See appended electronic signature page}
NAME N/A
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Danae Christodoulou, Ph.D.
Acting Branch Chief
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment

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

/s/

SWAPAN K DE
11/12/2013

DANAE D CHRISTODOULOU
11/12/2013