CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205434Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

30 May 2014

NDA: 205434

Drug Product Name
Proprietary: Flonase Allergy Relief
Non-proprietary: Fluticasone Proprionate Aqueous Nasal Spray

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
21 SEP 2013	23 SEP 2013	25 SEP 2013	30 SEP 2013
23 MAY 2014	23 MAY 2014	N/A	N/A

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

Name of Reviewer: John W. Metcalfe, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: 505 (b)(1)

2. SUBMISSION PROVIDES FOR: The conversion of an approved drug from requiring a prescription to over the counter.

3. MANUFACTURING SITE:
GlaxoSmithKline Inc.
7333 Mississauga Rd North
Misssissauga
Ontario L5N 6L4
Canada

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:
- Aqueous Suspension
- Nasal Spray
- 50 µg/metered spray

5. METHOD(S) OF STERILIZATION: The product is not sterile.

6. PHARMACOLOGICAL CATEGORY: Anti-allergy.

B. SUPPORTING/RELATED DOCUMENTS: The subject NDA references NDA 20-121 for all information pertaining to the drug product manufacturing process.

C. REMARKS:
The application is submitted electronically in the CTD format.

A Microbiology Information Request was forwarded to the applicant by the OND Project Manager on 06 December 2013. The Information Request is copied below in italic font.

We acknowledge that NDA 205434 references NDA 20-121 for all information pertaining to the drug product manufacturing process, controls and release testing. Currently, CDER is implementing a Burkholderia cepacia testing policy for aqueous, non-sterile drug products which was not in place at the time of approval of NDA 20-121 (OCT 1994). Please note the following comment and request for additional information.

Non-sterile aqueous drug products may potentially be contaminated with organisms in the Burkholderia cepacia complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can

survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see PDA J Pharm Sci Tech 2011; 65(5): 535-43.
In order to control for the presence of BCC in your product you should consider the following:

1. *Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.*

2. *Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.*

As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product without preservatives to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.

For more information, we refer you to Envir Microbiol 2011; 13(1):1-12 and J. Appl Microbiol 1997; 83(3):322-6.

File Name: N205434R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 205434 is recommended for approval from the standpoint of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – Not applicable.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The bulk drug aqueous suspension is (b) (4)

B. Brief Description of Microbiology Deficiencies – There are no microbiology deficiencies identified.

C. Assessment of Risk Due to Microbiology Deficiencies – Not applicable.

D. Contains Potential Precedent Decision(s) ☒No

III. Administrative

A. Reviewer's Signature _____

John W. Metcalfe, Ph.D.
Senior Microbiology Reviewer
CDER/OPS/NDMS

B. Endorsement Block_____

Bryan S. Riley, Ph.D.
Team Leader (Acting)
CDER/OPS/NDMS

C. CC Block
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE

The drug substance is not the subject of this review.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product**
  The drug product is an aqueous suspension presented in an amber glass bottle.

- **Drug product composition**
  The batch formula is shown in table 1, which is copied from table 2, module 3.2.P.3.2 of NDA 20-121.

Table 1. Batch Formula of Flonase Nasal Spray, 50 µg.

Component	Grade	Quantity/ (b) (4) batch
Fluticasone propionate (b) (4)	GlaxoSmithKline	(b) (4)
Dextrose (b) (4)	USP	
Microcrystalline Cellulose and Carboxymethylcellulose Sodium (b) (4)	NF	
Phenylethyl Alcohol	USP	
Benzalkonium Chloride (b) (4)	NF	
Polysorbate 80	NF	
Purified Water	USP	

Note: (b) (4)

- **Description of container closure system**
  The container closure system is comprised of a Type 1 amber glass bottle which is sealed with an (b) (4) spray pump with a nasal adapter/actuation device and a dust cap.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity**
  Container closure integrity studies are not warranted for a non-sterile drug product.

- **Preservative Effectiveness**
  The subject NDA references NDA 20-121 regarding CMC. The subject drug product formulation (b) (4) of NDA 20-121, and contains both benzalkonium chloride and phenylethyl alcohol.

- **Justification for not having a microbial limit specification for a non-sterile drug product**
  Not applicable. The subject NDA release and stability specifications include testing for microbial limits.

Satisfactory

Reviewer's Comment
The subject NDA provides reference to NDA 20-121 and states that the formulation of the product under NDA 205434 is unchanged from that under approved NDA 20-121. NDA 20-121 received Agency approval in 1994. Additional demonstration of antimicrobial effectiveness is not warranted at this time.

P.3 Manufacture

P.3.1 Manufacturer

GlaxoSmithKline Inc.
7333 Mississauga Rd North
Misssissauga
Ontario L5N 6L4
Canada

P.5 Control of Drug Product

P.5.1 Specifications

The drug product release specification includes the testing for microbial limits that is summarized below in table 2, which is copied from table 2 of module 3.2.P.5.1 of NDA 205434.

Table 2. Microbiological Release Testing

Test	Specification
Microbial Limits:	
Total microbial count	Not more than (b) (4)
Total yeasts and mold	Not more than
Specified Organisms	Absence of: In a sample size of (b) (4) *Staphylococcus aureus* *Pseudomonas aeruginosa* *Escherichia coli* Bile Tolerant Gram Negative Bacteria In a sample size of (b) (4) *Salmonella* species *Burkholderia cepacia* complex[1]

P.5.2 Analytical Procedures

- **Microbial Limits**
  The applicant tests the final product for Total Aerobic Microbial Count (TAMC), Total Yeasts and Molds Count (TYMC) and the specified

organisms (*S. aureus*, *P. aeruginosa*, *E. coli and Bile Tolerant Gram Negative Bacteria)* according to procedures consistent with USP<61> and <62>. The verification of the suitability of use of these test methods with the subject drug product is summarized in Document Number QC/MR/2013/022 (*Microbial Limit Test (MLT) Method Validation Report for Flonase Aqueous Nasal Spray (FANS), Fluticasone Propionate Nasal Spray*) (module 3.2.P.5.3 of the NDA).

Three batches of the subject drug product (2H003, 2L002 and 2N002) were used in the verification study. The challenge microorganisms used in the study are presented below in tables 3 and 4, and for each organism, the inoculum was (b) (4) CFUs. The applicant's acceptance criteria for the TAMC and TYMC included "a mean recovery of (b) (4) % or greater". Data from this verification study are provided in tables 3 and 4, which are copied from table's 6-C and 6-D of Document Number QC/MR/2013/022, respectively.

Table 3. Verification Study: TAMC and TYMC

(b) (4)

Table 4. Verification Study: Specified Organisms

Test No.	Batch No	Test For Specified Organisms Enrichment Recovery				
		S. aureus ATCC 6538	*P. aeruginosa* ATCC 9027	*Escherichia coli* ATCC 8739	*Salmonella enterica* ATCC 14028	*Gram Negative Bile Tolerant Bacteria* *E. coli (ATCC 8739)*
1	2H003	Typical growth	Typical growth	Typical growth	Typical growth	Typical Growth
2	2L002	Typical growth	Typical growth	Typical growth	Typical growth	Typical Growth
3	2N002	Typical growth	Typical growth	Typical growth	Typical growth	Typical Growth

The applicant tests the final product for *Burkholderia cepacia Complex* (BCC) according to a method developed at the subject manufacturing facility. Briefly, a (b) (4) product sample is dilute (b) (4)

The validation of the suitability of use of the BCC test method with the subject drug product is summarized in Document Number QC/MR/2014/06 (*Microbial Limit Test (MLT) Method Validation Report for B. Cepacia Complex Recovery from Fluticasone Propionate Aqueous Nasal Spray, 50 mcg*) (module 3.2.P.5.3 of the NDA).

Three batches of the subject drug product (2H003, 2L002 and 2N002) were used in the validation study. The applicant states that the challenge BCC were (b) (4) (b) (4) prior to use in the validation study. The challenge microorganisms used in the study are identified in table 5 (copied from table 1 of Document Number QC/MR/2014/06), and included three strains of *B. cepacia* and the additional species of *B. multivorans*, *B. stabilis* and *B. cenocepacia*.

Table 5. BCC Challenge Microorganisms

Test Method	Challenge Microorganism
Tests for Specified Microorganisms:	*Burkholderia cepacia* ATCC 25416
B. cepacia complex	*Burkholderia cepacia* ATCC 700450
	Burkholderia cepacia ATCC 25608
	Burkholderia multivorans ATCC BAA- 247
	Burkholderia stabilis ATCC BAA-67
	Burkholderia cenocepacia ATCC BAA-245

The inoculum was (b) (4) CFUs for each of the challenge organisms. Data from this verification study are provided in table 6, which is copied from table 6-A of Document Number QC/MR/2014/06. The recovered organisms were verified to be organisms of the BCC using a 16S RNA genotypic test method.

Table 6. Verification Study: BCC

Test No.	Batch No	Test For Specified Organisms Enrichment Recovery					
		B. cepacia ATCC 25416	*B. cepacia* ATCC 25608	*B. cepacia* ATCC 700450	*B. multivorans* ATCC BAA-247	*B. stabilis* ATCC BAA-67	*B. cenocepacia* ATCC BAA-245
1	2N002	Growth	Growth	Growth	Growth	Growth	Growth
2	2H003	Growth	Growth	Growth	Growth	Growth	Growth
3	0000573620	Growth	Growth	Growth	Growth	Growth	Growth

Satisfactory

Reviewer's Comments: Microbial Enumeration Testing

1. The drug product release test acceptance criteria regarding Total Microbial Count, Total Yeasts and Mold Count, absence of *S. aureus*, *P. aeruginosa* and *E. coli* are consistent with recommendations in USP<1111> for products administered to the nasal mucosa.
2. There is no compendial test method for BCC at this time. The applicant has demonstrated that the BCC test method developed in-house is capable of recovering challenge strains of the organism from the drug product. The challenge organisms were acclimated to the (b) (4) that is used in the subject manufacturing facility prior to their use in the validation study. The drug product release specification has been amended to reflect that each batch of the drug product will be tested for BCC.
3. The applicant has met CDER expectations for microbiological release testing of a non-sterile, aqueous drug product.

P.7 Container Closure System

Refer to section P.1 of this review.

P.8 Stability

P.8.1 Stability Summary and Conclusion

The applicant placed four batches (2A001, 2A002, 2B003 and 2L001) of the subject drug product on stability at the following conditions:

- 25°C/40% RH
- 25°C/60% RH
- 30°C/35% RH
- 30°C/65% RH
- 40°C/25% RH
- 40°C/75% RH

Microbiological testing was performed on the 25°C & 30°C samples after 12, 24, 30 and 36 months of storage. (b) (4)

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant commits to the completion of on-going stability studies and the placement of one batch per year into the stability testing program.

P.8.3 Stability Data

Data from the microbiological and preservative content are provided in module 3.2.P.8.1 and meet acceptance criteria.

Satisfactory

Reviewer's Comment

The microbiological testing of samples in the stability program is consistent with regulatory expectations for non-sterile, aqueous products.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

Not applicable.

A.2.1 Materials of Biological Origin

Not applicable.

A.2.2 Testing at Appropriate Stages of Production

Not applicable.

A.2.3 Viral Testing of Unprocessed Bulk

Not applicable.

A.2.4 Viral Clearance Studies

Not applicable.

R REGIONAL INFORMATION

R.1 Executed Batch Record

Copies of executed batch records are provided in module 3.2.R.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

This reviewer read the three documents (*Professional* (b) (4) *Carton Leaflet*, *Question Answer Book and Quick Start Guide*) in module 1.14.1.3 (*Draft Labeling Text*) of the subject NDA.

Satisfactory

Reviewer's Comment

The information provided in the Draft Labeling Text does not present a concern regarding the microbiological quality of the drug product or its intended use.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

There are no microbiology deficiencies identified.

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/s/

JOHN W METCALFE
05/30/2014

BRYAN S RILEY
05/30/2014
I concur.

PRODUCT QUALITY MICROBIOLOGY NON-STERILE

DRUG PRODUCT FILING CHECKLIST

NDA Number: 205434 **Applicant:** GlaxoSmithKline Consumer Healthcare **Letter Date:** SEP 21, 2013

Drug Name: Fluticasone propionate aqueous nasal spray, 50 mcg/metered spray **NDA Type:** 505(b)(1) **Stamp Date:** SEP 23, 2013

Dosage Form: Aqueous **Reviewer:** John W. Metcalfe, PhD

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		Module 3.2.P.
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		The subject NDA references NDA 20-121 for manufacturing process information.
3	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Module 3.2.P.5.1.
4	Has the applicant submitted the results of analytical method verification studies?	X		Module 3.2.P.5.3.
5	Has the applicant submitted preservative effectiveness studies (if applicable)?	X		The subject NDA references NDA 20-121 regarding the formulation.
6	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: NDA 205434 is submitted to market a currently approved prescription drug (NDA 20-121) as an Over-The-Counter product. The subject NDA references NDA 20-121 for all information pertaining to the drug product manufacturing process, controls and release testing. Currently, CDER is implementing a *Burkholderia cepacia* testing policy for aqueous, non-sterile drug products which was not in place at the time of approval of NDA 20-121 (OCT 1994).

Product Quality Microbiology Information Request: Refer to page 2 of this review.

02 December 2013

John W. Metcalfe, Ph.D. Date
Senior Microbiology Reviewer, CDER/OPS/NDMS

02 December 2013

Stephen E. Langille, Ph.D. Date
Senior Microbiology Reviewer, CDER/OPS/NDMS

Microbiology Information Request to be Forwarded to Applicant

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/s/

JOHN W METCALFE
12/02/2013

STEPHEN E LANGILLE
12/02/2013