CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205434Orig1s000

OTHER REVIEW(S)

Addendum Labeling Review for Flonase Allergy Relief

SUBMISSION DATES:	June 19, 2014 July 15, 2014 (memo to file) July 16, 2014 (memo to file) July 17, 2014 (memo to file) July 18, 2014 (memo to file) July 21, 2014 (memo to file) July 22, 2014 (via email)
NDA/SUBMISSION TYPE:	205434
ACTIVE INGREDIENTS:	Fluticasone propionate 50 mcg/spray
DOSAGE FORMS:	Spray, metered
SPONSOR:	GlaxoSmithKline Consumer Healthcare Erin Oliver Head, US Regulatory Affairs (973) 889-2516
REVIEWER:	Elaine Abraham RPh
TEAM LEADER:	Steven Adah PhD
PROJECT MANAGER:	Jung Lee RPh

I. BACKGROUND

FDA provided labeling comments for NDA 205434 Flonase Allergy Relief (fluticasone propionate) on June 3, 2014. The sponsor submitted revised labels on June 19, 2014. Additional comments were provided to the sponsor on July 8 and 11, 2014 (both posted in DARRTS on July 15, 2014) following the two internal labeling meetings. The sponsor responded to the comments in a July 15, 2014 email (posted in DARRTS on July 15, 2014), which was used as the basis for the discussion with the sponsor in a teleconference on that date. The sponsor also submitted a proposed change to the Question and Answer Book on July 16, 2014. Comments on this submission were provided to the sponsor on July 16, 2014. The sponsor submitted changes to the Question and Answer Book on July 17, 2014. Revised labels were submitted by e-mail and posted in DARRTS on July 18, 2014. (b) (4)

(b) (4)
Two final comments on these labels were sent to the sponsor on July 21, 2014. Revised draft labels were submitted by e-mail on July 22, 2014. This final submission did not contain all labels originally submitted. (b) (4)

Submitted Labeling – July 22, 2014	Representative of Following SKUs
60-spray count immediate container	N/A
120-spray count immediate container	N/A
60-spray count PDP	N/A
120-spray count PDP	N/A
3 x 120-spray count club pack label	N/A
Drug Facts label (peel-back label attached to back of all clamshell packs)	N/A
Quick Start Guide	N/A
Question & Answer Book	N/A

II. REVIEWER'S COMMENTS

A. June 19, 2014 submission

1. Principal Display Panel (PDP) for (b) (4)-, 60-, 120- (b) (4) -spray count SKUs

a. Statement of identity

(1) FDA Request - The drug class "(glucocorticoid)" should immediately follow the established name of the drug.

Sponsor's response - The drug class "glucocorticoid" has been added to immediately follow the established name "fluticasone propionate" and precede "50 mcg".

Reviewer's comment – This revision is acceptable.

(2) FDA Request - We recommend that the dosage form, "nasal spray" follow either the established name or the dosage strength.

Sponsor's response - The dosage form "nasal spray" remains on the second line following "Allergy Symptom Reliever" to enable the complete statement of identity to appear on a single line and in direct conjunction with the proprietary name.

Reviewer's comment - As the dosage form is not required by regulation to be part of the statement of identity under 21 CFR 201.61, the FDA request was a recommendation. The sponsor's response is acceptable.

(3) FDA Request - The pharmacological category, "nasal allergy symptom reliever", should be used in place of (b) (4)

Sponsor's response - "Allergy symptom reliever" replaces the former (b) (4); however, we have not included the term "nasal" as a descriptor due to the proposed ocular indication and the potential for consumer confusion. By including the term "nasal", a consumer may inappropriately interpret that the product is not suitable for the relief of their eye symptoms.

Reviewer's comment – This is acceptable per team review and discussion.

(b) (4)

c. "NEW!" Flag on 60-count SKU (flag representative for all SKUs)

FDA Request - A "New!" flag may be acceptable if truthful and not misleading. However, in order for the "New!" flag to be truthful and not misleading, it must specify the aspect of the product that is new. The "New!" flag must be revised to specify the aspect of the product that is new or be deleted from the PDP.

FDA Request - The "NEW!" flag on the 60-count SKU is listed as being representative for all SKUs. As our policy is not to accept representative labeling for new applications, the PDP with flag should be submitted for all SKUs and not as representative labeling. It is not necessary to submit PDPs without the flag as we understand that the flag will be removed after 6 months of marketing.

Sponsor's response - We acknowledge the Agency's comments and agree that in certain situations the description "new" in isolation may not be adequate for a consumer to understand the specific aspects of the product which are new. However, we believe that since all aspects of the product are new to the consumer in the OTC setting, the use of the term "New" is not untruthful or misleading and an additional descriptor is not necessary. PDPs with two different flags were submitted – "New" (b) (4)

Reviewer's comment – The "New" flag is acceptable per team review and discussion (see below under B. July 15, 2014 submission).

(b) (4)

3. Tamper evident statement

FDA Request - The statement reads "TAMPER-EVIDENT features for your protection. The product is packaged in a sealed plastic container. Under the cap and nozzle, each bottle has an aluminum seal around bottle neck. Do not use if any of these features are torn or damaged." We remind you if an identifying feature is contained on the seal around the bottle neck, it should be included in the labeling (see 21 CFR 211.132).

Sponsor's response - We appreciate the Agency's comment. No changes are proposed to the Draft labeling.

Reviewer's comment – This comment was a reminder to the sponsor and the sponsor's response is acceptable.

(b) (4)

(b) (4)

[redacted]

5. **Drug Facts Label – All SKUs**
   FDA Request -
   a. The ***Active*** ingredient should include the drug class "(glucocorticoid)" after the active ingredient and before the strength. A space should be added to "50mcg" so that is reads "50 mcg".
   b. (b) (4)
      [redacted]
   c. ***Uses***
      Remove the bullet before the words "temporarily relieves these symptoms…"
   d. ***Warnings***
      (1) The first statements under Warnings "Only for use in the nose. Do not spray into your eyes or mouth." are bolded. Bolding is generally reserved for headings and subheadings and too much bolding can make a label difficult to read. As this is the first warning statement, this concern is given prominence on the label. The bolding is not necessary and should be removed.
      (2) Ask a doctor before use if you have
      As there is only one condition listed here, the bullet before glaucoma should be removed (see 21 CFR 201.66(d)(4)).
      (3) Ask a doctor or pharmacist before use if you are taking
      As there is a single bulleted condition under this subheading, the bullet before "ketoconazole pills (medicine for fungal infection)" should be removed (see § 201.66(d)(4)).
   e. ***Directions***
      (1) The first bulleted statement under Directions, "Read the Quick Start Guide for how to (b) (4) [redacted] should be revised to include abbreviated instructions (such as priming, shaking before use, and cleaning the device) and refer to the Quick Start Guide.
      (2) The Directions should be revised to include use down to 4 years of age.
   f. ***Other information***
      A period should be placed after the last sentence of the third bullet, after "…important additional information."

Sponsor's response - Drug Facts label has been revised to address FDA's Comments other than *Purpose*. (b) (4) With respect to including directions down to age 4, we have revised the label to include instructions related to use in children from 4 - 11 years of age.

Reviewer's comment (b) (4) *The review team agreed that "Allergy symptom reliever" is acceptable as the pharmacological class. Under the heading "Ask a doctor or pharmacist before use if you are taking" the following bulleted statement has been added: "a steroid medicine for asthma, allergies or skin rash". This is based on our request that the sponsor consider adding such language as it is included in the Question and Answer Book. The other changes to Drug Facts based on our preliminary June 3, 2014 comments are acceptable.* (b) (4)

g. Annotated Specifications for Drug Facts Labels

FDA Request - Provide the following annotated font specifications (see § 201.66(d)(3)):

- characters per inch
- leading

Sponsor's response – The revised draft labeling provided in the current submission for all components with Drug Facts labeling has been updated to include an "Information Box" that provides specifications for the Drug Facts label, including information related to characters per inch and leading.

Reviewer's comment – The font size for "Drug Facts (continued)" should be provided. Otherwise, this response is acceptable. This specification was requested by email on July 16, 2014 and included in the sponsor's response of July 18, 2014. The annotated specifications for Drug Facts are acceptable.

h. Immediate Container Labels

FDA Request - The bottle label contains the statement "IMPORTANT: (b) (4) "Read the Drug Facts label and enclosed material…"

Sponsor's response – We have revised the proposed bottle label to specifically refer to the Drug Facts label.

Reviewer's comment – The requested change has been made and is acceptable.

i. Lot number and Expiration Date

FDA Request - Confirm that the lot number and expiration date is provided and visible to the consumer on all outer cartons.

Sponsor's response – Yes, the lot number and expiration data will be visible to the consumer at the point of purchase for all SKUs. For those retail packs that will be packaged in clear, clamshell packaging, the lot number and expiration date printed on the bottle label will be readily visible through the clear packaging. For the club (b) (4) packaged (b) (4), the back panel will be printed with the lot number and expiration date.

Reviewer's comment – Based on the sample provided, we agree with the sponsor that for the single retail packs, the lot number and expiration date would be visible. The lot number and expiration area should be provided for the club (b) (4) packs when they are resubmitted. The sponsor agreed to this in their July 15, 2014 response (see below).

j. Package Inserts

(b) (4)

2. Question & Answer Book

FDA Request –

(b) (4)

(b) (4)

Sponsor's response – The Question & Answer Book has been revised to address FDA's comments. We've also modified the Q&A book to supplement the important safety information that appears on the Drug Facts pertaining to the safe use in children.

Reviewer's comment – In the Question & Answer Book, (b) (4) *"glucocorticoid" as requested. Labeling for children 4-11 has been added with warnings about growth and duration of use before seeing a doctor.* (b) (4) *The Question & Answer Book advises the consumer to "Talk to your doctor or pharmacist before using FLONASE" if they are taking Medicines with glucocorticoids including some medicines for skin rash such as eczema, asthma, inflammation, allergic reactions, or eye conditions". Similar language has been added to Drug Facts (see above). See discussion of the Question & Answer Book below under B. July 15, 2014 submission.*

3. **Quick Start Guide**
   The Quick Start Guide was revised to include children 4 -11.

   Reviewer's comment – The children's dosing directions were added to the guide. See discussion of the Quick Start Guide below under B. July 15, 2014 submission.

B. July 15, 2014 submission (and July 15 teleconference)

(b) (4)

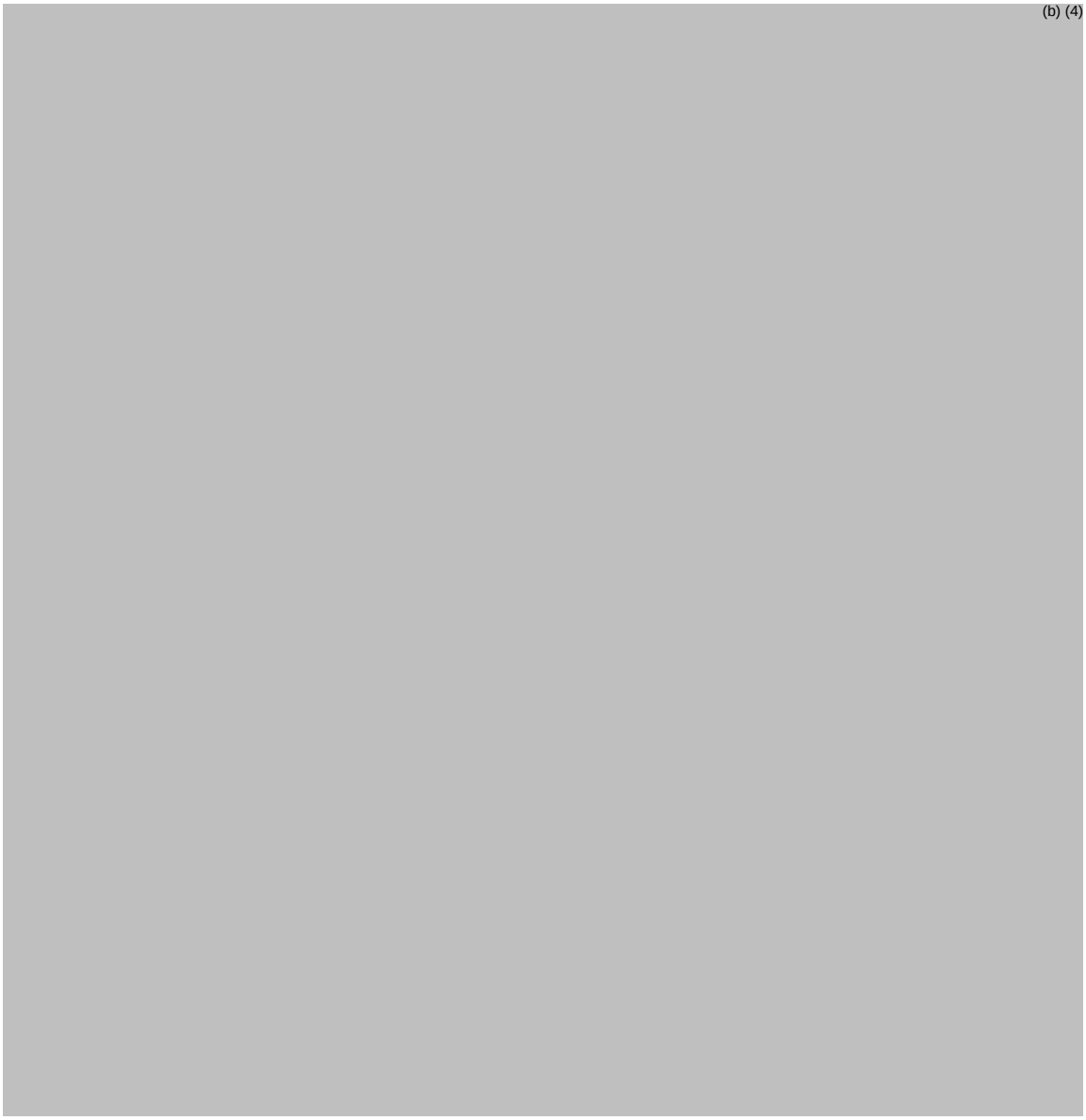
2. "New" OTC Flag

   FDA Request – We prefer the "New Now OTC" flag.

   Sponsor's response – Upon reflection, we do not believe that the addition of "Now OTC" adequately describes what is NEW to the consumer in relation to Flonase Allergy Relief. The "Now OTC" describes the change in legal status from Rx to OTC; however, it does not capture the new ocular indication that is different from the original Rx product and significant to the OTC offering. Therefore, to avoid misrepresenting or diminishing the aspects of the product that are new to the consumer we request to retain the original "NEW" flag, consistent with the appearance of the flag for recently approved switch products like Nexium and Oxytrol.

   Reviewer's comment – The review team agreed that the "New" flag is acceptable.

3. (b) (4)



(b) (4)

4. Graphics

FDA Request – Combining symptom graphics with nose and eye graphics may be confusing. There is concern that consumers would think they can spray the product in their eye. Either remove the graphic or include explanatory language. If the graphic is retained, we recommend revising it as some reviewers had trouble discerning that the graphic was of an eye.

Sponsor's response – The proposed graphics were included in the label comprehension test and the human factors tests. There was no evidence of confusion in terms of product use or safety concerns related to misuse in the eye.

GSKCH conducted two Human Factors tests to evaluate how consumers use the product in a naturalistic setting based on the proposed labeling only. The labeling reflected the intended commercial graphics, including the proposed eye icon. There was no evidence of consumer confusion or misinterpretation of the eye icons. GSKCH proposes to retain an eye icon, but will revise the appearance to make it look more realistic.

Reviewer's comment – The Drug Facts label includes a warning not to spray the product in the eye. The package inserts also contain this information. This response is acceptable.

(b) (4)

6. Statements above Drug Facts: "See below for important information about use in children. Children 4-11: "Do not use daily for more than 2 months"

FDA Request – The statements above Drug Facts "See below for important information about use in children. Children 4 – 11: Do not use daily for more than 2 months" are not necessary and should be deleted.

Sponsor's response – Need to clarify if this comment applies to the front panel of the Peel-Back Drug Facts Label (b) (4).

- For the front panel of the Peel-Back Drug Facts Label, we propose to retain the precautionary language that appears in the yellow highlighted flag, but modify to read, "IMPORTANT - Peel here for complete Drug Facts label. Children 4-11: do not use for more than 2 months a year. We believe it is important that consumers have visibility to this information at point of purchase without the need to unfold the label.
- For the Club Pack; (b) (4) We propose to retain the text that reads "See below for important information about use in children." to draw parent's attention to this information.

Reviewer's comment – The children's directions cannot be viewed on the peel-back label without opening the label so making this information visible to the consumer through the use of a flag is acceptable. The review team agreed that the proposals for the peel-back label and the club pack are acceptable.

7. Adult directions boxes "after 6 months of daily use" and "Ask a doctor if you can keep using"

   FDA Request – The adult boxes, "after 6 months of daily use" and "Ask a doctor if you can keep using" are not needed.

   Sponsor's response – GSKCH acknowledges FDA's comments but proposes to retain the proposed label statements. The statement 'do not use for more than 6 months continuously without consulting a doctor for adults and children 12+ is mandatory to ensure that patients seek periodic supervision by a physician to assess the benefit-risk of continuous use of intranasal corticosteroids. This guidance is provided in an effort to reinforce the need for periodic physical examination of the patient to assess any long-term effects associated with intranasal administration. Albeit the extensive body of data indicates that the risks associated with OTC use are low, GSK nonetheless considers such statements in the patient labeling for OTC use to be warranted.

   Reviewer's comment – The review team agreed that the proposal is acceptable.

8. Statement on time needed for symptom relief under *Other information*.

   FDA Request – Under "Other information", change the first bullet to "[bullet] some symptoms may get better on the first day of treatment. It may take up to one week of daily use to feel the most symptom relief".

   Sponsor's response – The current GSKCH proposed label statement reads "you (b) (4) start to feel relief (b) (4) the first (b) (4) and full effect after several days of regular, once-a-day use". We believe that reference to several days is more consistent with the current approved Rx label which states, "Maximum benefit may not be reached for several days". In fact, clinical data support that most users will experience significant symptom relief within 3 - 4 days. Reference

to **1 week** may be confusing to consumers in relation to other label statement that caution to stop use and ask a doctor if symptoms don't get better after 7 days. (b) (4)

Reviewer's comment – The review team agreed that the statement is acceptable if revised as follows: "you may start to feel relief the first day and full effect after several days of regular, once-a-day use".

(b) (4)

(b) (4)

10. Other FDA requests

The sponsor agreed with FDA on the following items and will resubmit labeling with these revisions:

a. PDP

(b) (4)

(2) Strength – Add "per spray" to the strength in the statement of identity so that is reads "50 mcg per spray".

(3) Allergy Symptom Reliever – This is acceptable as the pharmacological category.

b. Include text of symptoms relieved to better explain 24-hour relief.

(b) (4)

e. Drug Facts

(1) The purpose, Allergy symptom reliever, is acceptable.

(2) Move "[bullet] if you are taking medicine for HIV infection" from the subheading "Do not use" to "Ask a doctor or pharmacist before use."

(3) Revise the HIV warning above to "Ask a doctor or pharmacist if you are taking (b) (4) medicines for HIV infection ((b) (4) ritonavir)" or similar warning. (This request was communicated to the sponsor following the July 15, 2014 teleconference.)

(4) Under "Ask a doctor before use if you", revise the glaucoma statement to "have or had glaucoma or cataracts".

(5) Under "Ask a doctor or pharmacist before use if you are taking", order the statements as follows:

- HIV warning
- Steroid warning
- Ketoconazole warning

(6) Under "When using this product" the word "some" can be added to the growth statement so that it reads "the growth rate of some children may be slower".

(7) (b) (4) revise the statement and include under "Stop use and ask a doctor if". See revision below under (9).

(8) Add "[bullet] remember to tell your doctor about all the medicines you take, including this one"

(9) Under "Stop use and ask a doctor if", add

- you have, or come into contact with someone who has, chickenpox, measles or tuberculosis
- you have severe or frequent nosebleeds

(10) Under "When using this product" add "[bullet] do not share this bottle with anyone else as this may spread germs".

(11) Under "Stop use and ask a doctor if", combine the first two bullets "do not get better in 7 days" and "severe facial pain or thick nasal discharge".

(12) Under "Directions" we find the format of the table difficult to follow. Consider following the directions format used in the approved glucocorticoid label (Nasacort 24 HR) but adjusting for Flonase Allergy Relief. We believe following the approved directions will be easier for the consumer to read and correct the specific changes we recommend.

(13) The first two bullets under the children's directions are better combined into one bullet to explain that the growth issue is the reason for the 2-month use limit. The word "some" can be added to the growth statement so that it reads "the growth rate of some children may be slower". We recommend the statement "Talk to your child's doctor if your child needs to use the spray for longer than two months a year" to express that the product should not be used for more than 2 months (see approved glucocorticoid label).

(b) (4)

(15) Under directions, include an instruction to shake the bottle before each use.

(b) (4)

g. Question and Answer Book

(1) Changes discussed above that affect the Question and Answer Book should also be made to the Question and Answer Book.

(b) (4)

(3) Revise the graphic showing not to spray into the eye on page 21. We recommend the commonly used circle with a slash or an "X" over the picture as a clearer way to show that this practice should be avoided.

h. Quick Start Guide

(1) Changes discussed above under Drug Facts that affect the Quick Start Guide should also be made to the Quick Start Guide.

(2) We recommend the following changes to the page titled "Get the relief you need":
   (a) Under 2 Prime, design the picture so that it clearly shows the product should be pointed and sprayed away from the face.
   (b) Under 3 Blow, revise the graphic showing not to spray into the eye as discussed above under the Question and Answer Book.
   (c) Under 5 Breathe and spray, (b) (4) to "sniff gently".

i. Lot and Expiration Date
Indicate the location of the lot number and expiration date for all club packs (b) (4) in your resubmitted labels.

(b) (4)

(b) (4)

D. July 22, 2014 submission

An information request was sent to the sponsor on July 21, 2014 with the two items listed below. The July 22, 2014 submission contained revised labels responding to this request.

1. FDA request

(b) (4)

2. FDA request

(b) (4) "help block" in the statement "It works directly in the nose to block your allergic reactions". This statement is found on Page 5 of the Question and Answer book (b) (4)

Reviewer's comment – This revision has been made in the Question and Answer Book and it is acceptable. (b) (4)

III. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted Flonase Allergy Relief nasal spray immediate container (bottle) and outer carton labels and package inserts.

Request that the sponsor submit final printed labeling (FPL) identical to the following labeling submitted on July 22, 2014 when available:

- 60- and 120-spray count immediate containers
- 60- and 120-spray count PDPs
- 3 x 120-spray count club pack carton
- Drug Facts (peel-back label attached to back of all clamshell packs)
- Question & Answer Book
- Quick Start Guide

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

27 Page(s) of Draft Labeling have 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/

ELAINE E ABRAHAM
07/23/2014

STEVEN A ADAH
07/23/2014

SOCIAL SCIENCE REVIEW

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research, Division of
Nonprescription Clinical Evaluation (DNCE), Office
of Drug Evaluation IV

NDA:	**205434**
Sponsor:	**GlaxoSmithKline Consumer Healthcare (GSKCH)**
Subject:	**label comprehension, self-selection and human factors studies**
Drug Name/Strength:	**fluticasone propionate / 50 mcg**
Product Name:	**Flonase Allergy Relief**
Proposed Indications:	**temporary relief of the following symptoms due to hay fever, other respiratory allergies (b) (4) (b) (4) (b) (4): nasal congestion, runny nose, sneezing, itchy nose, itchy and itchy watery eyes**
Dosage Form:	**nasal spray, 50 mcg**
Route of Administration:	**intranasal**
Date of Submission:	**September 13, 2013**
Review Completed:	**June 5, 2014**
Reviewer:	**James P. Stansbury**
Team Leader:	**Nair Narayan**

EXECUTIVE SUMMARY

This review summarizes evidence from consumer knowledge and behavioral studies conducted in support of a proposal to switch fluticasone propionate nasal spray from prescription to nonprescription status. The evidence includes 2 label comprehension studies, a self-selection study, and a pair of human factors studies. The sponsor proposes the name Flonase Allergy Relief for the new product.

In addressing social scientific issues for this NDA approval, this summary references earlier communications with the sponsor and reviews of the label comprehension (B. Cohen, 03/05/2012) and human factors (D. Windt, 04/17/2013) study protocols under IND 109805. Tables are also drawn from the biometrics review prepared for the NDA mid-cycle meeting (S. Komo, 2/26/2014) summarizing independent statistical results on key findings from the array of studies.

Of continued concern, studies found that:

- the ability to correctly self-select was very low among HIV-positive patients who receive ritonavir. According to the sponsor, these results reflect the fact that many HIV patients do not know what medications they are using, particularly when taking complex, combination therapies. (b) (4)
- the instruction to **Stop use and ask a doctor** when *symptoms do not get better within 7 days* was more frequently unnoticed under the compound subheading than other items tested in the pilot label comprehension studies, particularly by low-literate respondents.

  The wording of the scenarios testing warnings under the **Stop use and ask a doctor if** subheading were changed in the targeted label comprehension study. However, results likely improved because recognition of *ask a doctor* without identifying the need to *stop use* on first effort was redefined as "adequate" in the pivotal study scoring algorithm.
- the pivotal study result was slightly weaker than expected for the *new symptoms* item in the **Stop use and ask a doctor if** section among low-literate respondents.

  Other significant directions and warnings apart from those identified were adequately understood and identified in the label comprehension studies.

Additionally, all behavioral and knowledge studies were conducted with adults. Regulatory advice to the sponsor (D. Brum, 12/06/2013) initially noted that the application triggered PREA, however the sponsor sought a waiver of pediatric studies on the basis of growth concerns. The Division has informed the sponsor that no additional data are required for the application, (b) (4) (J.E. Lee, 03/26/2014).

On the basis of study results and previous communication with the sponsor, we suggest:

- (b) (4) We appreciate that the ritonavir warning has been expanded to all HIV treatment on the basis of the sponsor's self-selection study. However, the revised warning has not been retested and informs consumers about a serious risk for drug-drug interaction.
- the sponsor may wish to make the *new symptoms* and *symptoms do not get better within 7 days* warnings under the **Stop use and ask a doctor if** subheading of the DFL more prominent.
- that while the Division has advised no further data for the application is required, the sponsor may wish to conduct post-market label testing with adolescents and older children. (b) (4)

[1] *See for example* Abel C, Johnson K, Waller D, Abdalla M, Goldsmith C . (2012) Nonprescription medication use and literacy among New Hampshire eighth graders. *Journal of the American Pharmacists Association* 52(6):777-82.

OVERVIEW OF CONSUMER BEHAVIOR STUDIES

Background

The sponsor first sought input for its behavioral study program in a meeting package submitted January 21, 2011 under IND 109805. The conduct of the label comprehension studies and self-selection studies were addressed in the meeting held February 22, 2011 (A. Leonard Segal, 03/14/2011). With respect to the proposed label comprehension studies, FDA advised:

We recommend you submit the full protocol for the label comprehension study and ancillary materials for our review and comments prior to conducting the study. We have the following preliminary comments about the design of the study:

- *According to the current national data, 30% of the adult population has basic literacy skills. Therefore, at least 30% of the study population should consist of low literate subjects.*
- *All the scenario questions should be followed up with a probing question asking why the subject answered as he/she did.*

With reference to the proposed self-selection study, FDA advised:

We recommend you submit the full protocol for the self-selection study and ancillary materials for our review and comments prior to conducting the study. We have the following preliminary comments about the design of the study:

- *In the selection and purchase question 1b the probe if yes should be "why did you say that?" not "is there anything you would do before starting to use the medication" because this is a leading question that might bias the answer of the subject.*
- *The exclusion criteria should exclude participants who have participated in research studies in the past 12 months (not 6 months).*
- *For the self-selection study we recommend testing be done with a significance level of 2.5% for one sided tests.*

The sponsor submitted the protocol for label comprehension studies October 10, 2011 with the review filed in DARRTS in March, 2012 as noted above. The protocol submission was based on use of the methods in a pilot label comprehension study, the results of which were also reported in the submission.

The 2012 review noted that many of the concerns to be tested were either not unique to the product, appearing elsewhere in OTC labeling, or had been tested adequately in the pilot study. Hence the objectives of the label comprehension study could be narrowed. However, the review stressed that unique labeling elements, important risks, and particularly items that did not test well in the pilot should be retested in the pivotal label comprehension study. The FDA comments to the sponsor stressed that:

- targeting the comprehension and human factors studies solely to persons with a history of nasal allergies was viewed as suboptimal—the proposed population should include the general population.
- there was very poor comprehension of the warning about *get[ting] better within 7 days* under the **Stop use and ask a doctor if** subheading. Additional information explaining

the finding was requested, with the suggestion that labeling changes might be needed.

- (b) (4)

The sponsor submitted the human factors usability test protocol January 25, 2013 with the review filed April 17, 2013. FDA shared advice regarding the study including requests to provide a detailed moderator's workbook, improve precision of follow-up questions to establish root cause of usage errors, and clarify that participants will be able to review packaging and labeling. Additionally, the sponsor was encouraged to:

- recruit an additional user group of low-literate adults
- develop a strategy for participant replacement for patients stopping use in line with warnings
- increase time since last study participation to 6 months as an exclusion criterion for human factors participation.

FDA also emphasized that the inclusion of 15 naïve users of the product would be sufficient as preliminary data, but would not be considered adequate for fully examining safety concerns.

Label Comprehension Studies of Drug Facts Label (DFL) – RH01305 & RH01318

Objectives

The initial objectives of both the pilot (RH0135) and the pivotal (RH01318) label comprehension study were similar, although FDA suggested that objectives in the latter could be refined based on the results of the pilot. The primary objectives of the pilot study addressed consumer's comprehension of the following label components:

1. Uses

   Relieves symptoms of indoor and outdoor allergies: sneezing, itchy nose, runny nose, nasal congestion

2. Warnings
   a. Do not use to treat asthma
   b. Ask a doctor or pharmacist before use if you are taking ritonavir (medicine for HIV infection)
   c. Stop use and ask a doctor if
      i. Your symptoms do not get better within 7 days of starting use. You may have something more than allergies, such as an infection.
      ii. You get new symptoms such as severe facial pain or thick nasal discharge. You may have something more than allergies, such as an infection.
3. Directions
   a. (b) (4)
   b. (b) (4) years of age and older, Week 1, use 2 sprays in each nostril once daily
   c. (b) (4) years of age and older, Week 2 onwards, use 1 or 2 sprays in each nostril once daily, as needed to treat your symptoms
   d. (b) (4) years of age and older, After (b) (4) months of daily use, ask your doctor if you can keep using.

Secondary objectives were directed to additional warnings:

a. Do not use if you have an injury or surgery to your nose that is not fully healed
b. Ask a doctor before use if you have glaucoma
c. Ask a doctor or pharmacist before use if you are taking ketoconazole pills (medicine for fungal infection)
d. Stop use and ask a doctor if
    i. You get a constant whistling sound from your nose; this may be a sign of damage inside your nose
    ii. You get an allergic reaction to this product. Seek medical help right away
    iii. You get changes to your vision that do not get better as your allergy symptoms improve.

In the targeted study, primary objectives were organized in line with key concerns that emerged in results from the pilot study. Objectives focused on warnings and revised instructions:

1. Warnings
    a. Stop use and ask a doctor if
        i. Your symptoms do not get better within 7 days of starting use. You may have something more than allergies, such as an infection.
        ii. You get new symptoms such as severe facial pain or thick nasal discharge. You may have something more than allergies, such as an infection.
2. Directions
    a. (b) (4) years of age and older, Week 1, use 2 sprays in each nostril once daily
    b. (b) (4) years of age and older, Week 2 onwards, use 1 or 2 sprays in each nostril once daily, as needed to treat your symptoms

Reviewer note: The pivotal study primary objectives addressed significant items testing poorly in the pilot identified by FDA. Indication was a secondary objective, with generous "mitigation" (scoring coding). Thus, while the question about ***Uses*** *tested the full description, including "triggers" found in the label, scoring allowed for a partially correct response such as "allergic symptoms" or "allergies."* (b) (4)

Methodology

The design followed in both the pilot and pivotal studies involved multi-site, single visit label comprehension testing. In the pivotal study, participants were screened by telephone and arrived at a research facility to complete the protocol. The protocol called for 500 participants representative of the general population of allergy sufferers, with an additional 100 low-literacy respondents to obtain a total of 600 interviews.

Exclusion criteria were typical, excluding marketing and healthcare industry professionals; persons participating in a study during the last year; and individuals who were non-readers, non-literate in English, or reliant on corrective eyeware that was not brought to the interview. The inclusion criteria targeted adults with a history of nasal allergies during the previous year, additionally targeting subjects with REALM scores < 60 for the low-literacy group.

During the visit, the REALM was administered following completion of informed consent and a

confidentiality agreement. After reconfirmation of eligibility and a brief overview of the study, the participant reviewed the full label and was administered the label comprehension interview. The comprehension questionnaire used open-ended queries with 2 or 3 pre-codings for situational questions that apply concepts found in the label. These were followed by an open-ended follow-up question that was coded separately (see exemplar Appendix A). The two question "Net Codes" were then combined in the dichotomous, composite "Final Code" to calculate the proportion of the sample with comprehension for the label item. The algorithm to determine the "Final Code" for questions identified as dichotomous and for those having a partial-credit structure can be seen below. The justification for the partial-credit approach rested on the idea that an incomplete answer might reflect a safe course of action even it were not fully congruent with the content of the label.

Dichotomous Item Final Scoring Definition

Initial/Follow-up Net Code	Final Code
Correct initially, Correct at follow-up	Correct Overall Response
Correct initially, Incorrect at follow-up	Incorrect Overall Response
Incorrect initially, Correct at follow-up	Correct Overall Response
Incorrect initially, Incorrect at follow-up	Incorrect Overall Response

Partial-Credit Item Final Scoring Definition

Initial/Follow-up Net Code	Final Code
Correct initially, Correct at follow-up	Correct Overall Response
Correct initially, Acceptable at follow-up	Correct Overall Response
Correct initially, Incorrect at follow-up	Incorrect Overall Response
Acceptable initially, Correct at follow-up	Correct Overall Response
Acceptable initially, Acceptable at follow-up	Correct Overall Response
Acceptable initially, Incorrect at follow-up	Incorrect Overall Response

Initial/Follow-up Net Code	Final Code
Incorrect initially, Correct at follow-up	Correct Overall Response
Incorrect initially, Acceptable at follow-up	Correct Overall Response
Incorrect initially, Incorrect at follow-up	Incorrect Overall Response

The target threshold for comprehension was set as the lower confidence limit attaining 90% for the 4 primary objectives.

Reviewer note: Attention to the scoring algorithm and protocol suggests that the proportion of correct final responses is apt to be inflated. Note that 6 of 9 coding possibilities result in a correct overall response. It would be unremarkable if results did not appear favorable even when they do not reach the proposed threshold. Poor results therefore merit attention if they carry some implication for safe use.

The sponsor accepted FDA's earlier advice regarding the structure of follow-up questions. The query about actions before using the medication was changed to the form: "Why do you say that?"

Key Findings

The sponsor reported on 130 respondents defined as eligible in the pilot study, although the data allowed for internal analyses with a total sample of 137. A total of 617 subjects were interviewed for the pivotal study, with 607 considered evaluable by the sponsor. Demographic and baseline characteristics for the pivotal study are reproduced in Appendix B.

Reviewer note: The sponsor extended sampling to the general population beyond those diagnosed with a history of allergies as advised by FDA. (b) (4)

The results from the pilot comprehension study (RH01305) were adequate for most of the messages examined (below). The instructions and most of the warnings were well-comprehended by respondents. However, low-literate respondents did very poorly (54.8%, 36.0% LCB for correct), with the general population performing only moderately well (79.2%, 70.3% LCB correct) when asked what to do if the product was ineffective in symptoms reduction within a week. The low-literate respondents also tested poorly on the directions to consult a physician about continued use after 3 months of daily use and the direction to use the product once a day.

Pilot Label Comprehension Study (RH01315 Results).

	General Population		Low Literate Population	
Primary Objective	% (n/N)	LCB*	% (n/N)	LCB*
(b) (4) years of age and older, Week 1, use 2 sprays in each nostril once a day	100 (106/106)	96.6	100 (31/31)	88.8
(b) (4) years of age and older, Week 2 onwards, use 1 or 2 sprays in each nostril once a day, as needed to treat your symptoms	100 (106/106)	96.6	96.8 (30/31)	83.3
Ask a doctor or pharmacist before use if you are taking ritonavir	99.1 (105/106)	94.9	96.8 (30/31)	83.3

Product indication (Uses)	99.1 (105/106)	94.9	96.8 (30/31)	83.3
(b) (4) years of age and older, afte (b) (4) months of daily use, ask your doctor if you can keep using	96.2 (102/106)	90.6	80.6 (25/31)	62.5
Do not use to treat asthma	96.2 (102/106)	90.6	93.5 (29/31)	78.6
Stop use and ask a doctor if you get new symptoms such as severe facial pain or thick nasal discharge	95.3 (101/106)	89.3	100 (31/31)	88.8
Use this product only once a day	92.5 (98/106)	85.7	80.6 (25/31)	62.5
Stop use and ask a doctor if your symptoms do not get better within 7 days of starting use	79.2 (84/106)	70.3	54.8 (17/31)	36.0

The targeted comprehension study focused on the warnings under the **Stop use and ask a doctor if** subheading that had tested poorly in the pilot study (below). Although the general population adequately comprehended the new symptoms item, low-literate performance remained somewhat weaker.

The sponsor also changed the proposed labeling (b) (4) in the indication. Two questions asked about directions targeted to those (b) (4) years of age and older, both of which tested well, although all respondents were above 18 years.

Targeted Label Comprehension Study (RH01318) Results.

	General Population		Low Literate Population	
Primary Objective	% (n/N)	LCB	% (n/N)	LCB
Stop use and ask a doctor if your symptoms do not get better within 7 days of starting use	91.0 (464/510)	88.2	93.5 (143/153)	88.3
Stop use and ask a doctor if you get new symptoms such as such as severe facial pain or thick nasal discharge	95.1 (485/510)	92.8	85.0 (130/153)	78.3
(b) (4) years of age and older, Week 1, use 2 sprays in each nostril once a day	99.8 (509/510)	98.9	98.7 (151/153)	95.4
(b) (4) years of age and older, Week 2 onwards, use 1 or 2 sprays in each nostril once a day, as needed to treat your symptoms	99.8 (509/510)	98.9	97.4 (149/153)	93.4

Targeted Self-Selection Study with People Using Antiretroviral Drugs for HIV – RH01442
Perhaps the key safety concern in switching fluticasone propionate to the over-the-counter market is the risk for glucocorticoid side-effects when used in combination with ritonavir. The HIV medication is a potent CYP 3A4 inhibitor, which can substantially increase fluticasone propionate in plasma, resulting in reduced serum cortisol concentrations. The initial, proposed label warning provided the advice: [redacted] (b) (4) use if you are taking ritonavir (medicine for HIV)."

Objectives
The objectives of the self-selection study were focused on this key risk element, ensuring that people with HIV taking ritonavir would make an appropriate decision about Flonase use. The sponsor proposed the following objectives:

Primary Objective
The primary objective of this study is to demonstrate that subjects who are taking ritonavir make a correct self-selection decision.

Secondary Objective
The secondary objective of this study is to assess the reasons why subjects make incorrect self-selection decisions.

Methodology
The study was a multi-site, single-visit interview study with HIV patients prescribed ritonavir conducted in U.S. clinical sites and HIV clinics. Potential recruitments were pre-screened on the basis of medical records. Participants were provided with an appropriate confidentiality / non-disclosure agreement, orientation, and informed consent. Questions included a self-selection question, the REALM to assess literacy level, and a targeted medical history that included medication history.

The key inclusion criterion was that the participant be taking ritonavir for HIV. Other appropriate, typical exclusions were applied. The actual study demographic and clinical characteristics can be found in Appendix C.

Key Findings
Overall, the ability to self-select among HIV patients using ritonavir was poor. Over ½ the subjects (56.4%) failed to correctly recognize that Flonase use was contraindicated for them because they were taking ritonavir. The proportion of low-literate patients failing to self-select correctly was even worse (60.9%). The pattern of poor self-selection results was consistent across subsets of interest in the final sample (below).

Targeted Self-Selection Study (RHO1442) Results

Population	Correct Self-Selection Rate % (n/N)	95% CI
All subjects	43.6 (174/399)	(38.7, 48.6)
Low-literate	39.1 (36/92)	(29.1, 49.9)
Literate	45.0 (138/307	(39.3, 50.7)
History of nasal allergies	43.0 (99/230)	(36.6, 49.7)
No history of nasal allergies	44.4 (75/169)	(36.8, 52.2)
Used FP previously	37.5 (15/40)	(22.7, 54.2)
Never used FP	44.2 (84/190)	(37.0, 51.6)

The sponsor identified common responses that accounted for the poor results, including failure to recognize ritonavir by its generic name. Almost ¼ recognized the trade name of the drug rather than ritonavir (23.6%), with another 4% simply noting they did not recognize any of the drugs they received by that name. Others suggested that the drug was out of date, denying that they continued to use it (17.3%). Still others explained they had not paid attention or that their doctor said it was appropriate regardless of what was on the box.

The sponsor coded the 225 incorrect responses into categories, further assessing whether the response truly reflected risk (below). Overall, the vast majority of the incorrect responses were attributed to poor comprehension of the materials provided and the assessment was made that the errors presented a significant potential safety risk. About 10% simply missed the contraindication on the packaging, with another 7% admitting they would ignore it.

Table 4 Summary of General and Potential Safety Risk Categories with a Final Code of Incorrect, Eligible Subjects

Categories	Final code of incorrect (N=225)
General Categories n (%)	
Comprehension	182 (80.9 %)
Label Prominence	24 (10.7%)
Behavioral Override	16 (7.1%)
Other	3 (1.3%)
Potential Safety Risk Categories n (%)	
Potential Safety Risk	217 (96.4%)
Minimal/No Safety Risk	8 (3.6%)

Source: Section 9.2, Table 5

On the basis of the study, the sponsor proposed a revision to the label, suggesting that the [redacted] (b) (4) instruction should be extended to all patients receiving a drug for treatment of HIV:

These data indicate that the current proposed language, (b) (4) use if you are taking ritonavir (medicine for HIV infection)" did not adequately address the contraindication for use in a ritonavir prescribed population. Alternate wording, using a more generalized HIV medication statement, i.e. not naming a particular anti-viral medication, should effectively communicate the warning of concomitant use of FP and ritonavir. Examples of such wording are: " (b) (4) **…** if you are taking medicine for HIV infection". This wording responds directly to the observations in this study by removing the reference to the drug name that was an apparent source of confusion for consumers, and does not introduce new terminology that may also be potentially confusing (e.g. "prescription antiretroviral").

Reviewer note: FDA's replication of the main self-selection analyses provided the same results found in the sponsor's reporting. However, the coding of risk categories and assessment of responses was not verified and the sponsor's analysis is presented above. The definition of the potential risk/minimal or no risk distinction (below) clarifies that the comprehension issues are a source of significant risk and continued concern. We have proposed making this warning more prominent in the final labeling.

Category	Scenario Example
Potential Safety Risk	• Subject says product is right for them even though they are taking ritonavir
Minimal or No Safety Risk	• Subject indicates they have been prescribed ritonavir but are not currently taking it • Subject says they do not use OTC medications or only use medications prescribed by their doctor

Human Factors Studies Investigating Correct Use of Product Delivery System—RH01801 & RH01929

Both of the human factors studies conducted for this product were carried out during 2013, although exact dates for data collection are not detailed in the reporting. The final report for RH01801 is dated July 26, 2013, with the final report for RH01929 dated August 1, 2013. Protocols were approved by the Principal Investigator in April and July respectively.

Emphasis in both studies was given to subjects' abilities to correctly use the nasal spray apparatus including the correct route of administration, proper cleaning and priming, and the ability to use the apparatus again after a 2 week lag. RH01801 was focused on a general population while RH01929 was focused on the low-literacy population. The latter study was carried out based on advice from the agency that a low-literate sample be included in usability testing.

Objectives

The stated objective for RH01801 was presented as follows:

> The primary objectives of this usability test were to evaluate the use of the nasal spray by a consumer in an OTC environment, specifically to understand the consumer's ability to clean and prime the nasal spray apparatus correctly, and to demonstrate that the consumer understands how to use the nasal spray, including the correct route of administration of the product (intranasal versus intraocular).

Assessing the potential for inappropriate intraocular use of the spray was a key concern in the human factors testing.

The objectives statement for RH01929 was nearly identical, although the second study focused on respondents with a lower level of reading skills as determined by REALM performance.

Methodology

The usability tests involved a single facility, with a single testing visit by participants. The studies were conducted in line with FDA guidance and proper ethical practice, utilizing an open-label, placebo nasal spray. Participants were consented and then engaged in a one-on-one moderated task session lasting approximately one-hour in duration.

The key elements of the session involved giving the participant the placebo spray with packaging and labeling instructions. Following observation of how the participant used the nasal spray mechanism in a simulated environment, study personnel conducted a post-test interview as needed. The goal was to gain additional understanding when errors in use were detected.

Participants were observed for key elements of use such as route of administration [intranasal versus intraocular], shaking the bottle, priming the pump, and cleaning the actuator. Examples of use performance failures included not priming the pump or not washing/wiping (cleaning) the pump, and using the pump to dispense to the eyes.

Assessment of participant performance was based on a dichotomous pass/fail basis. A pass for most of the items involved completion of several sub-steps. For example, priming included four sub-steps: cap removal, shaking the bottle, pressing down and releasing the pump and priming for visible mist. Following the initial use attempt, the participant was presented the task with the hypothetical proposition that it was two weeks later. Those who failed a particular task during these trials were then questioned about their reasons for incorrectly performing the task.

Those who failed a particular task were also directed to the Quick Start Guide and asked to repeat the failed task. Passing the task in this phase of the study was taken as an indicator about the adequacy of the Quick Start instructions.

All recruits were 18 years of age or older. Above 40% of the participants in each study were naïve to the use of the nasal spray mechanism. Over ½ of the regular population had eye symptoms, while about 1/3 of the low-literate group reported eye symptoms. The demographic and baseline characteristics of the sample are reproduced from sponsor reporting in Appendix D.

Reviewer note: The sponsor adopted FDA's suggestions regarding use of the REALM for screening and adding 15 low-literate participants. Respondents with low-literacy were targeted in Study RH01929.

Key Findings

No participants attempted to spray the placebo product in their eyes, the key safety concern to be addressed in these usability studies. A positive result was seen in both samples. This dimension of safe use is unlikely to raise concern for broad market use.

Conversely, the proportion of participants able to correctly prime, clean, or clean following storage in the course of the 2 initial attempts ("initial use" and "two weeks later") was low. Items tested poorly without prompting to consult the package insert, both for low-literate and general samples. However, participants performed adequately on retry for all tasks with the exception of soaking the spay nozzle in warm water when clogged.

Human Factors Study (RH01801) General Population Correct Use Results—Initial Attempt

Task	Initial Use % (n/N) (95% CI)	Two Weeks Later % (95% CI)
Prime	67.5 (27/40) (53.0, 82.0)	46.2 (18/39) (30.5. 61.8)
Clean (Wipe/Rinse after each use)	52.5 (21/40) (37.0, 68.0)	46.2 (18/39) (30.5, 61.8)
Ocular use	100 (40/40)	100 (40/40)
Clean (after storing for at least 1 week)	NA	11.4 (4/35) (0.7, 19.8)

Human Factors Study (RH01801) General Population Correct Use Results—Repeat Failed Tasks

Task	Correct Use % (n/N) (95% CI)	95% CI
Prime	95 (21/22)	(86.8, 100)
Wipe/Rinse	93 (26/29)	(83.3, 100)
Clean	64 (21/33)	(47.2, 80.1)
Remove spray nozzle	87.9 (29/33)	(71.8, 96.6)
Rinse spray nozzle	84.8 (28/33)	(68.1, 94.9)

Replace spray nozzle	84.8 (28/33)	(68.1, 94.9)
Soak nozzle in warm water if Clogged	63.6 (21/33)	(45.1, 79.6)

Reviewer note: As the tables suggest, most of the poor performance on priming and cleaning resolved given encouragement to consult the Quick Start Guide package insert. However soaking a clogged nozzle continued to test poorly. There were also incidents where replacing the nozzle after cleaning proved difficult and one respondent spray himself in the face. The sponsor suggested that concerns about the cleaning items and poor performance reassembling the sprayer did not constitute a safety risk. We have generally concurred in internal discussions.

Human Factors Low-Literate Targeted Study (RH01929) Correct Use Results—Initial Attempt

Task	Initial Use % (n/N) (95% CI)	Two Weeks Later % (95% CI)
Prime	40 (6/15) (15.2, 64.8)	33.3 (5/15) (9.5, 57.2)
Clean (Wipe/Rinse after each use)	33.3 (5/15) (9.5, 57.2)	40 (6/15) (15.2, 64.8)
Ocular use	100 (15/15)	100 (15/15)
Clean (after storing for at least 1 week)	NA	100 (15/15)

Human Factors Low-Literate Targeted Study (RH01929) Correct Use Results—Repeat Failed Tasks.

Task	Correct Use % (n/N) (95% CI)	95% CI
Prime	100 (10/10)	
Wipe/Rinse	100 (11/11)	
Clean		
Remove spray nozzle	92.3 (12/13)	(64.0, 99.8)
Rinse spray nozzle	84.6 (11/13)	(54.6, 98.1)
Replace spray nozzle	92.3 (12/13)	(64.0, 99.8)
Soak nozzle in warm water if clogged	53.8 (7/13)	(25.1, 80.8)

Based on FDA review of the study protocol, the sponsor also agreed to include interviews assessing the root cause for errors in use. Although no in depth qualitative analysis seems to have been made, bulleted items supported by some illustrative participant explanations were provided.

With regard to the instructions regarding priming and delivery, the interviews revealed some common issues.

The reasons that participants skipped Priming include:

- perceived waste of product
- not considered a necessary step
- something to do if clogged, not normal use.

The reasons that participants did not blow their noses include:

- did not think it is useful when using a nasal spray
- did not have sufficient congestion

The reason that participants did not hold the other nostril closed during aim and spray include:

- directions seemed confusing because there were many simultaneous steps (e.g., spray, hold, breathe, etc.)
- stated they forgot

While detailed in the Quick Start Guide, the instructions for cleaning were also frequently overlooked with common errors, or some rationale provided for not cleaning the delivery mechanism.

Participants offered these reasons for not performing cleaning and wiping activities:

- single user for product (self)
- would not occur to them
- not necessary for such a product

Illustrative errors included instances where the participant:

- incorrectly put the bottle under the faucet and not the spray nozzle
- used alcohol wipe to clean rather than tissue
- did not see the instructions on the back of the Quick Start Guide

The sponsor stressed that the errors were characteristic of nasal sprays in general. To mitigate the errors, the sponsor proposed additional emphasis on problem areas in product FAQs or the instructional materials, referencing the emphasis on cleaning in the Quick Start Guide. Two areas for improvement were also identified outside of the three key elements; namely improving instructions to reduce inadvertent spraying in the face and to increase the prominence of the Quick Start Guide.

Reviewer note: The sponsor approach to making the Quick Start Guide cleaning instructions more prominent and advising the consumer to access the prominently on the carton seem to be reasonable solutions to the noted errors.

Continued concern about difficulties encountered in replacing the spray nozzle and the potential for adverse events was expressed during internal discussion. The internal consensus

reached agreed with the sponsor that potential discharges in the course of cleaning the sprayer did not really constitute a substantial safety risk.

DISCUSSION OF REVIEW ISSUES

As the background included in this review implies, most significant issues have been discussed and agreed upon with the sponsor. (b) (4) [redacted] The sponsor may be encouraged to make a post-market commitment to conduct a small study, particularly if the final label differs significantly from labeling for the first-in-class non-prescription product.

With regard to issues appearing in the behavioral studies, the ability to correctly self-select was very low among HIV-positive patients who receive ritonavir. (b) (4) [redacted]

Finally, the instruction to stop use when symptoms did not improve within 7 days was more frequently unnoticed under the **Stop use and ask a doctor if** subheading. Improvements seen on this item in the pivotal label comprehension study reflected a change in the study scoring algorithm more than anything else. Similarly, the *new symptoms* item in the **Stop use and ask a doctor if** section also tested poorly among low-literate respondents in the pivotal study.

It is likely that relatively poor performance reflects the "double-barreled" instruction in this **Warnings** section subheading. Given that the subheading formats are prescribed by CFR 21 § 201.66(c)(5)(ii) changes in the subheading may not be advised. However, the bulleted items that are performing poorly could be adjusted to better communicate the advised action. This can be raised as an option with the sponsor.

APPENDICES

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/s/

JAMES P STANSBURY
06/06/2014

NARAYAN NAIR
06/09/2014

Labeling Review for Flonase Allergy Relief

SUBMISSION DATES:	September 21, 2013 November 15, 2013 May 13, 2014 May 27, 2014
NDA/SUBMISSION TYPE:	205434
ACTIVE INGREDIENTS:	Fluticasone propionate 50 mcg/spray
DOSAGE FORMS:	Spray, metered
SPONSOR:	GlaxoSmithKline Consumer Healthcare Gregory D. Smith Director, Regulatory Affairs (973) 889-2540
REVIEWER:	Elaine Abraham RPh
TEAM LEADER:	Steven Adah PhD
PROJECT MANAGER:	Jung Lee RPh

I. BACKGROUND

NDA (b) (4) is submitted by GlaxoSmithKline Consumer Healthcare for Flonase Allergy Relief (fluticasone propionate) Nasal Spray as an OTC treatment for the relief of nasal and ocular symptoms associated with allergic (b) (4) rhinitis (b) (4) years and older. The indications are expressed within the proposed OTC labeling as "….temporarily relieves the symptoms of nasal congestion, runny nose, sneezing, itchy nose, itchy and watery eyes due to hay fever, other upper respiratory allergies, (b) (4) ."

The following labeling issues were provided to the sponsor in an information request communication dated November 12, 2013:

(b) (4)

2. Submit complete carton labels for the 60-, 120- (b) (4) -spray count SKUs.
3. Submit annotated font specifications for the complete carton labels you are submitting ((b) (4) 60-, 120- (b) (4) spray count SKUs).

(b) (4)

6. Submit one clamshell retail package (including Drug Facts) as it would appear to the consumer on the retail shelf.

The sponsor responded on November 15, 2013 and provided information and additional labeling (b) (4) that clarified the concerns noted in the filing review. The initial submission of labeling appeared to be pieces of the outer carton. The sponsor submitted a complete retail package which clarified the design of the carton in the November 15 submission. The construction of the clamshell outer cartons is such that the Drug Facts and annotated specifications are the same for all labels.

Submitted Labeling	Representative of Following SKUs
(b) (4)	N/A
60-spray count immediate container	N/A
(b) (4)	N/A
120-spray count immediate container	N/A
(b) (4)	N/A
(b) (4), 60- and 120-spray count PDPs	N/A
(b) (4)	N/A
60-spray count PDP with "NEW!" flag	Flag is representative of flag on other stock-keeping units (SKUs)
(b) (4)	N/A
(b) (4)	N/A
(b) (4)	N/A
(b) (4)	N/A
(b) (4)	N/A

3 x 120-spray count club pack container (with [redacted] t the "New" flag)	N/A
[redacted]	N/A
Drug Facts (peel-back) label attached to back of all cartons	N/A
[redacted]	N/A
Question & Answer Book ([redacted])	N/A
Quick Start Guide	N/A

II. REVIEWER'S COMMENTS

A. Principal Display Panel (PDP) for [redacted], 60-, 120- [redacted]-spray count SKUs

1. Proprietary Name

"Flonase Allergy Relief" was submitted on November 7, 2013 as the proprietary name and was accepted by DMEPA on November 20, 2013. DMEPA also conducted a review of the labeling dated May 12, 2014 to determine if there were any areas of vulnerability that could lead to medication error. The DMEPA review noted the graphic design of the letter "O" in Flonase but concluded that this was unlikely to cause medication errors.

2. Statement of identity

a. The drug class "(glucocorticoid)" should immediately follow the established name of the drug. Although this is a term unlikely to be known to the average consumer, during the review of the recently approved Nasacort Allergy 24 HR (NDA 020468/S-035) "glucocorticoid" was determined to be the best terminology to describe this class of intranasal corticosteroids and would eventually become known to the consumer as they used this type of product.

b. The dosage form, "nasal spray" should follow either the established name or the dosage strength.

c. According to 21 CFR 201.61, the last part of the statement of identity is the pharmacological category. The submitted labels use "allergy relief" as the pharmacological category. Since Flonase is in the same class of drugs as Nasacort Allergy 24 HR, the pharmacological category used for Nasacort, "nasal allergy symptom reliever", should be used in place of "allergy relief".

[redacted]

4. Six hexagonal graphical images on PDP – There are six hexagonal graphical images on the PDP [redacted]

(b) (4) This is actually an odd group of images because four allergy triggers are pictured plus the parts of the body that are affected by the allergens or have symptoms relieved by Flonase (a nose and eye). (b) (4)

5. **"Non-drowsy" claim** – Drowsiness is not listed in the prescription labeling as an adverse effect of Flonase. The acceptability of this claim was verified with the medical reviewer.
6. **"Full Prescription Strength" claim** – The OTC product will contain the same active ingredient and strength (50 mcg) as the current prescription product. As recommended by FDA, the patient population (down to 4 years of age) will be the same. According to our draft labeling SOPs, an "original prescription strength" statement should be reviewed by ODE IV. This similar statement should be brought to the attention of the review team to evaluate its appropriateness on the label.
7. **"24 hour relief" claim** – The product is dosed once daily so this is an accurate statement and is acceptable on the PDP.
8. **NDC number** – While not required, the NDC number is in an acceptable location on the PDP (see 21 CFR 207.35(b)(3)).
9. **Net quantity of contents** – The net quantity of contents conforms to 21 CFR 201.62. Besides the fluid measure, the PDP also lists the number of metered sprays in each SKU and how much drug each spray delivers. This is acceptable on the PDP.
10. **"NEW!" Flag on 60-count SKU (flag representative for all SKUs)**
    a. A "New!" flag may be acceptable if truthful and not misleading. However, in order for the "New!" flag to be truthful and not misleading, it must specify the aspect of the product that is new. The "New!" flag must be revised to specify the aspect of the product that is new or be deleted from the PDP.
    b. The sponsor states that the flag on the 60-count SKU is representative for all SKUs. As our policy is not to accept representative labeling for new applications, the PDP with flag should be submitted for all SKUs and not as representative labeling. It is not necessary to submit PDPs without the flag as it is accepted that the flag will be removed after 6 months of marketing.

(b) (4)

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E. Drug Facts Label – All SKUs

1. General – This discussion of the Drug Facts label provides preliminary comments for the sponsor. There may be changes or additions to the recommendations below based on discipline reviews or team discussion.
2. The ***Active*** ingredient should include the drug class "(glucocorticoid)" after the active ingredient and before the strength. A space should be added to "50mcg" so that is reads "50 mcg".
3. The ***Purpose*** is listed as "Allergy symptom relief". The purpose should be changed to the purpose recommended for this pharmacological class, "Nasal allergy symptom reliever".
4. ***Uses***
   a. (b) (4) The review team has accepted ocular claims for fluticasone so the use of "itchy, watery eyes" is an acceptable use. The other language in this section is consistent with labeling on other OTC allergic rhinitis products.
   b. Remove the bullet before the words "temporarily relieves these symptoms…"
5. ***Warnings***
   a. General – All of the warnings presented by the sponsor on the Drug Facts label are subject to review by the review team. Some decisions have been made by the team and are noted below. There are differences between the Flonase Allergy Relief and the Nasacort Allergy 24 HR Drug Facts labels that will be considered by the review team in labeling meetings.
   b. The first statements under ***Warnings*** "**Only for use in the nose. Do not spray into your eyes or mouth**." are bolded. These statements are important as there is some concern that with Flonase being allowed for ocular claims, some users may mistakenly spray the drug in their eyes. However, bolding is generally reserved for headings and subheadings in Drug Facts and too much bolding can make a label difficult to read. As the first warning, this concern is given prominence. The bolding is not necessary and should be removed.
   c. Do not use
   Under this subheading are the following bullets:
   - to treat asthma
   - (b) (4)
   - if you have an injury or surgery to your nose that is not fully healed
   - if you have ever had an allergic reaction to this product or any of its ingredients

   The sponsor states that the first bullet on asthma is to discourage any use of fluticasone propionate nasal spray in inappropriate patient populations. While both allergy and asthma are treated with topical corticosteroids, allergic rhinitis is treated with intranasal steroids, while asthma is treated with orally inhaled steroids under the supervision of a healthcare professional.
   (b) (4)

[redacted] (b) (4)

The warning about a nasal injury or surgery is based on a precaution in the current prescription labeling on the inhibitory effect of corticosteroids on wound healing.

The last bullet about allergic reactions is a standard warning for OTC products.

The warnings under the subheading "**Do not use"** appear reasonable based on the sponsor's justifications, would be understandable to the consumer, and are acceptable pending team review.

d. Ask a doctor before use if you have

There is one condition listed here, glaucoma. Rare instances of glaucoma and increased intraocular pressure have been reported following use of fluticasone as noted in the prescription label. As there is only one condition listed here, the bullet before glaucoma should be removed (see § 201.66(d)(4)). This warning is acceptable pending team review.

e. Ask a doctor or pharmacist before use if you are taking

There is a single bulleted condition under this subheading, "ketoconazole pills (medicine for fungal infection)". As discussed above, the bullet should be removed (see § 201.66(d)(4)). The review team has agreed to this warning, it will be included in the medical officer's review and is acceptable.

f. When using this product

The following bullets are under this subheading:

- stinging or sneezing may occur a few seconds right after use
- [redacted] (b) (4)

These conditions have been associated with fluticasone in the prescription label and are acceptable in the section of the warnings pending team review.

g. Stop use and ask a doctor if

The following bullets are under this subheading:

- your symptoms do not get better within 7 days of starting use. You may have something more than allergies, such as an infection.
- you get new symptoms such as severe facial pain or thick nasal discharge. You may have something more than allergies, such as an infection.
- you get a constant whistling sound from your nose. This may be a sign of damage inside your nose.
- you get an allergic reaction to this product. Seek medical help right away.
- you get new changes to your vision that develop after starting this product

According to the sponsor, the first two bullets direct the consumer to see their doctor for the appropriate treatment if they have something more serious than allergies, such as bacterial rhinosinusitis. The third bullet refers to the rare possibility of nasal septal perforation. The fourth bullet refers to the standard advice to stop use if there is an allergic reaction. The fifth bullet refers to the rare reports of eye problems such as cataracts or glaucoma in people who have used large amounts of corticosteroids over a period of several years. The statements under this subheading are acceptable pending team review.

h. The last warnings are the pregnancy/breast-feeding warning and "Keep out of reach of children". These follow 21 CFR 201.63(b) and 21 CFR 330.1(g) and are acceptable.

6. ***Directions***

a. The Directions begin with the following bulleted statements:

- read the Quick Start Guide for how to use the spray (b) (4)
- use this product only once a day

The first statement should give abbreviated instructions (such as priming, shaking before use, and cleaning the device) and refer to the Quick Start Guide for detailed instructions. The second statement is acceptable.

b. (b) (4)

c. The approved Nasacort Allergy 24 HR label informs the user to "spray two times into each nostril while sniffing gently". The Flonase Quick Start Guide informs the user to " (b) (4) while pressing down on the spray". Additional wording such as "while sniffing gently" may be useful in the directions but would be subject to team review.

d. The label includes the direction after 6 months of daily use, "Ask your doctor if you can keep using". The other approved glucocorticoid label, Nasacort Allergy 24 HR, does not include the duration of use. This statement and all other proposed directions are subject to review by the review team for acceptability.

7. ***Other information***

a. The acceptability of the first bulleted statement in this section, "you (b) (4) start to feel relief (b) (4) the first (b) (4) and full effect after several days of regular, once-a-day use" is subject to clinical review. According to the sponsor, as per the current approved Rx label, a decrease in nasal symptoms may occur as soon as 12 hours after starting therapy. The full benefit of fluticasone propionate nasal spray may not be achieved until treatment has been administered for several days. The other statements in this section follow § 201.66(c)(7) and are acceptable.

b. A period should be placed after the last sentence of the third bullet, after "…important additional information."

8. ***Inactive ingredients***

The inactive ingredient section follows § 201.66(c)(8) and is acceptable. Any issues with this section should be noted in the CMC review which is pending.

9. ***Questions and comments?***

The information in this section follows § 201.66(c)(9) and is acceptable.

F. Drug Facts Label (peel back)

1. The same general recommendations given for the Drug Facts label apply to the peel back Drug Facts label (see II.E above).

2. Tamper evident statement
   The tamper-evident statement appears on the front panel and is clearly visible without peeling back or folding out the label. This is consistent with FDA's recommendations in the ***Guidance for Industry: Labeling OTC Human Drug Products May 2009***.
   The same comments given for the tamper evident statement apply to the peel back Drug Facts label (see II.C.3 above).

(b) (4)

[redacted]

G. Annotated Specifications for Drug Facts Labels

The font specifications provided for the labels meet the annotated font specifications in 21 CFR 201.66. However, the specifications for characters per inch and leading need to be provided as per § 201.66(d)(3).

H. Immediate Container Labels

The bottle label contains reduced labeling information including proprietary name, established name, drug manufacturer and lot number, which are the minimal labeling required by 21 CFR 201.10(i). The bottle label also contains the statement (b) (4) [redacted] This is a necessary statement to inform the consumer how to use the product as the label has limited information. However this statement should be revised to refer the user to "Read the Drug Facts label and enclosed material…" The bottle label also contains some warnings, storage conditions and expiration date. Reduced labeling is acceptable as complete Drug facts are contained on the outer carton (see § 201.66(c)).

I. Lot number and Expiration Date

The lot number and expiration date are provided on the immediate containers (b) (4) [redacted]. It is also visible to the consumer on the sample of the 120-ct SKU submitted by the sponsor as an example of the packaging of Flonase. The sponsor should confirm that this information is provided and visible to the consumer on all outer cartons.

J. Package Inserts

There may be further recommendations to the package inserts based on team reviews.

(b) (4)

[redacted]

3. **Quick Start Guide**
   This guide provides instructions for dosing, using and cleaning. The instructions and illustrations are clear to follow. The guide is acceptable pending team review.

III. RECOMMENDATIONS

Issue an Information Request communication to the sponsor for the submitted Flonase Allergy Relief labeling and provide the following preliminary comments. Additional recommendations may be forthcoming once all of the reviews are completed. Inform the sponsor that it must make the following labeling revisions:

Principal Display Panel (PDP) for all SKUs

1. **Statement of identity (see 21 CFR 201.61)**
   a. The drug class "(glucocorticoid)" should immediately follow the established name of the drug.
   b. We recommend that the dosage form, "nasal spray" follow either the established name or the dosage strength.
   c. The pharmacological category, "nasal allergy symptom reliever", should be used in place of "allergy relief".
2. (b) (4)

(b) (4)

"NEW!" Flag on 60-count SKU (flag representative for all SKUs)

1. A "New!" flag may be acceptable if truthful and not misleading. However, in order for the "New!" flag to be truthful and not misleading, it must specify the aspect of the product that is new. The "New!" flag must be revised to specify the aspect of the product that is new or be deleted from the PDP.
2. The "NEW!" flag on the 60-count SKU is listed as being representative for all SKUs. As our policy is not to accept representative labeling for new applications, the PDP with flag should be submitted for all SKUs and not as representative labeling. It is not necessary to submit PDPs without the flag as we understand that the flag will be removed after 6 months of marketing.

Tamper evident statement

The statement reads "TAMPER-EVIDENT features for your protection. The product is packaged in a sealed plastic container. Under the cap and nozzle, each bottle has an aluminum seal around bottle neck. **Do not use if any of these features are torn or damaged**." We remind you if an identifying feature is contained on the seal around the bottle neck, it should be included in the labeling (see 21 CFR 211.132).

Drug Facts Label – All SKUs

1. The ***Active*** ingredient should include the drug class "(glucocorticoid)" after the active ingredient and before the strength. A space should be added to "50mcg" so that is reads "50 mcg".
2. The ***Purpose*** should be changed from "Allergy symptom relief" to the purpose recommended for this pharmacological class, "Nasal allergy symptom reliever".
3. ***Uses***
   Remove the bullet before the words "temporarily relieves these symptoms…"
4. ***Warnings***
   a. The first statements under ***Warnings*** "Only for use in the nose. Do not spray into your eyes or mouth." are bolded. Bolding is generally reserved for

headings and subheadings and too much bolding can make a label difficult to read. As this is the first warning statement, this concern is given prominence on the label. The bolding is not necessary and should be removed.

b. **Ask a doctor before use if you have**
As there is only one condition listed here, the bullet before glaucoma should be removed (see 21 CFR 201.66(d)(4)).

c. Ask a doctor or pharmacist before use if you are taking
As there is a single bulleted condition under this subheading, the bullet before "ketoconazole pills (medicine for fungal infection)" should be removed (see § 201.66(d)(4)).

5. Directions

a. The first bulleted statement under ***Directions***, "Read the Quick Start Guide for how to use the spray bottle" should be revised to include abbreviated instructions (such as priming, shaking before use, and cleaning the device) and refer to the Quick Start Guide.

b. The ***Directions*** should be revised to include use down to 4 years of age.

6. Other information

A period should be placed after the last sentence of the third bullet, after "…important additional information."

(b) (4)

Annotated Specifications for Drug Facts Labels

Provide the following annotated font specifications (see § 201.66(d)(3)):

- characters per inch
- leading

Immediate Container Labels

The bottle label contains the statement "IMPORTANT: (b) (4) This statement should be revised to be more specific as to which label, such as "Read the Drug Facts label and enclosed material…"

Lot number and Expiration Date

Confirm that the lot number and expiration date is provided and visible to the consumer on all outer cartons.

(b) (4)

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

42 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ELAINE E ABRAHAM
05/30/2014

STEVEN A ADAH
05/30/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 12, 2014
Requesting Office or Division:	Division of Nonprescription Clinical Evaluation (DNCE)
Application Type and Number:	NDA 205434
Product Name and Strength:	Flonase Allergy Relief (Fluticasone Proprionate) Spray, 50 mcg per spray
Product Type:	Single Ingredient
Rx or OTC:	OTC
Applicant/Sponsor Name:	GlaxoSmithKline Consumer Healthcare
Submission Dates:	September 21, 2013 and November 15, 2013 (amendment)
OSE RCM #:	2013-2182
DMEPA Primary Reviewer:	Otto L. Townsend, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container labels and carton labeling, and instructions for use (IFU) for Flonase Allergy Relief (NDA 205434) for areas of vulnerability that could lead to medication errors.

Flonase (Fluticasone Propionate) Nasal Spray, 50 mcg per spray, was approved on October 19, 1994 for management of seasonal and perennial allergic rhinitis and nonallergic rhinitis. The Sponsor is now seeking a partial Rx (prescription) to over-the-counter (OTC) switch to market Flonase Allergy Relief Nasal Spray for temporary relief of symptoms due to hay fever, other respiratory allergies, (b) (4) If the OTC version is approved, the Rx Flonase will remain marketed for children and adolescents between 4 and 18 years old.

GlaxoSmithKline (GSK) requested a review of the proposed proprietary name, Flonase Allergy Relief, on June 12, 2013 under IND 109805; and on November 7, 2013 under NDA 205434. DMEPA found the proposed name, Flonase Allergy Relief, acceptable on November 20, 2013 (See DARRTS NDA 205434 Proprietary Name Granted, dated 11/20/2013).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D – N/A
ISMP Newsletters	E
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note the all capital letter presentation of the proprietary name and the graphic letter “O” in the “Flonase” part of the proprietary name, Flonase Allergy Relief. However, we don’t anticipate that the proposed presentation of the proprietary name will contribute to medication errors. Therefore, we will not recommend any changes at this point.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container labels and carton labeling are acceptable from a medication error perspective.

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/s/

OTTO L TOWNSEND
05/12/2014

CHI-MING TU
05/12/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 205434 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Flonase Allergy Relief Established/Proper Name: fluticasone propionate Dosage Form: Spray, Metered Strengths: 50 mcg		
Applicant: GlaxoSmithKline Consumer Healthcare Agent for Applicant (if applicable):		
Date of Application: 9/21/13 Date of Receipt: 9/23/13 Date clock started after UN:		
PDUFA Goal Date: 7/23/14	Action Goal Date (if different):	
Filing Date: 11/22/13	Date of Filing Meeting: 11/7/13	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 8		
Proposed indication(s)/Proposed change(s): Temporarily relieves symptoms due to hay fever, other upper respiratory allergies. [redacted] (b) (4) : nasal congestion, runny nose, sneezing, itchy nose, watery eyes		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☒ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☒ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☒ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): DPARP

List referenced IND Number(s): IND 109805 (OTC)/ IND 028636 (Rx)

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☐	☒	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	☐	☒	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐	☒	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be*	☒	☐		PeRC Mtg Scheduled for 2/26/14 Ocular indication = New indication?

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	☒	☐	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☐	☒	☐	No, as FDA has not provided feedback regarding PREA requirements; therefore "Request for Waiver" is not included per Applicant
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☐	☐	☒	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☐	☒	
Prescription Labeling	☒ **Not applicable**			
Check all types of labeling submitted.	☐ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☐	☐		
Is the PI submitted in PLR format?[4]	☐	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☐	☐	☒	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☐	☐	☒	
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☒ Outer carton label ☒ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) (b) (4) ☐ Consumer sample ☒ Other (Club pack, (b) (4), PDP & DFL for Clamshell packages)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☒	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☒	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☒	☐	☐	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☒	DMEPA consulted for labeling

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 10/22/12 (Pre-IND Mtg)—Mtg minutes provided to Sponsor on 11/20/12 2/22/11 (Type B Mtg)—Mtg minutes provided to Sponsor on 3/14/11 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 5/16/13 (Pre-NDA Mtg)—Mtg minutes provided to Sponsor on 6/5/13 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** (b) (4) ***If yes, distribute letter and/or relevant minutes before filing meeting***				(b) (4)

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 7, 2013

BLA/NDA/Supp #: NDA 205434

PROPRIETARY NAME: Flonase Allergy Relief

ESTABLISHED/PROPER NAME: Fluticasone propionate

DOSAGE FORM/STRENGTH: Metered Spray/50 mcg

APPLICANT: GlaxoSmithKline Consumer Healthcare

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Temporarily relieves the symptoms of nasal congestion, runny nose, sneezing, itchy nose, itchy and watery eyes due to hay fever, other upper respiratory allergies. (b) (4)

BACKGROUND: The Applicant submitted a 505(b)(1) application for a partial Rx-to-OTC switch for NDA 205434, Flonase Allergy Relief Nasal Spray, 50 mcg, for the treatment of the relief of the nasal and ocular symptoms associated with allergic (b) (4) rhinitis (b) (4) . The proposed OTC indication includes a new claim for the relief of ocular symptoms. Flonase is currently marketed as an Rx product under NDA 020121 which was approved on October 19, 1994. The Rx is indicated for the management of the nasal symptoms of seasonal and perennial allergic rhinitis and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

Flonase Allergy Relief, if approved, will be the second corticosteroid nasal spray for OTC use. The first product, Nasacort Allergy 24 HR, was approved on October 11, 2013. Nasacort Allergy 24 HR provides for the temporary relief of symptoms of hay fever or other respiratory allergies (nasal congestion, runny nose, sneezing, and itchy nose) in adults and children ages 2 years and older.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jung Lee	Y
	CPMS/TL:	Dan Brum	Y
Cross-Discipline Team Leader (CDTL)	Lesley Furlong		Y
Clinical	Reviewer:	Steven Osborne (DNCE) Stacy Chin (DPARP)	Y Y

	TL:	Lesley Furlong (DNCE) Anthony Durmowicz (DPARP)	Y Y
Social Scientist Review (*for OTC products*)	Reviewer:	Barbara Cohen	Y
	TL:	Lesley Furlong	Y
OTC Labeling Review (*for OTC products*)	Reviewer:	Elaine Abraham	Y
	TL:	Steven Adah	Y
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:		
Clinical Pharmacology	Reviewer:	Yunzhao Ren	Y
	TL:	Satjit Brar	Y
Biostatistics	Reviewer:	David Hoberman (DPARP) Scott Komo (Behavioral Studies)	N Y
	TL:	Joan Buenconsejo(DPARP) Karen Higgins (Behavioral Studies)	Y Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wafa Harrouk	Y
	TL:	Paul Brown	N
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Nina Ni	Y Y
	TL:	Swapan De Danae Christodoulou (Branch Chief)	Y Y
Quality Microbiology *(for sterile products)*	Reviewer:	John Metcalfe	N
	TL:		
CMC Labeling Review	Reviewer:	N/A	
	TL:		

Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Alice Tu	Y
	TL:	Jo Wyeth	N
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers	Carolyn Volpe (OSE/DPV) Peter Diak (OSE/DPV TL)		N Y
Other attendees	Joel Schiffenbauer (DNCE DD) Theresa Michele (DNCE Director) Lydia Gilbert-McClain (DPARP DD) Badrul Chowdhury (DPARP Director) Rebecca McKnight (CMC PM) Sheetal Agarwal (OCP)		Y Y Y Y Y Y

FILING MEETING DISCUSSION:

GENERAL	
• 505(b)(2) filing issues:	☒ Not Applicable
○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☐ YES ☐ NO
Describe the scientific bridge (e.g., BA/BE studies):	
• Per reviewers, are all parts in English or English	☒ YES

translation? **If no**, explain:	☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: The sites used to conduct both pivotal ocular studies were completed over 10 years ago.	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY	☒ Not Applicable

Comments:	☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)?	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

Comments:	
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**: IR requests for 74 Day Letter	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO

• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Theresa Michele

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): n/a

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): CMC, Quality Microbiology Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

JUNG E LEE
12/05/2013

Date: November 20, 2013

NDA Number: 205434

Applicant: Glaxo Smithkline

Drug Name: Fluticasone proprionate aqueous
nasal spray (Flonase Allergy Relief)

NDA: for relief of the nasal and ocular symptoms associated with allergic (b) (4)
rhinitis in (b) (4) years and older.

Consumer studies submitted:

- Pilot label comprehension study
- Targeted label comprehension study – stop use if not better in seven days, or severe facial pain
- Targeted self-selection study – with HIV sufferers
- Human Factors – normal literacy – 40
- Human Factors – low literacy - 15

There are no filing issues from a social science perspective.

Barbara Cohen
Social Science Analyst, DNCE

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/s/

BARBARA R COHEN
11/20/2013

LESLEYANNE FURLONG
11/20/2013

Filing Review for Flonase Allergy Relief

SUBMISSION DATE:	September 21, 2013
NDA/SUBMISSION TYPE:	205434
ACTIVE INGREDIENTS:	Fluticasone propionate 50 mcg/spray
DOSAGE FORMS:	Spray, metered
SPONSOR:	GlaxoSmithKline Consumer Healthcare Gregory D. Smith Director, Regulatory Affairs (973) 889-2540
REVIEWER:	Elaine Abraham RPh
TEAM LEADER:	Steven Adah PhD
PROJECT MANAGER:	Jung Lee RPh

Submitted Labeling	Representative of Following SKUs
(b) (4)	N/A
60-spray count immediate container	N/A
60-spray count immediate container with flag	Flag is representative of flag on other SKUs
(b) (4)	N/A
120-spray count immediate container	N/A
(b) (4)	N/A
(b) (4)	N/A
(b) (4)	(b) (4)
(b) (4)-, 60-, 120- (b) (4) -spray count PDPs	N/A

Drug Facts label	Representative sizes not specified
(b) (4)	N/A
	N/A
Quick Start Guide	N/A

Issues	Yes/No	Comments
Is the supplement correctly assigned as a PA, CBE0, CBE30?	N/A	This is a new NDA
Are the outer container and immediate container labels, and consumer information leaflet and other labeling included for all submitted SKUs?	No	Outer container for 60, 120 (b) (4) spray counts needed. (b) (4)
If representative labeling is submitted, does the submitted labeling represent only SKUs of different count sizes (same flavor and dosage form)?	N/A	(b) (4)
Is distributor labeling included?	No	
Does the submission include the annotated specifications for the Drug Facts label?	Yes	DFL specifications are not associated with particular SKU
Is Drug Facts title and Active ingredient/Purpose section of Drug Facts label visible at time of purchase?	Yes	
Do any of the labels include "prescription strength" or similar statements?	Yes	"Full Prescription Strength"
Do any of the labels include "#1 doctor recommended" or similar endorsement statements?	No	
Do any labels include text in a language other than English?	No	
Is a new trade name being proposed? If multiple trade names, is the primary or preferred trade name identified?	Yes	Flonase Allergy Relief
Does a medical officer need to review any clinical issues?	Yes	New NDA
If SLR, should ONDQA also review?	N/A	

Reviewer's comments:

(b) (4)

PDPs were submitted for the (b) (4), 60-, 120- (b) (4)- spray count SKUs and a representative Drug Facts label, but no complete outer container labeling was submitted. The sponsor states that the (b) (4), 60- and 120-spray count retail packages are identical in layout and labeling content, with the exception of the necessary changes to the net contents statement and NDC number. (b) (4)

The sponsor states that the (b) (4)-, 60-, 120- (b) (4)-count sprays intended for retail use will be packaged in clear, clamshell packaging, with a molded base to allow it to sit upright on the retail shelf. Each clamshell will be completely sealed (b) (4) This packaging serves as a tamper-evident feature. It is not clear from this description and the submission whether complete Drug Facts will be available to the consumer at the time of purchase without destroying the tamper evident feature. The sponsor should submit one clamshell retail package.

(b) (4)

Annotated font specifications were provided for a Drug Facts label but were not associated with a particular SKU. The sponsor should submit annotated font specifications for the complete carton labels as noted above (b) (4) 60-, 120- and (b) (4)- spray count SKUs).

The statement "Full Prescription Strength" on the PDP should be brought to the attention of the review team to evaluate its appropriateness on the label.

Information Request:

The following should be requested in the 74-day letter:

(b) (4)

2. Submit complete carton labels for the 60-, 120- and (b) (4) spray count SKUs.
3. Submit annotated font specifications for the complete carton labels you are submitting (b) (4) 60-, 120- (b) (4) spray count SKUs).

(b) (4)

6. Submit one clamshell retail package (including Drug Facts) as it would appear to the consumer on the retail shelf.

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/s/

ELAINE E ABRAHAM
10/11/2013

STEVEN A ADAH
10/11/2013