CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205434Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2013
See OMB Statement on Page 3.

NDA NUMBER: 205-434

NAME OF APPLICANT/NDA HOLDER: GlaxoSmithKline Consumer Healthcare

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME): Flonase Allergy Relief (fluticasone propionate aqueous nasal spray)

ACTIVE INGREDIENT(S)	STRENGTH(S)
Fluticasone propionate	50 mcg/spray

DOSAGE FORM: Nasal spray

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent

d. Name of Patent Owner	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Graphics (301) 443-1090 EF

Reference ID: 3602882

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

5. No Relevant Patents

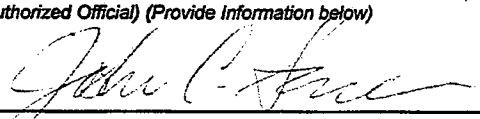
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☒ Yes

Reference ID: 3602882

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	July 23, 2013

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/ holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Joshua C. Sanders, Esq	
Address 709 Swedeland Rd., UW2220	City/State King of Prussia, Pennsylvania
ZIP Code 19406	Telephone Number 610-270-4853
FAX Number *(if available)* 610-270-5090	E-Mail Address *(if available)* joshua.c.sanders@gsk.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

1.3.5.3 Request for Exclusivity

GlaxoSmithKline Consumer Healthcare (GSK CH) is submitting an original New Drug Application (NDA 205-434), filed in accordance with section 505(b)(1) of the Federal Food, Drug and Cosmetic (FD&C) Act, to switch Flonase®[1] (fluticasone propionate) Nasal Spray, 50 mcg, (herein referred to as FPANS) from prescription to OTC status.

FPANS has been approved in the United States as a prescription product since 1994 and is currently available for the relief of the nasal symptoms of seasonal, perennial and nonallergic rhinitis in adults and children 4 years and older.

The current application seeks approval to market FPANS as an OTC product for the treatment of the nasal and ocular symptoms associated with allergic (b) (4) rhinitis in adults 18 years and older.

To demonstrate the suitability of the safety profile of FPANS for the proposed OTC use and to support the proposed labeling (indications, dosing and directions for use), the current application contains data from new clinical safety, efficacy and consumer behaviour studies. The Sponsor considers the data from these studies to meet the requirements for the granting of new product exclusivity and has summarized the basis for this position in the current document to assist FDA in its Waxman-Hatch exclusivity determination for NDA 205-434.

Basis for New Drug Product Exclusivity

The regulations described in 21 CFR 314.108 outline the following four basic requirements that must be met for the granting of new drug product exclusivity attributed to clinical studies submitted as part of a product application.

1. The study or studies meets the definition of "clinical investigation" as any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects.

2. The clinical investigation is "new" in that the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that

[1] Flonase is a registered trademark of the GlaxoSmithKline group of companies.

was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.

3. The clinical investigation was conducted, sponsored or substantially supported by the applicant (as named in Form FDA-1571).

4. This clinical investigation is considered essential to approval in that no other data are available that could support approval of the application product for its intended use as described within the product labeling.

GSK Studies to Support Efficacy - Ocular Symptom Relief

The current application seeks to include the ocular symptoms of allergic rhinitis (i.e. itchy, watery eyes) within the proposed OTC labelling. As such, this application provides new clinical evidence to support the effectiveness of FPANS in the relief of the ocular symptoms of allergic rhinitis. The Integrated Summary of Efficacy (ISE) for NDA 205-434 provides efficacy data from a total of 10 U.S. clinical trials conducted by GSK. These data include 3 clinical studies (2 pivotal studies and 1 supplementary study) in which ocular symptom relief was assessed as a primary clinical endpoint and 7 additional studies in which ocular symptoms were assessed as a secondary endpoint (See Table 1). The data from these studies constitute "new clinical evidence" as these studies have not previously been relied on by FDA to demonstrate substantial evidence of effectiveness. All studies have been conducted by GSK (GSK Pharmaceuticals and/or GSK Consumer Healthcare). Although clinical guidelines recognize the effectiveness of intranasal corticosteroids in relieving ocular eye symptoms associated with allergic rhinitis, these studies provide definitive evidence of the effectiveness of FPANS 200 mcg once daily dosing for the relief of itchy, watery eyes and support the proposed OTC conditions of use as communicated in the submitted labeling. The published literature is not sufficient to independently demonstrate the effectiveness of the product.

Table 1
Clinical Studies Submitted in NDA 205-434 in Support of Ocular Efficacy
(Not Previously Submitted to Rx NDA 20-121)

Studies with Ocular Symptoms as Primary Endpoints			
FNM30033	FNM30034	RH01619	
Studies with Ocular Symptoms as Secondary Endpoints			
FLN-401	FLN-402	FLN-411	FLN-412
FLTA4004	FLTA4006	FLTA4024	

GSK Studies to Support Safety

To provide evidence that the safety profile of FPANS is suitable for OTC use, GSK was requested by FDA (see minutes from Feb 2011 Pre-IND meeting with FDA, dated 14 March 2011) to provide a summary and analysis of safety information from clinical studies conducted for fluticasone propionate nasal spray including data from studies supporting the original prescription NDA and studies conducted subsequent to the Rx approval. GSK was also requested to provide targeted analyses for the following safety issues:

- HPA axis suppression
- Effect on growth
- Effect on bone metabolism
- Effect on glucose metabolism
- Potential drug-drug interactions (with CYP3A4 inhibitors including but not limited to protease inhibitors and azole antifungals)
- Bacterial rhinosinusitis
- Local adverse events such as perforation of the nasal septum

In response, GSK CH has prepared an extensive and detailed assessment of the safety of FPANS by presenting data from a total of 43 clinical studies, global post-marketing events from prescription and nonprescription markets, published literature, and behavioral studies in the Integrated Summary of Safety (ISS). Of these 43 clinical studies, 28 have been pooled to provide an integrated analysis of the overall adverse event profile and 15 non-pooled studies provide safety data to address the specific safety topics that may be associated with nasal corticosteroids as identified above. Of the 43 studies contained in the ISS, a total of 24 studies have not previously been submitted to the Rx NDA (See Table 2). Among the studies listed in Table 2 is Study number R1810198, a pharmacy-based, actual-use trial conducted without physician intervention to simulate actual OTC use. This study was conducted in 2003-04 based in part on FDA's contention at the time that "*...GSK will need to show that consumers will be able to follow the limitations and advice on the label*" to help establish the suitability of the product for a switch to the OTC environment (see minutes from May 2001 Pre-IND meeting with FDA, dated 21 May 2001). Although the label has significantly evolved since the conduct of the study, GSK has included the study within the current application as it remains relevant to the support of safety.

Table 2
Flonase Studies for Pooled and Non-Pooled Safety Analysis
Not Previously Submitted to Rx NDA 20-121

FLN-230	FLN-260	FLN-261	FLN-270	FLN-401
FLN-402	FLN-411	FLN-412	FLTA4004	FLTA4006
FLTA4024	FLTB1009	FLTB3052	FLTB3053	FNM30030
FNM30031	FNM30033	FNM30034	R1810198	R1810220
R1810221	FNM40181	FNS30003	RH01619	

The data from these studies constitute "new clinical evidence" as these studies have not previously been relied on by FDA to demonstrate substantial evidence of effectiveness or safety for a new patient population. All studies have been conducted by GSK (GSK Pharmaceuticals and/or GSK Consumer Healthcare). Lastly, these data are submitted in fulfilment of FDA's request and are considered by the Sponsor to be essential to adequately address the identified safety issues of interest and establish the suitability of the safety profile of FPANS for use in an OTC setting without the intervention of a healthcare professional.

Studies to Support Proposed OTC Dose

In consideration of the appropriate dose for OTC use, GSK conducted two randomized, double blind, placebo controlled, parallel group studies of FPANS 100 mcg QD for the treatment of perennial allergic rhinitis (Study R1810220) and seasonal allergic rhinitis (Study R1810221). These studies were prompted by FDA's observations in 2001 that evidence provided to date have not established a dose-response effect in the range of 100 to 200 mcg and that GSK would need to support that the proposed OTC dose was appropriate in terms of overall efficacy and time to onset (see minutes from May 2001 Pre-IND meeting with FDA, dated 21 May 2001). This question remains relevant today, particularly in light of the potential OTC use of intranasal corticosteroids in the pediatric population as discussed during the July 31, 2013 Advisory Committee meeting for triamcinolone acetonide.

Both studies were conducted by GSK Consumer Healthcare and the data constitute "new clinical evidence" as these studies have not previously been relied on by FDA to demonstrate substantial evidence of effectiveness or safety for a new patient population. GSK considers these data to be essential to confirm the appropriateness of the proposed dosing regimen for the OTC product, i.e. 200 mcg QD consistent with the adult dosing regimen for the approved prescription product.

Summary and Conclusion

NDA 205-434 is an original application containing reports of new clinical investigations essential to approval of the application and the OTC conditions of use communicated in the labeling proposed therein. All relevant studies were conducted by the Sponsor (GSK).

As such, in accordance with the provisions of 21 CFR 314.108(b)(4)(iv), GSK requests to be awarded 3 years of Waxman-Hatch exclusivity associated with NDA 205-434 at the time of approval by the Agency.

EXCLUSIVITY SUMMARY

NDA # 205434 SUPPL # N/A HFD # 560

Trade Name Flonase Allergy Relief

Generic Name fluticasone propionate

Applicant Name GlaxoSmithKline Consumer Healthcare

Approval Date, If Known July 23, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

b) If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Reference ID: 3597973

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	020121	Flonase (fluticasone propionate)
NDA#	202236	Dymista (azelastine HCl, fluticasone propionate)
NDA#	022051	Veramyst (fluticasone furoate)
NDA#	204275	Breo Ellipta (fluticasone furoate, vilanterol trifenatate)
NDA#	021433	Flovent HFA (fluticasone propionate)
NDA#	021152	Cutivate Lotion (fluticasone propionate)
NDA#	019957	Cutivate Ointment (fluticasone propionate)
NDA#	020833	Flovent Diskus (fluticasone propionate)
NDA#	021254	Advair HFA (fluticasone propionate, salmeterol xinafoate)
NDA#	021077	Advair Diskus (fluticasone propionate, salmeterol xinafoate)

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

Clinical studies were submitted to this NDA to support the additional symptom of "itchy, watery eyes." The studies were considered essential to approval of the additional symptom (itchy, watery eyes) included in the Drug Facts Label under the heading Uses. The other symptoms listed under Uses were approved previously; therefore, no additional clinical studies were required or relied upon. Note that had this NDA been submitted without the clinical studies to support the additional symptom of "itchy, watery eyes," it would have been approved, just without the text "itchy, watery eyes."

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

Reference ID: 3597973

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

FNM30033
FNM30034
RH01619

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been

relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 (FNM30033)	YES ☐	NO ☒
Investigation #2 (FNM30034)	YES ☐	NO ☒
Investigation #3 (RH01619)	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 (FNM30033)	YES ☐	NO ☒
Investigation #2 (FNM30034)	YES ☐	NO ☒
Investigation #3 (RH01619)	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

FNM30033
FNM30034
RH01619

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Study Number	IND #	Serial	Date Submitted	Study Sponsor
FNM30033	28,636	329	28 Feb 2001	Glaxo Wellcome Inc.
FNM30034	28,636	329	28 Feb 2001	Glaxo Wellcome Inc.
RH01619	109,805	010	01 Oct 2012	GlaxoSmithKline Consumer Healthcare

Investigation #1 (FNM30033) !
!
IND #28636 YES ☒ ! NO ☐
! Explain:

Investigation #2 (FNM30034) !
!
IND #28636 YES ☒ ! NO ☐
! Explain:

Investigation #3 (RH01619) !
!
IND # 109805 YES ☒ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

N/A

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

Reference ID: 3597973

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Jung Lee
Title: Regulatory Project Manager
Date: July 23, 2014

Name of Office/Division Director signing form: Theresa Michele
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12;

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

/s/

JUNG E LEE
07/23/2014

THERESA M MICHELE
07/23/2014

NDA 205-434

Flonase Allergy Relief

(fluticasone propionate aqueous nasal spray, 50 mcg)

Debarment Certification

GlaxoSmithKline Consumer Healthcare hereby certifies that it did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) in connection with the New Drug Application for *Flonase Allergy Relief* (NDA 205-434).

Bruce V. Hicks

Bruce Hicks
Asst General Counsel, Legal Operations
GlaxoSmithKline Consumer Healthcare

10/9/13

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 205434		
Proprietary Name: Flonase Allergy Relief Established/Proper Name: fluticasone proprionate Dosage Form: Spray, Metered		Applicant: GlaxoSmithKline Consumer Healthcare Agent for Applicant (if applicable):
RPM: Jung Lee, RPh		Division: Division of Nonprescription Clinical Evaluation

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

Actions	
• Proposed action • User Fee Goal Date is July 23, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Reference ID: 3602882

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 8
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☒ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Reference ID: 3602882

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval Letter dated 7/23/14
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	n/a
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included 7/22/14
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s)):* • Review(s) *(indicate date(s):*	• 11/20/13 (Acceptable Letter) • 11/13/13
❖ Labeling reviews *(indicate dates of reviews):*	RPM: ☒ None DMEPA: 5/12/14 DMPP/PLT (DRISK): ☒ None OPDP: ☒ None SEALD: ☒ None CSS: ☒ None Other: 5/30/14; 7/23/14 (DNRD)
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	• 12/5/13 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

Reference ID: 3602882

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Application does not trigger PREA	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	By Mail Acknowledge NDA: 9/23/13 Proprietary Name Granted: 11/20/13 Filing Review Issues: 12/6/13 Labeling Comments: 6/3/14
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Memos to File: 11/7/13*, 11/12/13 (2)*, 5/19/14*, 6/10/14*, 6/16/14*, 6/20/14, 6/24/14*, 6/30/14, 7/7/14*, 7/15/14* (2), 7/16/14 (2), 7/17/14, 7/18/14, 7/21/14 (2), 7/21/14*, 7/22/14, 7/23/14 (2) [*= Information Requests] Internal Mtg Minutes: 3/26/14
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg Pre-NDA Mtg: 5/16/13
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg): Post Mid-Cycle T-Con*	☐ N/A T-con: 3/20/14
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	IND 109805: Type B IND Mtg: 10/22/12 Type B PIND Mtg: 2/22/11
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None
Division Director Summary Review *(indicate date for each review)*	Review Date: 7/23/14
Cross-Discipline Team Leader Review *(indicate date for each review)*	Review Date: 7/1/14
PMR/PMC Development Templates *(indicate total number)*	☐ None
Clinical	
❖ Clinical Reviews	

Reference ID: 3602882

• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	DNCE Filing Review: 11/12/13 DNCE Primary Review: 6/5/14 DPARP Filing Review: 11/20/13 DPARP Primary Review: 6/12/14
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	Filing Review: 11/20/13 Primary Review: 6/9/14
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	6/18/14
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	Filing Review: 11/22/13 Primary Review: 5/30/14 Behavioral Stats: Filing Review: 11/20/13 Primary Review: 6/26/14
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	Filing Review: 11/25/13 Primary Review: 6/12/14
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Reference ID: 3602882

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	Filing Review: 11/7/13 Primary Review: 6/27/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	Filing Review: 11/12/13 Primary Review: 6/13/14; 7/24/14
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	Filing Review: 12/2/13 Primary Review: 5/30/14
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Review Date: 3/12/14 as noted in CMC's Primary Review dated 6/13/14
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: 7/17/14 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Reference ID: 3602882

NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

Reference ID: 3602882

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	N/A
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

Reference ID: 3602882

1.3.4 Financial Certification & Disclosure By Clinical Investigators

In accordance with 21 CFR 54.4(a)(3) all clinical investigators that were involved in the conduct of a study as part of this new drug application were evaluated to determine whether completion of Forms FDA 3454 and FDA 3455, certifying and disclosing any financial interests and arrangements for "covered studies" as defined in 21 CFR 54.2, was required.

This application contains data from a total of 45 clinical studies. As part of the assessment of financial certification and disclosure requirements, the sponsor considered the role of the clinical study within the context of the submission (e.g. used to establish effectiveness of the product), whether these studies had been previously submitted in a marketing application, and the timing of the conduct of the study. Specifically, financial interest information is provided for clinical investigators participating in studies included in this application in compliance with the Final Rule on Financial Disclosure by Clinical Investigators published on February 2, 1998 (63 FR 5233), as subsequently revised by publication on December 31, 1998 (63 FR 72171) (hereafter collectively referred to as the "rule").

The studies included in this application within the Integrated Summary of Safety for the sole purpose of supporting the safety of the product are not considered to be "covered studies" for the purposed of financial reporting.

Studies completed prior to February 1998

For this NDA submission, seven (7) studies relevant to the support of the effectiveness of the product at treating ocular symptoms associated with allergic rhinitis were completed prior to the FDA Financial Disclosure Rule. These studies are listed in Table 2 on the following page.

From a historical perspective, even though the seven studies listed in Table 2 were completed prior to the implementation of the Final Rule, the sponsor already had processes in place to account for financial payments to investigators who participated in clinical studies, as outlined in Table 1 below.

Table 1
Glaxo Wellcome/GlaxoSmithKline Pre-Final Rule Compliance with the Financial Disclosure by Clinical Investigators

Provisions of the Final Rule	Legacy Processes for Compliance
Any compensation made to the investigator by any sponsor of the covered clinical study in which the value of compensation could be affected by study outcome.	It was not at the time (and never has been) part of Glaxo Wellcome or GlaxoSmithKline practice to compensate an investigator in a way that could be affected by study outcome.
A proprietary interest in the tested product including, but not limited to, a patent, trademark, copyright or licensing agreement.	Flonase is wholly owned by the company and none of the investigators used in the clinical trials had proprietary interest
Any equity interest in any sponsor of the covered clinical study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices. The requirement applies to interests held during the time the clinical investigator is carrying out the study and for one year following completion of the study	Glaxo Wellcome/GlaxoSmithKline stock has always been publicly traded (as opposed to non-public stock "whose value cannot be readily determined through reference to public prices")

Reference ID: 3602882

Table 2
Seven Flonase Efficacy Studies Completed Prior to the Final Financial Disclosure Rule

Protocol No.	Protocol Title	Study Phase	Study End Date	Sponsor(s) (GlaxoSmithKline and/or name of third party sponsor*)
FLN-401	A double-blind, double-dummy, randomized, parallel group comparison of the efficacy and safety of fluticasone propionate aqueous nasal spray 200mcg QD versus terfenadine 60mg BID versus placebo for two weeks in patients with seasonal allergic rhinitis in the mountain cedar season.	IV	20-Mar-91	GlaxoSmithKline
FLN-402	A double-blind, double-dummy, randomized, parallel group comparison of the efficacy and safety of fluticasone propionate aqueous nasal spray 200mcg QD versus terfenadine 60mg BID versus placebo for four weeks in patients with seasonal allergic rhinitis	III	24-Jul-91	GlaxoSmithKline
FLN-411	A double-blind, double-dummy, randomized, parallel group comparison of the efficacy and safety of fluticasone propionate aqueous nasal spray 200mcg QD versus astemizole 10mg QD versus placebo for two weeks in patients with seasonal allergic rhinitis	IV	30-Oct-91	GlaxoSmithKline
FLN-412	A double-blind, double-dummy, randomized, parallel group comparison of the efficacy and safety of fluticasone propionate aqueous nasal spray 200mcg QD versus astemizole 10mg QD versus placebo for four weeks in patients with seasonal allergic rhinitis.	IV	13-Jul-92	GlaxoSmithKline

Reference ID: 3602882

Table 2
Seven Flonase Efficacy Studies Completed Prior to the Final Financial Disclosure Rule

Protocol No.	Protocol Title	Study Phase	Study End Date	Sponsor(s) (GlaxoSmithKline and/or name of third party sponsor*)
FLTA4004	Double-Blind, Double-Dummy, Randomized, Parallel-Group Comparison of the Efficacy and Safety Outcomes of Fluticasone Propionate Aqueous Nasal Spray Versus Encapsulated Loratadine Tablets Versus Placebo for Four Weeks in Subjects with Seasonal Allergic Rhinitis	IV	1-Jan-98	GlaxoSmithKline
FLTA4006	Double-blind, double-dummy, randomized, parallel group comparison of the efficacy and safety of fluticasone proprionate aqueous nasal spray vs encapsulated loratadine tablets vs a combination of fluticasone proprionate and loratidine vs placebo for two weeks in subjects with seasonal allergic rhinitis.	IV	20-Feb-96	GlaxoSmithKline
FLTA4024	Double-blind, double-dummy, randomized, parallel group comparison of fluticasone proprionate aqueous nasal spray versus encapsulated loratadine tablets versus a combination of fluticasone proprionate and loratadine versus placebo for two weeks in subjects with seasonal allergic rhinitis	IV	10-Jan-97	GlaxoSmithKline

A list of principal/sub investigators for each study listed in Table 2 above is included in this NDA.

Collection of investigator financial interest information

GlaxoSmithKline (GSK) relied upon investigator financial interest information provided by the investigators through questionnaires. To the extent investigators have provided financial interest information via questionnaires, they were asked to do so based on site-specific (or if shorter, their individual) study start and completion dates. If, according to their written commitment to GSK, investigators filed questionnaires of updated financial interest information to account for any changes in the 1-year period following study completion, these additional questionnaires were relied on as well.

All investigators have supplied information upon commencement of their participation in the study. No investigator had a financial interest in GSK at the time they started their participation in the covered study. If GSK has been unable to collect financial information at the end of the study, then these investigators are included in listing 3454b Data Not Obtained. The appropriate due diligence process as per GSK SOPs, which is up to 3 documented attempts to collect, was carried out to ensure the best achievable data collection, and documented in the Sponsor Study Record.

It is the policy of GSK not to allow the participation of investigators in a clinical study if they, their spouse or dependent children have proprietary interest in the tested product. It is also the policy of GSK not to compensate Investigators in a way that the amount of compensation received could be affected by the outcome of the study. The questionnaire does include collection of this information since these GSK policies are in place.

Financial interest information is not collected from investigators who are also GSK employees during the conduct of the study. Investigators who become GSK employees during the one year period following their completion of the study are instructed to report changes in financial interest information, within the 1 year period following their completion of the study.

Current or Former employees of the Sponsor

From the data collected, there has not been any reported case of any current or former GlaxoSmithKline employees being used as an investigator in the covered studies.

Significant payments of other sorts

From the data collected there has not been any Significant Payments of Other Sorts reported from the sponsor of the covered study as per 21 CFR 54.4(a)(3)(ii), 54.2(f).

Proprietary interest in the tested product

From the data collected there has not been any Proprietary Interest reported as per 21 CFR 54.4(a)(3)(iii), 54.2(c).

Significant equity interest

From the data collected, there were three Investigators/sub-investigators within the covered clinical studies for this NDA (see Table 3) with significant equity interest reported as per 21 CFR 54.4(a)(3)(iv), 54.2(b).

In Study FNM30033, site number (b) (6) recruited (b) (6) subjects from a total of (b) (6) subjects which was (b) (6) % of the total recruitment. Additionally, sub-investigator (b) (6) reported $103,500.00 in equity. An impact analysis was carried out and it was concluded that the results of the study were not impacted by the data generated by the subjects recruited by site (b) (6)

In Study (b) (4) sub-investigator (b) (6) within site number (b) (6) (b) (6) - Principal Investigator) reported an equity interest of $148,707. (b) (6) of the (b) (6) subjects (b) (6) were enrolled in (b) (6) (b) (6) site. An impact analysis was carried out and it was concluded that the results of the study were not impacted by the data generated by the subjects recruited by (b) (6) site.

In Study (b) (4) investigator (b) (6) (site number (b) (6)) reported $60,000 in equity at the height of the study. (b) (6) of the (b) (6) subjects (b) (6) were enrolled in (b) (6) No impact analysis was performed as the percentage of subjects enrolled in site number (b) (6) were less than (b) % and unlikely to impact overall study outcome.

Covered Clinical Studies

The studies listed in Table 3 are the "covered clinical studies" for purposes of the rule for this NDA. All of the studies in the table below were:

- Conducted by either GSK Pharmaceuticals or GSK Consumer Healthcare;
- Initiated after the Final Rule came into effect;
- Have not been submitted in a previous marketing application for Flonase.

Table 3
Flonase Studies Included Within NDA 205-434 Covered Under the Financial Disclosure Rule

Protocol No.	Protocol Title	Sponsor
FNM30033	A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy of a Four-Week Course of Fluticasone Propionate Aqueous Nasal Spray (200mcg QD) on Ocular Symptoms Commonly Associated with Allergic Rhinitis	GlaxoSmithKline Pharmaceuticals
FNM30034	A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy of a Four-Week Course of Fluticasone Propionate Aqueous Nasal Spray (200mcg QD) on Ocular Symptoms Commonly Associated with Allergic Rhinitis	GlaxoSmithKline Pharmaceuticals

Table 3
Flonase Studies Included Within NDA 205-434 Covered Under the Financial Disclosure Rule

Protocol No.	Protocol Title	Sponsor
R1810198	An Actual Use Study in Support of the Over-the-Counter Switch of Flonase® Allergy	GlaxoSmithKline Consumer Healthcare
R1810220	An Efficacy and Safety Study of Fluticasone Propionate Aqueous Nasal Spray in Subjects with Perennial Allergic Rhinitis	GlaxoSmithKline Consumer Healthcare
R1810221	An Efficacy and Safety Study of Fluticasone Propionate Aqueous Nasal Spray in Subjects with Seasonal Allergic Rhinitis	GlaxoSmithKline Consumer Healthcare
RH01619	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Multi-center Study to Assess the Efficacy of once daily Fluticasone Propionate Aqueous Nasal Spray 200mcg for 14 Days on Ocular Symptoms Associated with Allergic Rhinitis	GlaxoSmithKline Consumer Healthcare

T-Con with GSK July 22, 2014 at 11:15am

RE: Revised Labeling Email Received 7/21/14 for NDA 205434 Flonase Allergy Relief (fluticasone proprionate) Rx-to-OTC switch

FDA Participants:
Daniel Brum, PharmD, MBA, BCPS, RAC Chief, Project Management Staff
Jung Lee, RPh, Regulatory Project Manager
Jade Pham, PharmD, MHSc, Regulatory Project Manager

GSK Participants:
Erin Oliver, MBA, RAC – Director, US Regulatory Affairs
Peter Kratochvila, BSC, LLB, MA – Vice President, Regulatory Affairs, Wellness and North America
Sue James - Vice President, Worldwide Regulatory Affairs, Quality and Compliance

T-Con Meeting Minutes:

(b) (4)

FDA reminded GSK of the stipulations outlined in the Durham-Humphrey Amendment which specifically defines a drug as a prescription or OTC product. FDA explained that a product could be marked as both Rx and OTC if there was a clinically meaningful difference between them. However, if there was no meaningful difference between the Rx and OTC product, then they could not be marketed under both status. Miralax OTC was cited as such an example.

GSK asked if final agreed labeling would need to be submitted formally through the Electronic Submission Gateway (ESG). FDA responded, under the circumstances (e.g., GSK said they were having technical problems), FDA is amenable to receiving final agreed labeling via email. Given the pending action date of July 23, 2014, GSK asked if representative labeling could be submitted for the labeling components provided in an email dated July 21, 2014. FDA stated that representative labeling is typically not acceptable for a new NDA and complete labeling would need to be submitted for review. However, if this is not feasible, given the limited amount of time, GSK may consider submitting labeling for some SKU's prior to the action date, and immediately after approval consider submitting a labeling supplement for the remaining SKU's for review. GSK agreed to provide revised labeling by the end of the day. To expedite the review process, FDA suggested providing components of the revised labeling as they become available.

GSK sought to get more insight into the exclusivity review process. FDA explained the exclusivity summary forms are published in the Action Packages which are posted on the Drugs@FDA website. FDA noted the exclusivity summary is reviewed by an exclusivity board that meets periodically. The granting of exclusivity is published in the Orange Book and no formal notification is provided to the Applicant.

From: Erin Oliver
To: Lee, Jung E (OND)
Cc: Brum, Dan
Subject: RE: NDA 205434 (Flonase Allergy Relief): Revised Labeling
Date: Monday, July 21, 2014 8:27:39 PM
Attachments: image004.png
image001.png

Hi Jung and Dan,

Can you please confirm when you need to receive final agreed labeling and if you need to receive as formal correspondence through the ESG.

Given our action date of Wednesday – since we have just received the Agency's final feedback – would you accept the submission of representative labeling as stipulated below to support the Agency's final labeling review.

We will commit to providing updated artwork for the remainder of the labeling components with final printed labeling to be submitted within 30 days of approval.

Please let me know if this approach is acceptable.

Thanks and best regards.

Erin

(b) (4)

Erin Oliver
Head US Regulatory Affairs
Wellness & NA GRQ
Research & Development

GSK Consumer Healthcare,
1500 Littleton Road, Parsippany, NJ 07054
Email Erin.E.Oliver@gsk.com
Tel +1 973 889 2516

gsk.com | Twitter | YouTube | Facebook | Flickr

From: Lee, Jung E (OND) [mailto:JungE.Lee@fda.hhs gov]
Sent: Monday, July 21, 2014 4:22 PM
To: Erin Oliver
Cc: Brum, Dan
Subject: RE: NDA 205434 (Flonase Allergy Relief): Revised Labeling

Hi Erin,

We have the following labeling comments:

(b) (4)

Once you are finished revising all labels and package inserts, you will need to resubmit all labels (no representative labels) for our review.

Thanks,
Jung

From: Erin Oliver [mailto:Erin.E.Oliver@gsk.com]
Sent: Monday, July 21, 2014 4:14 PM
To: Lee, Jung E (OND); Brum, Dan
Subject: RE: NDA 205434 (Flonase Allergy Relief): Revised Labeling

Hi Jung and Dan,

Should we still expect to receive feedback today?

Erin

Erin Oliver

Head US Regulatory Affairs
Wellness & NA GRQ
Research & Development

GSK Consumer Healthcare,
1500 Littleton Road, Parsippany, NJ 07054
Email Erin E.Oliver@gsk.com
Tel +1 973 889 2516

gsk.com | Twitter | YouTube | Facebook | Flickr

From: Lee, Jung E (OND) [mailto:JungE.Lee@fda.hhs gov]
Sent: Friday, July 18, 2014 5:09 PM
To: Erin Oliver
Subject: RE: NDA 205434 (Flonase Allergy Relief): Revised Labeling

Most likely our response will not come before Monday afternoon.

From: Erin Oliver [mailto:Erin.E.Oliver@gsk.com]
Sent: Friday, July 18, 2014 5:07 PM
To: Lee, Jung E (OND)
Subject: RE: NDA 205434 (Flonase Allergy Relief): Revised Labeling

Jung, thank you for your comments and for getting back to us so quickly.

We will amend page 5 of the Question & Answer Guide accordingly and await the Agency's final comments related to (b) (4).

I think you or Dan mentioned the next team meeting was on Monday. Can you give us a sense of timing – and when we might hear back from you?

BR,

Erin

Erin Oliver
Head US Regulatory Affairs
Wellness & NA GRQ
Research & Development

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Email Erin E.Oliver@gsk.com
Tel +1 973 889 2516

gsk.com | Twitter | YouTube | Facebook | Flickr

From: Lee, Jung E (OND) [mailto:JungE.Lee@fda.hhs gov]
Sent: Friday, July 18, 2014 5:01 PM
To: Erin Oliver
Subject: RE: NDA 205434 (Flonase Allergy Relief): Revised Labeling
Importance: High

Hi Erin,

We are reviewing your revised, draft labeling submitted via e-mail on Friday, July 18, 2014, and have the following comments:

- On page 5 of the Question & Answer book, modify the second sentence of the first statement to: "It works directly in the nose to **help** block your allergy reactions."
- As noted in our previous labeling comments, we continue to have concerns regarding (b) (4). Additional labeling comments regarding these claims will be forthcoming.

Other than the first comment and labeling comments related to (b) (4) above, we find all the other changes acceptable.

Thanks,
Jung

From: Erin Oliver [mailto:Erin.E.Oliver@gsk.com]
Sent: Friday, July 18, 2014 7:04 AM
To: Lee, Jung E (OND)
Subject: NDA 205434 (Flonase Allergy Relief): Revised Labeling

Hi Jung,

Attached please find revised draft labeling for NDA 205434 Flonase Allergy Relief (fluticasone propionate nasal spray).

The labeling has been revised from the versions submitted to FDA via e-mail on 11 Jun 2014 (S-0012, submitted 19 Jun 2014) to address FDA's comments from July 8th and July 11th.

The revisions reflect the agreements of our teleconference from 15 July 2014 and the Agency's agreement to the Question & Answer Booklet as communicated to GSK yesterday.

(b) (4) We've replaced this information with the icons from the front of the package and language consistent with the Question & Answer Booklet.

(b) (4)

The (b) (4) is in progress and will be sent to you today.

If you have any questions, please let me know.

We look forward to receiving the Agency's feedback.

Best regards.

Erin

Erin Oliver
Head US Regulatory Affairs
Wellness & NA GRQ
Research & Development

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Email Erin.E.Oliver@gsk.com
Tel +1 973 889 2516
Mobile (b) (6)

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/s/

JUNG E LEE
07/22/2014

From: Lee, Jung E (OND)
To: Erin Oliver
Cc: Brum, Dan
Subject: RE: NDA 205434 (Flonase Allergy Relief): Revised Labeling
Date: Monday, July 21, 2014 4:22:22 PM
Attachments: image001.png

Hi Erin,

We have the following labeling comments:

- (b) (4)
-

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Jung

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From: Lee, Jung E (OND) [mailto:JungE.Lee@fda.hhs.gov]
Sent: Friday, July 18, 2014 5:01 PM
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Importance: High

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We look forward to receiving the Agency's feedback.

Best regards.

Erin

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/s/

JUNG E LEE
07/21/2014

From: Erin Oliver
To: Lee, Jung E (OND)
Subject: RE: NDA 205434 (Flonase Allergy Relief): Revised Labeling
Date: Friday, July 18, 2014 5:06:43 PM
Attachments: image002.png
image003.png

Jung, thank you for your comments and for getting back to us so quickly.

We will amend page 5 of the Question & Answer Guide accordingly and await the Agency's final comments related to (b) (4)

I think you or Dan mentioned the next team meeting was on Monday. Can you give us a sense of timing – and when we might hear back from you?

BR,

Erin

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From: Lee, Jung E (OND) [mailto:JungE.Lee@fda.hhs.gov]
Sent: Friday, July 18, 2014 5:01 PM
To: Erin Oliver
Subject: RE: NDA 205434 (Flonase Allergy Relief): Revised Labeling
Importance: High

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If you have any questions, please let me know.

We look forward to receiving the Agency's feedback.

Best regards.

Erin

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/s/

JUNG E LEE
07/21/2014

From: Erin Oliver
To: Erin Oliver; Lee, Jung E (OND)
Subject: RE: NDA 205434 (Flonase Allergy Relief): Revised Labeling
Date: Friday, July 18, 2014 4:46:08 PM
Attachments: image003.png
image004.png
(b) (4)

Hi Jung,

(b) (4)

If you send me your direct mailing address I can send you an actual mock-up once we have finalized the labeling.

Thanks.

Erin

Erin Oliver
Head US Regulatory Affairs
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Sent: Friday, July 18, 2014 7:04 AM
To: 'Lee, Jung E (OND)'
Subject: NDA 205434 (Flonase Allergy Relief): Revised Labeling

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(b) (4)

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(b) (4)

If you have any questions, please let me know.

We look forward to receiving the Agency's feedback.

Best regards.

Erin

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JUNG E LEE
07/21/2014

From: Erin Oliver
To: Lee, Jung E (OND)
Subject: NDA 205434 (Flonase Allergy Relief): Revised Labeling
Date: Friday, July 18, 2014 7:05:30 AM
Attachments: image003.png
Revised Labeling_17 Jul 14.pdf

Hi Jung,

Attached please find revised draft labeling for NDA 205434 Flonase Allergy Relief (fluticasone propionate nasal spray).

The labeling has been revised from the versions submitted to FDA via e-mail on 11 Jun 2014 (S-0012, submitted 19 Jun 2014) to address FDA's comments from July 8th and July 11th.

The revisions reflect the agreements of our teleconference from 15 July 2014 and the Agency's agreement to the Question & Answer Booklet as communicated to GSK yesterday.

(b) (4)

We've replaced this information with the icons from the front of the package and language consistent with the Question & Answer Booklet.

(b) (4)

If you have any questions, please let me know.

We look forward to receiving the Agency's feedback.

Best regards.

Erin

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Research & Development

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/s/

JUNG E LEE
07/18/2014

From:	Erin Oliver
To:	Lee, Jung E (OND)
Subject:	RE: Follow-up to 15 Jul 14 teleconference-Revised Question & Answer Booklet
Date:	Thursday, July 17, 2014 10:33:47 AM
Attachments:	image003.png image004.png image005.png

Hi Jung, that's great! thanks very much. I'll share with the team so we can progress the artwork revisions.

BR,

Erin

Erin Oliver
Head US Regulatory Affairs
Wellness & NA GRQ
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Tel +1 973 889 2516

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From: Lee, Jung E (OND) [mailto:JungE.Lee@fda.hhs.gov]
Sent: Thursday, July 17, 2014 10:27 AM
To: Erin Oliver
Subject: RE: Follow-up to 15 Jul 14 teleconference-Revised Question & Answer Booklet

Hi Erin,

We find the all latest proposed changes below acceptable.

Thanks,
Jung

From: Erin Oliver [mailto:Erin.E.Oliver@gsk.com]
Sent: Wednesday, July 16, 2014 6:25 PM
To: Lee, Jung E (OND)
Subject: RE: Follow-up to 15 Jul 14 teleconference-Revised Question & Answer Booklet
Importance: High

Jung,

Thanks so much.

(b) (4)

On page 7, (b) (4)
"Flonase acts on multiple types of inflammatory substances…

From an educational perspective, we would like to retain reference to the other mediators in addition to histamine to explain the term "multiple".

We propose "Flonase acts on multiple types of inflammatory substances, including histamine, prostaglandins, cytokines, tryptases, chemokines, and leukotrienes."

We'd like to continue to leverage the information within the Rx detail aid, so it would be really helpful to have the consumer materials be consistent.

Is this acceptable to the Agency?

Erin

Erin Oliver
Head US Regulatory Affairs
Wellness & NA GRQ
Research & Development

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Tel +1 973 889 2516

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From: Lee, Jung E (OND) [mailto:JungE.Lee@fda.hhs.gov]
Sent: Wednesday, July 16, 2014 4:38 PM
To: Erin Oliver
Subject: RE: Follow-up to 15 Jul 14 teleconference-Revised Question & Answer Booklet
Importance: High

Hi Erin,

Here are some additional labeling comments.

We agree to your 7/16/14 revisions to the Question & Answer Booklet but have the following edits:

- On page 6, remove [redacted] (b) (4).
- On page 7, change [redacted] (b) (4) to "Flonase acts on multiple types of inflammatory substances…"
- The statement "Most common OTC allergy pills act on histamine alone" is acceptable.

Thanks,
Jung

From: Lee, Jung E (OND)
Sent: Wednesday, July 16, 2014 4:22 PM
To: Erin Oliver
Subject: RE: Follow-up to 15 Jul 14 teleconference-Revised Question & Answer Booklet
Importance: High

Hi Erin,

We have the following labeling information request:

- *All annotated specifications provided are acceptable. However, the font size for "Drug Facts (continued)" should be provided.*

Can you let me know when you expect to provide us the revised labels? I know there are still some outstanding issues regarding the labeling but if you have something you can send us now that would be much appreciated since I know we are running low on time. I will also forward any additional labeling comments as I receive them to help facilitate the labeling process. In addition, we are willing to accept representative labeling for one spray size for now and ask that you provide all SKU labels for the remaining spray sizes prior to the action date (July 23), preferably by Monday, July 21. Please let me know if you have any questions.

Thanks,
Jung

From: Erin Oliver [mailto:Erin.E.Oliver@gsk.com]
Sent: Wednesday, July 16, 2014 6:33 AM
To: Lee, Jung E (OND)
Subject: Follow-up to 15 Jul 14 teleconference-Revised Question & Answer Booklet

Jung,

During yesterday's teleconference with the Agency, we discussed the following 2 labeling comments:

[redacted] (b) (4)

We request to retain page 7 of the Question & Answer Booklet. The question "How does Flonase work?" is among the most frequently asked questions and we believe it is important to address this question within the package insert which provides additional space to include the appropriate context and explanatory language.

We appreciate the Agency's consideration of this request and look forward to receiving your feedback.

Best regards.

Erin

Erin Oliver
Head US Regulatory Affairs
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/s/

JUNG E LEE
07/17/2014

From:	Lee, Jung E (OND)
To:	Erin Oliver
Subject:	RE: Follow-up to 15 Jul 14 teleconference-Revised Question & Answer Booklet
Date:	Wednesday, July 16, 2014 4:38:22 PM
Attachments:	image001.png
Importance:	High

Hi Erin,

Here are some additional labeling comments.

We agree to your 7/16/14 revisions to the Question & Answer Booklet but have the following edits:

- On page 6, remove [redacted] (b) (4).
- On page 7, change [redacted] (b) (4) to "Flonase acts on multiple types of inflammatory substances…"
- The statement "Most common OTC allergy pills act on histamine alone" is acceptable.

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JUNG E LEE
07/16/2014

From: Erin Oliver
To: Lee, Jung E (OND)
Subject: Follow-up to 15 Jul 14 teleconference-Revised Question & Answer Booklet
Date: Wednesday, July 16, 2014 6:32:51 AM
Attachments: image002.png
Q&A Booklet Pages 6 to 7_Updated 15JUL2014 post FDA meeting.pdf

---

Jung,

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(b) (4)

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(b) (4)

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Best regards.

Erin

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/s/

JUNG E LEE
07/16/2014

From:	Erin Oliver
To:	Lee, Jung E (OND)
Subject:	RE: NDA 205434 (Flonase): Additional Labeling Comments
Date:	Tuesday, July 15, 2014 6:40:24 AM
Attachments:	image002.png image003.png GSK Response to FDA Label Comments 8 and 11 Jul 14 FDA Pre-read.docx NDA205434 Pre-read for 15 July 14 tcon.pdf

Hi Jung,

Attached please find 2 documents intended to facilitate our discussion today – we wanted to provide in advance of our call so the Agency had the information available for use during your internal meeting.

The WORD document is a summary of the Agency's comments from July 8th and July 11th and GSK's responses. You'll note that we agree to implement the majority of the Agency's labeling comments as is; for several (shaded in orange) we require additional discussion to proceed or have an alternative proposal for the Agency's consideration.

(b) (4)

Any questions, please let me know.

Thanks very much.

Erin

Erin Oliver
Head US Regulatory Affairs
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From: Lee, Jung E (OND) [mailto:JungE.Lee@fda.hhs.gov]
Sent: Monday, July 14, 2014 2:38 PM
To: Erin Oliver
Subject: RE: NDA 205434 (Flonase): Additional Labeling Comments

Hi Erin,

Narayan Nair, MD, Medical Officer Team Leader (Acting), DNCE will also be on the call.

Thanks,
Jung

From: Erin Oliver [mailto:Erin.E.Oliver@gsk.com]
Sent: Monday, July 14, 2014 1:03 PM
To: Lee, Jung E (OND)
Subject: RE: NDA 205434 (Flonase): Additional Labeling Comments

Thanks very much, Jung.

We look forward to a productive discussion tomorrow.

Best regards.

Erin

Erin Oliver
Head US Regulatory Affairs
Wellness & NA GRQ
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From: Lee, Jung E (OND) [mailto:JungE.Lee@fda.hhs.gov]
Sent: Monday, July 14, 2014 1:01 PM
To: Erin Oliver
Subject: RE: NDA 205434 (Flonase): Additional Labeling Comments

Hi Erin,

Thank you for providing the information below. I am confirming tomorrow's T-con with FDA and GSK. The T-con will be from 10:30am to 11:30am. We look forward to speaking with you too.

FDA Participants:

Theresa Michele, MD, Director, DNCE
Dan Brum, PharmD, Chief, Project Management Staff
Elaine Abraham, RPh, Interdisciplinary Scientist Reviewer, DNRD
Steven Adah, PharmD, Interdisciplinary Scientist Team Leader, DNRD
James Stansbury, Social Scientist, DNCE
Stacy Chin, MD, Medical Officer, DPARP
Anthony Durmowicz, MD, Medical Officer Team Leader, DPARP

Thanks,
Jung

From: Erin Oliver [mailto:Erin.E.Oliver@gsk.com]
Sent: Monday, July 14, 2014 12:25 PM
To: Lee, Jung E (OND)
Subject: RE: NDA 205434 (Flonase): Additional Labeling Comments

Hi Jung,

Can you please confirm tomorrow's scheduled teleconference. I've provided information related to GSK participants, desired topics of discussion and the teleconference dial-in information below.

Let me know if there's anything else you need; look forward to speaking with you tomorrow.

MEETING DATE / TIME:

Tuesday, 15 July 2015 from 10:30 to 11:30am

CONFERENCE CALL NUMBERS:

USA Toll Free.....
UK Freefone.....
GSK VPN.....
USA Toll.....
China .....
Participant Code.....
Chairperson Code.....

(b) (4)

GSK ATTENDEES:

Erin Oliver, Head US Regulatory Affairs
Peter Kratochvila, Vice President, Regulatory Affairs, Global Wellness and North America
Vidhu Bansal-Dev, Vice President, Respiratory Healthcare R&D
Aman Bhatti, Director, Medical Affairs, Respiratory Healthcare

TOPICS OF DISCUSSION:

1. (b) (4)
2. (b) (4)
3. Page 7 of Question and Answer Book
4. Timings & Next Steps to finalize labeling components

Topics 1 - 4 are our priority discussion topics, If time permits we'd also like to discuss GSK's proposals related to the following labeling comments:

5. New Flag
6. Pediatric use statement on bottle label and outside Drug Facts
7. 6 month duration of use limitation
8. Other Information statement related to onset of action

To facilitate our discussion, I plan to send you written feedback to the Agency's labeling comments from July 8th and July 11th via e-mail by the end of today. If we run out of time, you can use this information to let us know if our proposals to items 5 – 8 are agreeable to the Agency.

Best regards.

Erin

Erin Oliver
Head US Regulatory Affairs
Wellness & NA GRQ
Research & Development

GSK Consumer Healthcare,
1500 Littleton Road, Parsippany, NJ 07054
Email Erin.E.Oliver@gsk.com
Tel +1 973 889 2516

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From: Erin Oliver
Sent: Friday, July 11, 2014 4:50 PM
To: 'Lee, Jung E (OND)'

Subject: RE: NDA 205434 (Flonase): Additional Labeling Comments

Thanks so much Jung – that's sounds great.

Have a great weekend.

Erin

Erin Oliver
Head US Regulatory Affairs
Wellness & NA GRQ
Research & Development

GSK Consumer Healthcare,
1500 Littleton Road, Parsippany, NJ 07054
Email Erin.E.Oliver@gsk.com
Tel +1 973 889 2516

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From: Lee, Jung E (OND) [mailto:JungE.Lee@fda.hhs.gov]
Sent: Friday, July 11, 2014 4:27 PM
To: Erin Oliver
Subject: RE: NDA 205434 (Flonase): Additional Labeling Comments

Hi Erin,

In case we need more time to discuss the labeling comments, I have tentatively reserved an hour for the t-con (10:30 to 11:30am). I will confirm the details of the t-con on Monday. Have a nice weekend!

Thanks,
Jung

From: Erin Oliver [mailto:Erin.E.Oliver@gsk.com]
Sent: Friday, July 11, 2014 10:02 AM
To: Lee, Jung E (OND)
Subject: RE: NDA 205434 (Flonase): Additional Labeling Comments

Thanks Jung.

In advance of our meeting on Tuesday, I will send you the dial-in details, list of GSK attendees and requested discussion items .

Best regards.

Erin

Erin Oliver
Head US Regulatory Affairs
Wellness & NA GRQ
Research & Development

GSK Consumer Healthcare,
1500 Littleton Road, Parsippany, NJ 07054
Email Erin.E.Oliver@gsk.com
Tel +1 973 889 2516

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From: Lee, Jung E (OND) [mailto:JungE.Lee@fda.hhs.gov]
Sent: Friday, July 11, 2014 9:59 AM
To: Erin Oliver
Subject: NDA 205434 (Flonase): Additional Labeling Comments
Importance: High

Hi Erin,

We have some additional labeling comments for your consideration. As the T-con is currently scheduled for 30 minutes, could you please let me know in advance which comments you would like to discuss further on Tuesday?

Flonase Allergy Relief labeling comments:

Bottle label

(b) (4)

Statements outside Drug Facts

(b) (4)

Drug Facts

There will be a revision to the HIV warning and we will inform you as soon as it is determined.

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

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

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 for your directions below:

The (b) (4) boxes, "after 6 months of daily use" and "Ask a doctor if you can keep using" are not needed.

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).

The children boxes, "after 2 months of daily use" and "Ask a doctor if you can keep using" are not needed as this information is already stated.

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

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".

Question and Answer Book

Changes discussed above under Drug Facts that affect the Question and Answer Book should also be made to the Question and Answer Book.

Remove the word (b) (4) from page 5.

Remove page 7. We believe (b) (4) We also consider this section promotional and unnecessary for consumer use of the product.

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.

Quick Start Guide

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

We recommend the following changes to the page titled "Get the relief you need":

Under 2 Prime, design the picture so that it clearly shows the product should be pointed and sprayed away from the face.

Under 3 Blow, revise the graphic showing not to spray into the eye as discussed above under the Question and Answer Book.

Under 5 Breathe and spray, (b) (4) "sniff gently".

Thanks,

Jung E. Lee, RPh
LT, US Public Health Service
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
FDA/CDER/OND/ODE IV
WO Bldg 22 Rm 5487
10903 New Hampshire Ave
Silver Spring, MD 20993
(301) 796-3599
JungE.Lee@fda.hhs.gov

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/s/

JUNG E LEE
07/15/2014

From: Lee, Jung E (OND)
To: Erin Oliver (Erin.E.Oliver@gsk.com)
Subject: NDA 205434 (Flonase): Labeling Comments
Date: Tuesday, July 08, 2014 2:10:57 PM

Hi Erin,

We have the following labeling comments. Please note, additional labeling comments are forthcoming.

Flonase Allergy Relief labeling comments (these comments are preliminary)

(b) (4)

PDP

1. We prefer the "New Now OTC" flag.

(b) (4)

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

5. Allergy Symptom Reliever – This is acceptable as the pharmacological category.

6. Graphics

a. Combining symptom graphics with nose and eye graphics may be confusing.

b. Eye graphic – 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.

c. (b) (4).

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

(b) (4)

(b) (4)

Bottle label

1. “Children’s” should be added to the proprietary name.

2. “Glucocorticoid” should be added as the drug class after the established name.

3. Bold “Do not use daily for more than 2 months”. Further changes to the children’s directions are possible pending team discussion of the children’s directions.

Drug Facts

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

2. (b) (4)

3. Move “[bullet] if you are taking medicine for HIV infection” from the subheading “(b) (4)” to “Ask a doctor of pharmacist before use”. We are discussing revisions to the HIV warning.

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:

[bullet] HIV warning

[bullet] steroid warning

[bullet] ketoconazole warning

6. Under “When using this product”

a. the word “some” can be added to the growth statement so that it reads “the growth rate of some children may be slower”.

b. remove the nosebleed statement from this subheading, revise the statement and include under “Stop use and ask a doctor if” (see below).

c. Add “[bullet] remember to tell your doctor about all the medicines you take, including this one”

7. Under “Stop use and ask a doctor if”, add

[bullet] you have, or come into contact with someone who has, chickenpox,

measles or tuberculosis

[bullet] you have severe or frequent nosebleeds

8. Annotated font specifications - The font size for “Drug Facts (continued)” should be provided.

9. Additional comments on Drug Facts are expected.

Package inserts

1. Changes discussed above that affect the package inserts should also be made to the package inserts.

(b) (4)

5. Additional comments on the package inserts are expected.

Lot number and Expiration Date

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

Once you are finished revising all labels and package inserts, you will need to resubmit all labels (no representative labels) for our review.

Thanks,

Jung E. Lee, RPh

LT, US Public Health Service

Regulatory Project Manager

Division of Nonprescription Clinical Evaluation

FDA/CDER/OND/ODE IV

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(301) 796-3599

JungE.Lee@fda.hhs.gov

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/s/

JUNG E LEE
07/15/2014

From:	Lee, Jung E (OND)
To:	Erin Oliver (Erin.E.Oliver@gsk.com)
Cc:	Sager, Nancy B; Brum, Dan
Subject:	NDA 205434 (Flonase) General Advice Letter
Date:	Monday, July 07, 2014 9:57:11 AM
Attachments:	Flonase 205434 labeling disclosure final.pdf

Hi Erin,

Please find attached a General Advice letter for NDA 205434 regarding the posting of approval letters and approved labeling.

Thanks,

Jung E. Lee, RPh

LT, US Public Health Service

Regulatory Project Manager

Division of Nonprescription Clinical Evaluation

FDA/CDER/OND/ODE IV

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205434

GENERAL ADVICE

GlaxoSmithKline Consumer Healthcare
Attention: Erin Oliver, MS, MBA, RAC
Head, US Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054

Dear Ms. Oliver:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flonase Allergy Relief (fluticasone propionate) Metered Spray, 50 mcg/spray. The PDUFA goal date for this application is July 23, 2014.

The policy of the Center for Drug Evaluation and Research (CDER) with respect to the posting of approval letters and approved labeling for NDA applications is to make the approval letters and approved labeling available on the agency's website within three business days of approval. As you may be aware, FDA was sued by sanofi-aventis U.S. LLC in November 2013 (sanofi-aventis v. FDA, No. 13-1753 (D.D.C. filed Nov. 6, 2013)) to enjoin FDA's posting of the approved labeling for Nasacort Allergy 24 HR, which was approved on October 11, 2013. That case was dismissed voluntarily on February 4, 2014. To clear up any uncertainty that may have resulted from that litigation, this letter is to inform you that if and when NDA 205434 for Flonase Allergy Relief (fluticasone propionate) Metered Spray is approved, the agency intends to act consistently with its policy regarding the posting of approval letters and approved labeling for NDAs, and post the approval letter and approved labeling within three business days of approval.

If you have any questions, you can contact me at 301-796-3491 or nancy.sager@fda.hhs.gov.

Sincerely yours,

{See appended electronic signature page}

Nancy B. Sager
Director
Division of Information Disclosure Policy
Office or Regulatory Policy
Center for Drug Evaluation and Research

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/s/

NANCY B SAGER
07/07/2014

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/s/

JUNG E LEE
07/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205434

GENERAL ADVICE

GlaxoSmithKline Consumer Healthcare
Attention: Erin Oliver, MS, MBA, RAC
Head, US Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054

Dear Ms. Oliver:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flonase Allergy Relief (fluticasone propionate) Metered Spray, 50 mcg/spray. The PDUFA goal date for this application is July 23, 2014.

The policy of the Center for Drug Evaluation and Research (CDER) with respect to the posting of approval letters and approved labeling for NDA applications is to make the approval letters and approved labeling available on the agency's website within three business days of approval. As you may be aware, FDA was sued by sanofi-aventis U.S. LLC in November 2013 (sanofi-aventis v. FDA, No. 13-1753 (D.D.C. filed Nov. 6, 2013)) to enjoin FDA's posting of the approved labeling for Nasacort Allergy 24 HR, which was approved on October 11, 2013. That case was dismissed voluntarily on February 4, 2014. To clear up any uncertainty that may have resulted from that litigation, this letter is to inform you that if and when NDA 205434 for Flonase Allergy Relief (fluticasone propionate) Metered Spray is approved, the agency intends to act consistently with its policy regarding the posting of approval letters and approved labeling for NDAs, and post the approval letter and approved labeling within three business days of approval.

If you have any questions, you can contact me at 301-796-3491 or nancy.sager@fda.hhs.gov.

Sincerely yours,

{See appended electronic signature page}

Nancy B. Sager
Director
Division of Information Disclosure Policy
Office or Regulatory Policy
Center for Drug Evaluation and Research

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/s/

NANCY B SAGER
07/07/2014

From: Erin Oliver
To: Erin Oliver; Lee, Jung E (OND)
Subject: RE: NDA 205434 (Flonase): Information Request RE: Ocular Studies
Date: Friday, June 27, 2014 1:36:15 PM
Attachments: image004.png
image001.png

Hi Jung,

With reference to the following information request received on 24 Jun 2014 related to the ocular studies included within NDA 205434, please find our response below.

Which IND(s) were each of the following ocular studies carried out under and was GSK identified as the Sponsor for each of these studies? (See e-mail below for list of studies)

NDA 205434 contains data from 10 clinical studies to provide direct evidence of the effectiveness of Flonase (fluticasone propionate nasal spray) in the relief of the ocular symptoms associated with allergic rhinitis. All studies were conducted under an investigational new drug application (IND).

GlaxoSmithKline (GSK) is the sponsor for the INDs under which each of these ocular studies was conducted. GSK, as identified by one or more of its predecessors or affiliate companies, is named in Form FDA-1571 filed with FDA as the sponsor of each of the studies.

Details are provided in the table below.

Study Number	IND #	Serial	Date Submitted	Study Sponsor
FNM30033	28,636	329	28 Feb 2001	Glaxo Wellcome Inc.
FNM30034	28,636	329	28 Feb 2001	Glaxo Wellcome Inc.
RH01619	109,805	010	01 Oct 2012	GlaxoSmithKline Consumer Healthcare
FLN-401	28,636	046	30 Nov 1990	Glaxo Inc.
FLN-402	28,636	050	27 Feb 1991	Glaxo Inc.
FLN-411	28,636	061	23 July 1991	Glaxo Inc.
FLN-412	28,636	072	28 Feb 1992	Glaxo Inc.
FLTA4004	28,636	126	23 Feb 1995	Glaxo Inc.
FLTA4006	28,636	154	05 Dec 1995	Glaxo Wellcome Inc.
FLTA4024	28,636	179	06 Aug 1996	Glaxo Wellcome Inc.

If have any additional questions, please feel free to contact me.

Best regards.

Erin

Erin Oliver
Head US Regulatory Affairs
Wellness & NA GRQ
Research & Development

GSK Consumer Healthcare,
1500 Littleton Road, Parsippany, NJ 07054

Email Erin.E.Oliver@gsk.com
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From: Erin Oliver
Sent: Tuesday, June 24, 2014 1:49 PM
To: 'Lee, Jung E (OND)'
Subject: RE: NDA 205434 (Flonase): Information Request RE: Ocular Studies

Hi Jung,

I'm well and hope you are too.

This e-mail confirms receipt of the Agency's information request and we will work to respond to you as soon as possible, no later than by Monday, June 30.

Best regards.

Erin

Erin Oliver
Head US Regulatory Affairs
Wellness & NA GRQ
Research & Development

GSK Consumer Healthcare,
1500 Littleton Road, Parsippany, NJ 07054
Email Erin.E.Oliver@gsk.com
Tel +1 973 889 2516

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From: Lee, Jung E (OND) [mailto:JungE.Lee@fda.hhs.gov]
Sent: Tuesday, June 24, 2014 12:43 PM
To: Erin Oliver
Subject: NDA 205434 (Flonase): Information Request RE: Ocular Studies

Hi Erin,

I hope you week is going well. We have the following information request:

Which IND(s) were each of the following ocular studies carried out under and was GSK identified as the Sponsor for each of these studies?
FNM30033
FNM30034

RH01619
FLN-401
FLN-402
FLN-411
FLN-412
FLTA4004
FLTA4006
FLTA4024

Please provide a response by Monday, June 30.

Thanks,

Jung E. Lee, RPh
LT, US Public Health Service
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
FDA/CDER/OND/ODE IV
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JungE.Lee@fda.hhs.gov

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/s/

JUNG E LEE
06/30/2014

From: Lee, Jung E (OND)
To: Erin Oliver (Erin.E.Oliver@gsk.com)
Subject: NDA 205434 (Flonase): Information Request RE: Ocular Studies
Date: Tuesday, June 24, 2014 12:43:00 PM

Hi Erin,

I hope you week is going well. We have the following information request:

Which IND(s) were each of the following ocular studies carried out under and was GSK identified as the Sponsor for each of these studies?

FNM30033

FNM30034

RH01619

FLN-401

FLN-402

FLN-411

FLN-412

FLTA4004

FLTA4006

FLTA4024

Please provide a response by Monday, June 30.

Thanks,

Jung E. Lee, RPh

LT, US Public Health Service

Regulatory Project Manager

Division of Nonprescription Clinical Evaluation

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/s/

JUNG E LEE
06/24/2014

Lee, Jung E (OND)

From: Erin Oliver <Erin.E.Oliver@gsk.com>
Sent: Tuesday, June 17, 2014 7:54 PM
To: Lee, Jung E (OND)
Subject: RE: NDA 205434 (Flonase): Information Request RE: Studies RH 0181 and RH01929

Categories: Print

Jung,

With reference to the information request received on 16 Jun 2014 (e-mail below), please see our response. For completeness, we've repeated the Agency's question in bold, followed by the GSK response.

If you or the reviewer has any additional questions or would like to discuss further, please feel free to contact me.

Best regards.

Erin

Please provide a clinical justification for the 80% criterion pass rate used in Studies RH01801 and RH01929.

Typical acceptance criterion applied to usability testing ranges from 80 - 95% (ANSI/AMMI HFE75:2009 Human Factors Engineering – Design of Medical Devices, 2010). For studies RH01801 and RH01929, the lower criterion of 80% was chosen based on the low safety risk associated with failing to perform any of the key steps related to how the product was dosed (nasal vs. ocular use), priming of the pump and cleaning of the actuator nozzle and a reasonable estimate of the frequency at which these user errors might occur.

For example, a failure to dose properly was considered to be of medium risk if sprayed directly in the eye. Although this action may cause user discomfort, it is not considered to be a significant safety concern as no safety issues have been identified as a result of post marketing reports of product misuse (spraying in eyes). Moreover, it is unlikely the consumer would repeat the action. Incomplete priming could result in suboptimal dosing which could affect efficacy, but would not be considered a safety concern. Similarly, improper cleaning could result in a clogged nozzle, which could subsequently lead to suboptimal dosing. However, this is not a safety concern and would most likely lead to a consumer re-reading the instructions to understand how to remove the clog or not using the product. Therefore, the clinical consequences associated with these identified failures were considered to be low in terms of overall product safety and any consequent risks appropriately managed through labeling.

The report purposely provided actual pass/fail rates to assure full transparency of success and failure rates for each step during route of administration (intranasal versus intraocular), priming, and cleaning of the device. Although an 80% criterion was applied to quantitatively assess the number of users completing identified tasks, the most important facet of human factors testing is the analysis of use errors and failures as a means to assess risk to the user and determine the need for risk mitigation. No matter what the acceptance criterion is set to and what level of pass/fail performance is observed, conducting a risk analysis for each and every usage error observed during the summative test is a priority.

As such, a thorough risk analysis was conducted on each and every usage error observed during testing - in several cases leading to enhancements to product labeling. The findings of these analyses are included within the study reports and support that the proposed Quick Start Guide provides sufficient information to enable consumers to use the product correctly.

Reference ID: 3528685

From: Lee, Jung E (OND) [mailto:JungE.Lee@fda.hhs.gov]
Sent: Monday, June 16, 2014 7:33 AM
To: Erin Oliver
Subject: NDA 205434 (Flonase): Information Request RE: Studies RH 0181 and RH01929

Hi Erin,

We have the following information request:

- Please provide a clinical justification for the 80% criterion pass rate used in Studies RH01801 and RH01929.

Please provide a response by no later than COB Tuesday, June 17.

Thank you,
Jung E. Lee, RPh
LT, US Public Health Service
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
FDA/CDER/OND/ODE IV
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JungE.Lee@fda.hhs.gov

Reference ID: 3528685

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/s/

JUNG E LEE
06/20/2014

Lee, Jung E (OND)

From: Lee, Jung E (OND)
Sent: Monday, June 16, 2014 7:33 AM
To: Erin Oliver (Erin.E.Oliver@gsk.com)
Subject: NDA 205434 (Flonase): Information Request RE: Studies RH 0181 and RH01929

Follow Up Flag: Follow up
Flag Status: Flagged

Hi Erin,

We have the following information request:

- Please provide a clinical justification for the 80% criterion pass rate used in Studies RH01801 and RH01929.

Please provide a response by no later than COB Tuesday, June 17.

Thank you,
Jung E. Lee, RPh
LT, US Public Health Service
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
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Reference ID: 3525697

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/s/

JUNG E LEE
06/16/2014

Sponsor responds regarding 3 topics related to the Floanse Allergy Relief NDA.

1and 2. They believe the claim for ocular symptoms [redacted] (b) (4) are both supported by their NDA submission. [redacted] (b) (4) (b) (4)

"In conclusion, the ability to understand the terminology [redacted] (b) (4) is not at issue

here anymore than the ability for consumers to understand the terminology "allergic rhinitis" has

ever been at issue. Labeling for allergic rhinitis products approved under the NDA construct or

legally marketed under the monograph paradigm describes the symptoms of allergic rhinitis and

mentions what those symptoms may be due to. This is the approach that GSK eH plans to take with

the proposed DFL for Flonase Allergy Relief so that the labeling is inclusive of the allergic rhinitis, allergic ocular, [redacted] (b) (4) indications".

3. Sponsor agrees to submit labeling down to age 4 (and not simply 18 and older)

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/s/

STEVEN F OSBORNE
06/16/2014

Lee, Jung E (OND)

From: Lee, Jung E (OND)
Sent: Monday, June 09, 2014 10:36 AM
To: Erin Oliver (Erin.E.Oliver@gsk.com)
Subject: NDA 205434 (Flonase) IR Request for Study RH01418

Follow Up Flag: Follow up
Flag Status: Flagged

Categories: Follow Up

Hi Erin,

We have the following information request:

- **For Study RH01318, provide a listing of the site number and corresponding location for the research sites used in** this study. Also, identify which sites were devoted to recruiting low literate subjects only.

We ask that you provide a response by Wednesday, June 11 or sooner.

Thanks,
Jung

Jung E. Lee, RPh
LT, US Public Health Service
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
FDA/CDER/OND/ODE IV
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JungE.Lee@fda.hhs.gov

Reference ID: 3522170

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/s/

JUNG E LEE
06/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205434

LABELING COMMENTS

GlaxoSmithKline Consumer Healthcare
Attention: Erin Oliver
Head US Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054

Dear Ms. Oliver:

Please refer to your New Drug Application (NDA) dated September 23, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flonase Allergy Relief (fluticasone propionate) Metered Spray, 50 mcg.

We also refer to our December 6, 2013, letter in which we notified you of our target date of June 25, 2014 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On September 23, 2013, November 18, 2013, and May 13, 2014, we received your proposed labeling submissions to this application. We have the following preliminary comments. Additional recommendations may be forthcoming once all of the reviews are completed.

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".

(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 are provided and visible to the consumer on all outer cartons.

(b) (4)

(b) (4)

We request that you resubmit labeling that addresses these issues by June 11, 2014. The resubmitted labeling will be used for further labeling discussions.

If you have any questions, call Jung Lee, Regulatory Project Manager, at (301) 796-3599.

Sincerely,

{See appended electronic signature page}

Daniel Brum, PharmD, MBA
Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

DANIEL BRUM
06/03/2014

Lee, Jung E (OND)

From: Lee, Jung E (OND)
Sent: Monday, April 21, 2014 10:24 AM
To: Greg Smith (Gregory.D.Smith@gsk.com)
Subject: Information Request for EPI Study

Follow Up Flag: Follow up
Flag Status: Flagged

Categories: Print

Hi Greg,

Based on the following information provided in your submission, we would like to request the final study report examining the adverse effects of prescription intranasal steroids in a large US-health records database conducted by the University of California at San Francisco.

Pharmacoepidemiology study (RH02027)
An additional case-control, pharmacoepidemiology study (RH02027) that GSK supported to examine the adverse effects of prescription intranasal steroids in a large US-health records database is complete, but a final study report is pending. The University of California at San Francisco conducted the study using a nested case-control design, focusing on events of glaucoma/raised intra-ocular pressure, cataract and adrenal suppression. The study was initiated in August 2012 and is considered a targeted safety study for fluticasone propionate. The sponsor states it will submit the report to NDA 205-434 when available.

If the final study report has already been completed, please provide this information as soon as possible. If it has yet to be completed, please provide us with the anticipated date for submission.

Thanks,
Jung E. Lee, RPh
LT, US Public Health Service
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
FDA/CDER/OND/ODE IV
WO Bldg 22 Rm 5487
10903 New Hampshire Ave
Silver Spring, MD 20993
(301) 796-3599
JungE.Lee@fda.hhs.gov

Reference ID: 3508979

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/s/

JUNG E LEE
05/19/2014

Post Mid-Cycle Teleconference Meeting Minutes

Meeting Type:	Teleconference
Meeting Category:	Post Mid-Cycle Meeting (application not in The Program)
Meeting Date and Time:	Thursday, March 20, 2014 9:45 AM to 10:15 AM EST
Meeting Location:	White Oak Bldg 22 Rm 5313
Application Number:	NDA 205434
Product Name:	Flonase Allergy Relief (fluticasone propionate) Nasal Spray
Indication:	Temporarily relieves symptoms due to hay fever, other upper respiratory allergies, (b) (4) nasal congestion, runny nose, sneezing, itchy nose, watery eyes
Sponsor/Applicant Name:	GlaxoSmithKline Consumer Healthcare
Meeting Chair:	Theresa Michele, MD
Meeting Recorder:	Jung Lee, RPh

FDA Participants:

Division of Nonprescription Clinical Evaluation
Theresa Michele, MD, Director
Daniel Brum, PharmD, MBA, BCPS, RAC Chief, Project Management Staff
Narayan Nair, MD, Acting Lead Medical Officer
Barbara Cohen, MPA, Social Science Analyst
Jade Pham, PharmD, MHSc, Regulatory Project Manager

Office of Translational Sciences/Office of Biostatistics
Division of Biometrics IV (OTS/OB/DBIV)
Karen Higgins, ScD, Mathematical Statistician Team Leader (Behavioral)
Scott Komo, DrPH, Mathematical Statistician Reviewer (Behavioral)
Division of Biometrics II (DBII)
Ruthanna Davi, Statistical Team Leader

Division of Pulmonary and Allergy and Rheumatology Products (DPARP)
Stacy Chin, MD, Medical Officer
Anthony Durmowicz, MD, Lead Medical Officer

Applicant Participants:
Vidhu Dev, PharmD – Head of Research & Development, Respiratory Health
Greg Smith, MPH, RAC – Director, Regulatory Affairs, Respiratory Health
Erin Oliver, MBA, RAC – Director, US Regulatory Affairs
Rachel Hickman – Director, Regulatory Affairs, Respiratory Health
Daniel Du, MD – Principle Clinical Research Scientist, Respiratory Health
Roxanne Kapikian, Dr. PH – Director, Biostatistics

Harmony Garges, MD, MPH – Chief Medical Officer, Vice President, Global Safety & Pharmacovigilance
Peter Kratochvila, BSC, LLB, MA – Vice President, Regulatory Affairs, Wellness and North America
Sue James - Vice President, Worldwide Regulatory Affairs, Quality and Compliance
Liam Kennedy - Director, Biostatistics

Background:

Although this NDA is not in The Program, this teleconference was offered to provide the Applicant insight and transparency into the topics that were discussed during the FDA mid-cycle meeting held on February 26, 2014. FDA noted that this teleconference was intended to highlight issues under discussion as part of an ongoing review, rather than any definitive conclusions. Formal minutes will not be issued to the Applicant.

Discussion:

1. Applicant's proposal to obtain an ocular claim – FDA stated that the clinical studies submitted seem to support the effectiveness of Flonase for ocular symptoms in SAR, which would suggest efficacy across allergic rhinitis subtypes; therefore, demonstration of efficacy in additional clinical studies is not the primary issue. However, any potential benefit for ocular symptoms would need to be considered in light of concerns about the safe use of Flonase by consumers as an OTC product. The Applicant asked what additional data would be needed to show safe use. FDA responded that the data required to evaluate safety has already been provided in their NDA submission.
2. (b) (4)
3. (b) (4)

(b) (4)

4. Actual Use Trial (AUT) – FDA acknowledged the Applicant included in their NDA an AUT conducted in 2003. The Applicant said the reason for providing the AUT data was to provide transparency with regard to all their available safety data given they had already conducted the study and because their intention was to originally submit a switch application in 2003. The Applicant remarked that the AUT was performed with a label that was quite different from the version submitted with the NDA. In addition, the Applicant said they hoped submission of the AUT data would afford product exclusivity. FDA responded that an exclusivity determination has not yet been completed. However, the likelihood of receiving exclusivity based on the AUT was improbable for several reasons: 1) In the presubmission meeting, the Agency stated the requirement of an AUT was unclear. At this time, FDA does not consider one is needed to support approval, and 2) the design of the previously conducted AUT relied on a label that was quite different from the labeling submitted in the NDA and would likely be of limited value. FDA also noted that since the results of the previously conducted AUT were rather unfavorable, it may be to the Applicant's advantage for them not to be considered a pivotal portion of the review.

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/s/

JUNG E LEE
03/26/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205434

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

GlaxoSmithKline Consumer Healthcare
Attention: Gregory D. Smith MPH, RAC
Director, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054

Dear Mr. Smith:

Please refer to your New Drug Application (NDA) received September 23, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Flonase Allergy Relief (fluticasone propionate) Metered Spray, 50 mcg.

We also refer to your amendments dated October 9, November 7, and November 15 (two), 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 23, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 25, 2014.

During our filing review of your application, we identified potential review issues and request that you submit the following information:

Chemistry, Manufacturing, and Controls

1. Provide a Letter of Authorization (LoA) to the Drug Master File (DMF (b) (4)) supporting the dust cap.

2. Submit updated stability data including an updated stability summary for the NDA batches.

3. Submit stability data to support your proposed storage statement "Store between 4° and 30°C (39° and 86°F)."

Microbiology

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

Non-sterile aqueous drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see *PDA J Pharm Sci Tech* 2011; 65(5): 535-43.

In order to control for the presence of BCC in your product:

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

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

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

validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.
For more information, we refer you to *Envir Microbiol* 2011; 13(1):1-12 and *J. Appl Microbiol* 1997; 83(3):322-6.

Regulatory

We have determined that your application triggers PREA because you are proposing to add an ocular indication to labeling. Please revise your Pediatric Study Plan (PSP) accordingly and submit a revised PSP within 30 days of this letter.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We have determined that your application triggers PREA (see above comments under "Regulatory"). Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Pulmonary, Allergy, and Rheumatology Products. Note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

If you have any questions, call Jung Lee, Regulatory Project Manager, at (301) 796-3599.

Sincerely,

{See appended electronic signature page}

Theresa Michele, M.D.
Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

DANIEL BRUM
12/06/2013
Signed on behalf of Theresa Michele, M.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205434

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

GlaxoSmithKline Consumer Healthcare
1500 Littleton Road,
Parsippany, NJ 07054

Attention: Gregory D. Smith, MPH, RAC
Director, Regulatory Affairs

Dear Mr. Smith:

Please refer to your New Drug Application (NDA) dated September 21, 2013, received September 23, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Propionate Aqueous Nasal Spray, 50 mcg per metered spray.

We also refer to your November 7, 2013, correspondence, received November 7, 2013, requesting review of your proposed proprietary name, Flonase Allergy Relief. We have completed our review of the proposed proprietary name, Flonase Allergy Relief, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your November 7, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Abiola Olagundoye-Alawode, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3982. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Jung Lee at (301) 796-3599.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
11/20/2013

From:	Lee, Jung E (OND)
To:	"Erin Oliver"; "Greg Smith"
Subject:	RE: NDA 205434: Flonase Allergy Relief Information Request for Human Factors Studies
Date:	Tuesday, November 12, 2013 2:23:00 PM

Hi,

I have one further request from the reviewer. Could you please also provide more details on the data structure for the non-CDISC datasets you propose to submit? We ask that you provide this information as soon as possible for us to review.

Thanks,
Jung

From: Lee, Jung E (OND)
Sent: Tuesday, November 12, 2013 1:59 PM
To: 'Erin Oliver'; Greg Smith
Subject: RE: NDA 205434: Flonase Allergy Relief Information Request for Human Factors Studies

Hi Erin and Greg,

The data format is acceptable to the reviewers, however, they ask that this information be provided no later than 9am on November 18.

Thanks,
Jung

From: Erin Oliver [mailto:Erin.E.Oliver@gsk.com]
Sent: Monday, November 11, 2013 6:23 AM
To: Greg Smith; Lee, Jung E (OND)
Subject: RE: NDA 205434: Flonase Allergy Relief Information Request for Human Factors Studies

Hi Jung,

We did not submit datasets and data definition tables for the two human factors studies, RH 01801 and RH 01929 in NDA 205434. Given the nature of these observational studies, we provided study reports with in-text data tables only.

If required, we can submit the study data as SAS datasets (non-CDISC) to module 5. Can you please confirm that this data format would be acceptable to the reviewers.

We will try to provide them to by COB on November 14th, but may need a few more days to complete the publishing activities. Would it be possible to extend the submission date to provide the information to you on or before November 21st?

Many thanks in advance for your help in this matter.

Best regards.

Erin

Erin Oliver, MS, MBA, RAC
Head, US Regulatory Affairs
GSK Consumer Healthcare

GlaxoSmithKline | 1500 Littleton Road | Parsippany, NJ
T (External) 973.889.2516 | **T** (Internal) (b) (6) | Mobile (b) (6) | erin.e.oliver@gsk.com

www.gsk.com | GSKvision on YouTube | Follow us on Twitter

From: Greg Smith
Sent: Friday, November 08, 2013 10:24 AM
To: Lee, Jung E (OND); Erin Oliver
Subject: RE: NDA 205434: Flonase Allergy Relief Information Request for Human Factors Studies

Hi Jung,

We received your information request and we are pulling together the necessary team members to respond.

We'll be in touch soon.

Best regards,

Greg

Gregory D. Smith, MPH, RAC
Director, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare
gregory.d.smith@gsk.com
973-889-2540

From: Lee, Jung E (OND) [mailto:JungE.Lee@fda.hhs.gov]
Sent: Thursday, November 07, 2013 11:46 AM
To: Greg Smith; Erin Oliver
Subject: NDA 205434: Flonase Allergy Relief Information Request for Human Factors Studies

Hi Greg and Erin,

We have the following information request for NDA 205434:

We are unable to locate the datasets and data definition tables for the two human factors studies, RH 01801 and RH 01929. Please either point us to the location of these in the submission or provide them to us by COB on November 14th.

Thanks,
Jung E. Lee, RPh
LT, US Public Health Service

Senior Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
FDA/CDER/OND/ODE IV
WO Bldg 22 Rm 5487
10903 New Hampshire Ave
Silver Spring, MD 20993
(301) 796-3599
JungE.Lee@fda.hhs.gov

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/s/

JUNG E LEE
11/12/2013

From: Lee, Jung E (OND)
To: Greg Smith (Gregory.D.Smith@gsk.com)
Subject: NDA 205434 (Flonase) Labeling Information Request
Date: Wednesday, October 23, 2013 2:21:11 PM

Hi Greg,

We have the following information request for labeling. We ask that you submit the response officially to the Central Document Room, and as a courtesy, an email response to me by Friday, November 8.

(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.

Thanks,

Jung E. Lee, RPh

LT, US Public Health Service

Senior Regulatory Project Manager

Division of Nonprescription Clinical Evaluation

FDA/CDER/OND/ODE IV

WO Bldg 22 Rm 5487

10903 New Hampshire Ave

Silver Spring, MD 20993

(301) 796-3599

JungE.Lee@fda.hhs.gov

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/s/

JUNG E LEE
11/12/2013

From:	Lee, Jung E (OND)
To:	Greg Smith (Gregory.D.Smith@gsk.com); Erin Oliver (Erin.E.Oliver@gsk.com)
Bcc:	Lee, Jung E (OND)
Subject:	NDA 205434: Flonase Allergy Relief Information Request for Human Factors Studies
Date:	Thursday, November 07, 2013 11:46:00 AM

Hi Greg and Erin,

We have the following information request for NDA 205434:

We are unable to locate the datasets and data definition tables for the two human factors studies, RH 01801 and RH 01929. Please either point us to the location of these in the submission or provide them to us by COB on November 14th.

Thanks,

Jung E. Lee, RPh

LT, US Public Health Service

Senior Regulatory Project Manager

Division of Nonprescription Clinical Evaluation

FDA/CDER/OND/ODE IV

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10903 New Hampshire Ave

Silver Spring, MD 20993

(301) 796-3599

JungE.Lee@fda.hhs.gov

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/s/

JUNG E LEE
11/07/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205434

NDA ACKNOWLEDGMENT

GlaxoSmithKline Consumer Healthcare
Attention: Gregory D. Smith MPH, RAC
Director, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054

Dear Mr. Smith:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Flonase Allergy Relief (fluticasone propionate nasal spray), 50 mcg

Date of Application: September 21, 2013

Date of Receipt: September 23, 2013

Our Reference Number: NDA 205434

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 22, 2013 in accordance with 21 CFR 314.101(a).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.
If you have any questions, call Jung Lee, Regulatory Project Manager, at (301) 796-3599.

Sincerely,

{See appended electronic signature page}

Jung Lee, RPh
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

JUNG E LEE
09/23/2013

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2013. See instructions for OMB Statement, below.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

1. APPLICANT'S NAME AND ADDRESS	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
GLAXOSMITH KLINE CONSUMER HEALTHCARE Gregory Smith 1500 LITTLETON ROAD PARSIPPANY NJ 079054 US	205-434
2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE 973-889-2540	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? [X] YES [ ] NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: [X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION [ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
3. PRODUCT NAME Flonase Allergy Relief (Fluticasone propionate aqueous nasal spray)	6. USER FEE I.D. NUMBER PD3013475

7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES? [ ] YES [X] NO

PRIORITY REVIEW VOUCHER NUMBER:

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.
[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION

Reference ID: 3602882

505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)
[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food,Drug, and Cosmetic Act
[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO
If a waiver has been granted, include a copy of the official FDA notification with your submission.

OMB Statement:
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Information Management (HFA-710)
1350 Piccard Drive, 4th Floor
Rockville, MD 20850

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Information Management (HFA-710)
1350 Piccard Drive, 4th Floor
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE	TITLE	DATE
Gregory D. Smith Digitally signed by Gregory D. Smith DN: cn=Gregory D. Smith, o=GlaxoSmithKline Consumer Healthcare, ou, email=gregory.d.smith@gsk.com, c=US Date: 2013.07.02 11:55:45 -04'00'	Director, Regulatory Affairs	2-July-2013

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$1,958,800.00

Form FDA 3397 (01/10)

Reference ID: 3602882

INSTRUCTIONS FOR COMPLETING PRESCRIPTION DRUG USER FEE COVER SHEET FORM FDA 3397

orm FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplemental application submitted to the Agency on or after April 30, 2001, unless specifically exempted below. Form FDA 3397 should be placed in the first volume of the application with the application (FORM FDA 356(h)) form. Form FDA 3397 is to be completed on-line at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119184.htm. If you need assistance in completing the form call 301-796-7200 or email: userfees@fda.gov.

NOTE: Form FDA 3397 need not be submitted for:

CDER

505(j) applications
Supplements to 505(j) applications

CBER

Any supplement that does not require clinical data for approval.
Applications and supplements for:

* Products for further manufacturing use only
* Whole blood or blood components for transfusion
* Bovine blood product for topical application licensed before September 1, 1992
* A crude allergenic extract product
* An in vitro diagnostic biological product licensed under Section 351 of the PHS Act

ITEM NO.	INSTRUCTIONS
1-2.	**Self-explanatory**
3.	**PRODUCT NAME:** Include generic name and trade name, as applicable.
4.	**BLA STN / NDA NUMBER - FOR AN ORIGINAL BIOLOGIC LICENSE APPLICATION (BLA) -** Indicate the 6-digit BLA number (Submission Tracking Number (STN)) if pre-assigned, otherwise leave blank. For A **SUPPLEMENT** enter the BLA STN. **FOR DRUG PRODUCTS:** Indicate the new drug application (NDA) number. NDA numbers can be obtained by completing the information at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm114027.htm.
5.	**CLINICAL DATA:** The definition of 'clinical data' for the assessment of user fees is found in FDA's Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees. FDA's guidance on the definition of clinical data can be found on FDA's web site: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.
6.	**USER FEE I.D. NUMBER:** Please include the ID number (generated when completing Form FDA 3397) on the application payment check.
7.	**PRIORITY REVIEW VOUCHER:** If you are redeeming a priority review voucher awarded to a sponsor of a tropical disease product application (see section 524 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)), please include the priority review voucher number assigned when the voucher was initially granted. See FDA´s Guidance for Industry: Tropical Disease Priority Review Vouchers for further information. FDA´s guidance can be found on FDA´s web site: http://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
8.	**EXCLUSIONS:** The application is for an orphan drug product. Under section 736(a) (1) (F) of the FD&C Act, a human drug application is not subject to an application fee if the proposed product is for a rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation) AND the application does not include an indication that is not so designated. A supplement is not subject to an application fee if it proposes to include a new indication for a rare disease or condition, and the drug has been designated pursuant to section 526 for a rare disease or condition with regard to the indication proposed in the supplement. A copy of the FDA letter granting orphan designation should be included with the BLA/NDA submission.
9.	**WAIVER:** Complete this section only if a waiver of user fees, including the small business waiver, has been

Reference ID: 3602882

	granted for this application. *A copy of the official FDA notification that the waiver has been granted must be provided with the BLA/NDA submission.*

Form FDA 3397 (01/10)(BACK)

Close Print Cover sheet

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 109805

MEETING MINUTES

GlaxoSmithKline Consumer Healthcare
Attention: Mr. Gregory D. Smith
Director, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054

Dear Mr. Smith:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Flonase® (fluticasone propionate) nasal spray.

We also refer to the meeting between representatives of your firm and the FDA on October 22, 2012. The purpose of the meeting was to discuss your proposal to expand the uses of Flonase in the OTC setting and your data submission plan for your application for the Rx-to-OTC switch of Flonase® (fluticasone propionate) nasal spray.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Daniel Reed, Regulatory Project Manager at (301) 796-2220.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, M.D., M.S.
Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: IND

Meeting Date and Time: October 22, 2012; 12:30P to 1:30P EST
Meeting Location: FDA White Oak

Application Number: 109805
Product Name: Flonase® (fluticasone propionate) nasal spray
Indication: Treatment of allergic (b) (4) rhinitis
Sponsor/Applicant Name: GlaxoSmithKline Consumer Healthcare

Meeting Chair: Andrea Leonard-Segal, M.D., M.S.
Director
Division of Nonprescription Clinical Evaluation

Meeting Recorder: Daniel Reed
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation

FDA ATTENDEES

Division of Nonprescription Clinical Evaluation
Andrea Leonard-Segal, M.D., M.S., Director
Joel Schiffenbauer, M.D., Deputy Director
Lesley-Anne Furlong, M.D., Medical Team Lead
Christina Chang, M.D., M.P.H., Medical Officer
Wafa Harrouk, Ph.D., Pharmacology Toxicologist Reviewer
Barbara Cohen, MPA, Social Scientist
Melissa Furness, Chief Project Management Staff
Janice Adams-King, Regulatory Project Manager
Daniel Reed, Regulatory Project Manager

Division of Nonprescription Regulation Development
Elaine Abraham, R.Ph., Interdisciplinary Scientist

Division of Clinical Pharmacology 2
Sheetal Agarwal, Ph.D., Clinical Pharmacology Reviewer

Division of Biometrics IV
Yan Wang, Ph.D., Statistical Reviewer
Feng Zhou Ph.D., Biomedical Statistician

Reference ID: 3219455

Division of Transplant and Ophthalmology Products
Wiley A. Chambers, M.D., Deputy Director
William Boyd, M.D., Clinical Team Leader

Division of Pulmonary, Allergy, and Rheumatology Products
Lydia Gilbert-McClain, M.D., Deputy Director
Sally Seymour, M.D., Deputy Director for Safety
Susan Limb, M.D., Medical Team Leader
Sofia Chaudhry, M.D., Medical Officer

SPONSOR ATTENDEES
GlaxoSmithKline Consumer Healthcare
Dr. Juby Jacob-Nara, MD, MPH, MBA, Director Medical Affairs, Respiratory Health
Vidhu Dev, PharmD, Director Medical Affairs, Wellness
Rita Wanser, MS, Principal Clinical Scientist Medical Affairs, Respiratory Health
Gregory Smith, MPH, RAC, Director Regulatory Affairs, Respiratory Health
Erin Oliver MS, MBA Director Regulatory Affairs, Respiratory Health
Cecilia Hale, PhD, Director, Biostatistics Respiratory Health & GI Health
Randy Koslo, PhD.,Vice President Research & Development Respiratory Health

1.0 BACKGROUND

Brief Statement of the Purpose of the Meeting
The purpose of this meeting is for GlaxoSmithKline Consumer Healthcare (GSK) to obtain the Agency's comments regarding their proposed data submission plan for their upcoming application, and the proposal to expand the uses of Flonase in the OTC setting to include treatment of (b) (4) rhinitis as well as the symptoms of "itchy, watery eyes."

2. DISCUSSION

On October 19, 2012 FDA sent preliminary response to the questions included in the sponsor's September 21, 2012 meeting package. The questions from GSK appear below followed by the preliminary FDA responses in italics. All questions were discussed in the meeting.

3.0 QUESTIONS

Data Submission Plan

1. Does the Agency agree with the scope and content of the data submission, specifically:

a. submission of legacy raw datasets (in SDTM format) for studies supporting pooled safety analysis?
b. submission of integrated analysis datasets for pooled safety analyses?
c. submission of legacy raw datasets (in SDTM format) for efficacy studies?
d. submission of legacy analysis datasets for efficacy studies?
e. submission of integrated analysis datasets for pooled efficacy analyses?

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FDA Preliminary response:
Ocular redness, ocular itching and watery eyes may each have different causes and responses to therapy. We believe that tearing and redness are signs which should be measured objectively, not subjectively to support a new indication in product labeling. Therefore, we do not agree with the methodology utilized in the two trials, FNM30033 and FNM30034. Per the information you have provided, efficacy was determined by mean change from baseline in reflective, subject-rated total ocular symptom scores (TOSS = sum of itching, tearing, and redness).

TOSS scores have not been used to support a new indication in either Rx or OTC labeling, although they have been included in the clinical trials section of prescription labeling of some products. It is possible that information about TOSS could be included in a consumer information leaflet for an OTC product, but we would need to consider how to do this and to test the comprehension of this information by consumers and the impact on the way they might use the product. It is difficult to consider how and where this information could fit on a Drug Facts Label.

It is inappropriate to treat redness and tearing as subjective symptoms and combine them with itching into a single measure. For the additional claim of "itchy eyes" studies should be submitted which demonstrate evidence of efficacy based on statistically significant and clinically relevant reductions of the single symptom of ocular itching. For the additional claim of "watery eyes", we recommend demonstrating a statistically significant and clinically relevant reduction in the amount of tears produced, measured objectively.

Otherwise, it appears that the scope and content of the data you propose to submit are acceptable. As a reminder, clinical trials research study designs should define the protocol for data collection. The Agency's methodology and submission structure supports research study design, as indicated in the Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications and the Study Data Specifications. The Agency's methodology and submission structure also supports integrating study data collection for Safety and Efficacy study submission. The Agency prefers implementation of analyses datasets to tabulations datasets traceability. In addition, the Agency prefers each study submitted to be complete and evaluated on its own merits. The Agency also prefers studies be maintained independently in the SEND datasets, SDTM datasets, and that analyses (ADaM) datasets provide traceability to the study's SDTM, including analyses that combine multiple studies (e.g. Safety and/or Efficacy analyses) (See SEND, SDTM and ADaM as referenced in Study Data Specifications).

The Study Data Specifications provide the current specifications for submissions. The specifications provide the most conducive data content definition and structure for the review team, although this may vary based on the submission and reviewing division (pg. 2). The review team assigned to the submission determines the acceptability. Therefore, you are encouraged to follow this best practice noted in the Study Data Specifications, "prior to submission, sponsors should discuss with the review division the datasets that should be provided, the data elements that should be included in each dataset and the organization of the data within the file" (p. 2).

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In addition, please reference the CDER Common Data Standards Issues Document for further information on data standardization in submissions.

If you have any further questions, please feel free to send an email to cder-edata@fda.hhs.gov.

Additional Links:

Electronic Regulatory Submissions and Review Helpful Links available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM085361

Electronic Common Technical Document (eCTD) available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htmIn

Discussion:

GSK stated that they have 28 legacy studies to be pooled for safety analysis; the parameters to be assessed will include demographics, duration of exposure, and subject disposition. Nine of these studies include endpoints assessing ocular symptoms and will be used to demonstrate support for efficacy in ocular symptom relief.

GSK stated they are working with [redacted] (b) (4), which is experienced with SDTM submission, to assist them with legacy data mapping and ADaM data conversion. The Agency acknowledged that its experience with converting legacy data is limited and would be eager to learn more about the process as well.

2. Does the Agency agree with the format of the data submission, specifically:

a. use of SDTM as the format for legacy raw data?
b. use of ADaM as the format for integrated safety and efficacy analysis datasets?
c. use of ADaM for legacy efficacy analysis datasets?
d. use of ADaM for analysis datasets from the behavioral studies?

FDA Preliminary response:

No. See response to Question #1.

It appears that the format of the data you propose to submit are appropriate for raw data, safety, and efficacy datasets. We agree with your proposal to include raw data (including verbatim consumer study responses) in the ADaM analysis datasets.

In addition, if the ADaM datasets were not used for creation of the statistical results described in the clinical study report, please submit the programs used for creating the main efficacy analysis datasets from submitted SDTM format datasets. Also, please provide the programs used for creating the efficacy and main safety analyses; documentation to explain what each program is used for should be included.

Reference ID: 3219455

Discussion:

GSK asked for clarification on the Agency's request for programs used to create efficacy and main safety analyses, as well as the documentation for each of these programs. GSK stated that the safety and efficacy information will be extracted from old datasets to create analysis SAS files using ADaM format. In addition, a statistical appendix will be provided; this appendix will include a SAS output detailing the derivations for all models used to generate ISE and ISS tables. To ensure complete traceability, GSK will submit a PDF document to cross-reference the original study data in SDTM. Furthermore, if needed, GSK will respond to any Information Request to provide additional data during the NDA review. The Agency confirmed that this approach is acceptable.

3. Does the Agency agree that the clinical data to be provided in the NDA, as described in the Data Submission Plan, is sufficient to enable FDA to review the safety and efficacy of Flonase Allergy Relief as an OTC treatment for allergic (b) (4) rhinitis?

FDA Preliminary Response:

(b) (4) *rhinitis would be a new OTC drug indication and would need to be supported by data that consumers can self-diagnose and self-treat this condition appropriately. This new indication would likely need to be discussed at an advisory committee meeting, as would a first-in-class switch OTC product, in general.*

Your NDA should be complete when it is submitted, containing all data to support the indication or indications for which you seek approval at that time. You state on page 14 of the briefing package that a "Human Factor study is in the planning stages." We note that final study report of the Human Factor study should be included at the time of initial NDA submission.

We refer you to our comments on the scope of safety information, which were provided as response to Question 2B in our February 22, 2011 Type B meeting. Based on your submission, it is unclear whether your planned NDA will include postmarketing safety information, a literature review, and translated foreign labels if fluticasone propionate is available OTC in other countries.

As communicated to you at the PIND meeting held in February 2011, we advise you to include discussion with regards to the drug-drug interaction potential of Flonase with potent CYP3A4 inhibitors in the NDA submission.

Discussion:

GSK stated that its intention is to submit a complete NDA. GSK will provide all information requested by the FDA in the 2011 meeting, including post marketing safety analysis, literature review, translated foreign labeling, and discussion of drug-drug interactions. GSK also confirmed that the NDA will include a final study report on the planned Human Factor Study.

4. Does the Agency agree that datasets for targeted safety studies will not be included in the submission since no pooling or analysis of this data is being planned for the NDA?

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FDA Preliminary Response:
Additional clarification is needed before we can fully answer this question. If you plan to include any targeted safety studies that have not been reviewed by the FDA, then we request that you provide the datasets and thorough analyses of the information.

If your question refers to studies that FDA has already reviewed, then the datasets for targeted safety studies will not be needed in your planned application. However, if additional safety issues are identified during the review process that necessitate that we dig into that previously reviewed information, we may request that you provide us the specific location of that information in your cross-referenced application or resubmit specific datasets as a reviewer aid in order to expedite our review.

Discussion:
GSK reiterated the commitment to provide a thorough analysis of available safety data on fluticasone. GSK will provide a comprehensive evaluation of adverse event profiles of fluticasone from clinical studies, a review of GSK's post marketing database, a review of WHO and AERS databases, and a robust review of literature.

Ocular Symptoms

5. Does FDA have any feedback for GSK CH on our approach to support the addition of the ocular symptoms to the Flonase Allergy Relief indication?

FDA Preliminary Response:
Yes. Please see our response to Question 1.

Additionally, we have safety concerns with your proposal to add ocular symptoms to the Flonase Allergy Relief indication. In the absence of counseling from a healthcare provider, consumers may mistakenly apply the product directly to the eye rather than the nose. To support the safety of an ocular claim for OTC Flonase, you will need to demonstrate in label comprehension that consumers understand that this product is to be used intranasally and not intraocularly.

Data will also be needed to show that consumers do not use Flonase in their eyes. The design of this study can be discussed more after you propose a study protocol. We could think about whether this would need to be an actual use study or could be some type of hybrid, for example, between an actual use study and a human factors study.

Discussion:
With respect to adding ocular symptom relief to the OTC proposal, the Agency stated that there are two main issues. The first issue is a concern over safe use – whether consumers may use the spray topically in the eye. The second issue arises from the use of TOSS scale as the measurement for efficacy.

Regarding the safe use concern, the Agency stated that nasal sprays, which are non-sterile products, have not been approved for simultaneous topical ophthalmic use, or for relief of ophthalmic symptoms. GSK stated their belief that safety concerns regarding potential

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misuse can be addressed via labeling, supplemented by information from a human factors study or a hybrid human factors/use study. To address the concern of potential misuse, the Agency recommended that the study include an assessment as to whether consumers would use the product in their eyes. Whether an actual use component may be needed is unclear. The Agency advised GSK to submit the human factors study protocol for FDA review and comment.

In general, the Agency expressed reservations that a human factors study and labeling would be adequate to address the safety concerns and noted that any proposed ocular claims would likely be subject to discussion at an advisory committee meeting.

When asked by the Agency if Flonase is approved for ocular symptom relief in other countries, GSK confirmed that Flonase does carry an ocular symptom indication in certain countries outside the U.S., and committed to provide translated foreign labeling for Agency review. The Agency requested that information on what type of access is available (i.e., general sale vs. behind-the-counter) be provided as well. Furthermore, GSK stated that there have been approximately 30 reports of unintentional eye exposure to Flonase in the postmarketing database. GSK believe that the most likely explanation for such exposure was that consumers inadvertently squirted the product in their eyes when starting and priming a new bottle, and not that consumers intended to administer the nasal product to the eye. GSK is considering including pictorials in a (b) (4) to reinforce appropriate use of Flonase.

GSK asked whether the TOSS scale would be an appropriate measurement for efficacy for treating the ocular symptoms listed (itchy, watery eyes), since the TOSS scale was used to assess ocular symptom relief for fluticasone furoate (Veramyst, NDA 22-051). The Agency responded that there were differing views within the Agency regarding the acceptability of the TOSS. DPARP stated that they accept TOSS for assessing ocular symptoms in the setting of allergic rhinitis. Therefore, the greater concern from the perspective of DPARP is the issue of safety. DTOP, on the other hand, does not accept the TOSS for assessing ocular symptoms in the setting of allergic conjunctivitis.

The Agency pointed out that ocular symptoms are part of the manifestations of allergic rhinitis. The Agency also emphasized that neither Veramyst nor Flonase has an indication for the treatment of ocular symptoms specifically.

For this reason, there would be challenges in how best to convey the data on ocular symptom relief, even if the use TOSS scale were permitted. The format of Drug Facts label is not conducive to conveying such information, as no sections of Drug Facts appear suitable for conveying efficacy information not based on primary endpoints evaluated in clinical trials. It is also unclear if the (b) (4) would be the appropriate platform.

The Agency then stated that more internal meetings may be needed and a post meeting addendum would be provided if additional comments are available.

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(b) (4)

GSK inquired about using the term (b) (4) "ocular symptoms" as previously proposed. The Agency stated that the use of (b) (4) would likely be too broad and confusing to consumers, since the specific mention of "itchy, watery eyes" would be eliminated. GSK responded they would assess how best to include (b) (4) specific symptoms: itchy, (b) (4) and watery eyes.

The Agency reiterated that the inclusion of ocular symptoms would likely need to be discussed with an advisory committee.

Additional Administrative Comments

Comments shared with you today are based upon the contents of the September 21, 2012 meeting package, which is considered to be an informational aid to facilitate the meeting discussion. The comments are not meant to be viewed as commitments from the Agency. Review of the information submitted as part of your new IND application on October 1, 2012 might identify additional comments or information requests.

Reference ID: 3219455

For applications submitted after February 2, 1999, applicants are required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

The July 9, 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) changes the timeline for submission of a Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes.

We encourage you to submit your requests for FDA review of your proposed proprietary name as early as possible. The content requirements for such a submission can be found in the draft Guidance for Industry entitled, "Contents of a Complete Submission for the Evaluation of Proprietary Names" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf).

We encourage you to request and attend an End-of-Phase 2 meeting to obtain regulatory agreements for clinical endpoints and study design for Phase 3 trials. Depending on your development program, we encourage you to request and attend, at a minimum, a pre-NDA meeting prior to submitting a new application in order to discuss the content and format of your planned application.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

- GSK will provide a thorough analysis of available safety data on fluticasone. GSK will provide a comprehensive evaluation of adverse event profiles of fluticasone from clinical studies, a review of GSK's postmarketing database, a review of WHO and AERS databases, and a robust review of literature.

- GSK will submit a human factors-type study protocol for FDA review and comment.

- In their NDA, GSK will provide all information requested by the FDA in the 2011 meeting, including post marketing safety analysis, literature review, translated foreign labeling, and discussion of drug-drug interactions. GSK also confirmed that the NDA will include a final study report on the planned Human Factor Study.

- GSK will extract the safety and efficacy information from old datasets to create analysis SAS files using ADaM format. In addition, a statistical appendix will be provided which includes a SAS output detailing the derivations for all models used to generate ISE and ISS tables. GSK will submit a PDF document to cross-reference the original study data in SDTM.

Reference ID: 3219455

6.0 ATTACHMENTS AND HANDOUTS

GSK provided the attached chart of the Flonase-OTC Data Submission Plan Pooled Studies (safety & efficacy).

7.0 POSTMEETING ADDENDUM

Internal discussions are ongoing regarding the approach that the Agency will recommend for assessing the efficacy of Flonase for ocular symptoms of allergic rhinitis. We cannot provide you with a final answer at this time, but will when we can.

Reference ID: 3219455

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

/s/

ANDREA LEONARD SEGAL
11/20/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 109805

MEETING MINUTES

GlaxoSmithKline Consumer Healthcare
Attention: Gregory D. Smith, MPH
Director, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3384

Dear Mr. Smith:

Please refer to your Pre-Investigational New Drug Application (PIND) for fluticasone propionate nasal spray.

We also refer to the meeting between representatives of your firm and the FDA on February 22, 2011. The purpose of the meeting was to discuss your proposed development program for switching fluticasone propionate nasal spray from prescription to over-the-counter (OTC) status.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Janice Adams-King, Regulatory Project Manager, at 301-796-3713.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, M.D., M.S.
Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type-B

Meeting Date and Time: February 22, 2011
9:00 AM to 10:00 AM EST

Meeting Location: FDA/White Oak
10903 New Hampshire Avenue
Room 1315
Silver Spring, MD 20993

Application Number: PIND 109805

Product Name: fluticasone propionate nasal spray

Indication: Relieves the symptoms of nasal allergies from pollen, dust, mold, and pets: sneezing, itchy nose, runny nose, and congestion

Sponsor/Applicant Name: GlaxoSmithKline Consumer Healthcare

Meeting Chair: Andrea Leonard-Segal, M.D., M.S.
Director
Division of Nonprescription Clinical Evaluation

Meeting Recorder: Janice Adams-King, RN, BSN, MS
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation

FDA ATTENDEES

CDER participants:

Division of Nonprescription Clinical Evaluation
Andrea Leonard-Segal, M.D., M.S., Director
Joel Schiffenbauer, M.D., Deputy Director
Lesley-Anne Furlong, M.D., Medical Team Leader
Christina Chang, M.D., M.P.H., Medical Officer
Oluwamurewa Oguntimein, MHS, CHES, Social Science Analyst
Melissa Furness, Chief Project Management Staff
Janice Adams-King, Regulatory Project Manager

Division of Clinical Pharmacology II
Partha Roy, Ph.D., Clinical Pharmacology Reviewer

Division of Nonprescription Regulation Development
Marina Chang, R.Ph., Interdisciplinary Scientist Team Leader
Elaine Abraham, R.Ph., Interdisciplinary Scientist

Division of Pulmonary and Rheumatology Products
Lydia Gilbert-McClain, M.D., Deputy Director
Susan Limb, M.D., Medical Team Leader
Sofia Chaudhry, M.D., Medical Officer

SPONSOR ATTENDEES:

GlaxoSmithKline Consumer Healthcare
Randy Koslo, PhD, Vice President, Venture Group
Sue James, Vice President, Worldwide Regulatory Affairs, Compliance & Quality
David Schifkovitz, Vice President, Regulatory Affairs
Gregory Smith, MPH, Director, Regulatory Affairs, Venture Group
Simon Gilburt, PhD, Director, Research and Development, Venture Group
Jeffrey Garwin, MD., PhD, Director, Medical Affairs, Venture Group
Cecilia Hale, PhD, Principal Biostatistician, Venture Group
Catherine Segal, RPh, MBA, Commercial Director, Venture Group
Daniel Keravich, RPh, MSc, MBA, Director, Regulatory Policy
(b) (4)

1.0 BACKGROUND AND MEETING OBJECTIVE

GSKCH is the innovator for prescription Flonase (fluticasone propionate) nasal spray, which was approved as a prescription product under NDA 20-121 in 1994, for the treatment of seasonal allergic rhinitis and perennial allergic rhinitis in patients 4 years of age and older. GSKCH requested a Type B Pre-IND Meeting to discuss their proposed development program, including labeling development and consumer studies, to support the nonprescription use in consumers (b) (4) years of age and older.

The Agency's preliminary responses to the questions contained in GlaxoSmithKline's January 21, 2011 meeting background package were provided to GlaxoSmithKline via e-mail on February 18, 2011. These preliminary responses appear in italics below. Following introductions, the meeting agenda consisted of further discussion regarding questions 2A, 2B, 5, 6, 7, 9, 10, 12, 14 and 15. For questions where no additional discussion is indicated, neither GlaxoSmithKline nor FDA raised any additional issues pertaining to these questions.

2.0 DISCUSSION

GlaxoSmithKline opened the discussion by sharing their handout, "Flonase Switch Challenges" with the Agency. The handout included four slides (attached) which shared information on the systemic and local effects of Flonase. Discussion pertinent to the presentation can be found under Discussion section for Question 6 in this document.

QUESTIONS

1. Information Cross-Reference

Question 1. GSKCH will file this IND for the OTC use of Flonase. We intend to cross-reference the chemistry, nonclinical and clinical sections of IND 28,636 and NDA 20-121.

Does the Agency consider this acceptable?

FDA Preliminary response:

Yes, this is acceptable. However, you will need to specify which sections of the IND and NDA you will be referencing, and provide a summary of these data in your IND submission. In addition, please provide the date of the specific submission and page number within the specified submission that each piece of cross-referenced data was originally submitted.

2. Clinical/Medical

2A. Efficacy

Question 2. The target population (age (b) (4) years and over) for Flonase-OTC (b) (4) approved under the Rx product. It is our belief that the efficacy of FP for the treatment of nasal allergy within our OTC population at the proposed dose is therefore well-established provided we can demonstrate OTC compliance with instructions for use. GSKCH does not intend to conduct any additional efficacy studies.

Does the Agency agree with this rationale and current plans?

FDA preliminary response:

We agree that no additional trials to support the efficacy of FP in allergic rhinitis are required, provided that the OTC indications correspond to the approved prescription indications appropriately. See response to Question 3 regarding the draft label below.

We are currently unaware of data that should definitely preclude the labeling of your proposed OTC product down to the age of 4 years (like the prescription product). (b) (4)

Discussion:

In response to the Agency's comment regarding the labeling of the product down to age 4 years, (b) (4) regimen; GSKCH confirmed that dosing instructions were the same. Noting that the results of the completed actual use study were not submitted as part of this

briefing package, the Agency stated that GSKCH should provide data to support OTC use of drug product for designated population(s).

2B. Safety

Question 3. The meeting package contains a summary and critical assessment of safety information emerging from both clinical and post marketing experience with FP nasal spray in the treatment of nasal allergy.

GSKCH requests Agency comments on the overall scope and conclusions regarding the safety of FP for the treatment of nasal allergy, as reflected in this summary.

Based upon the Agency's review of the safety information provided in this meeting package, does the Agency agree with GSKCH's assessment regarding the suitability of this product for OTC use?

FDA preliminary response:

Based on what you have presented in this meeting package, fluticasone propionate nasal spray appears to have a favorable safety profile for the OTC market. However, a determination of OTC suitability will require a complete safety package incorporating the following elements submitted for Agency review:

1. *A summary and analysis of safety information from all the clinical studies that you have conducted for fluticasone propionate nasal spray (including data from studies used to support the original prescription NDA and studies conducted subsequent to the Rx approval). Provide safety analysis for each study separately, as well as pooled study results.*

2. *Provide a narrative summary and analysis of postmarketing safety information for currently marketed fluticasone propionate products from the following safety databases:*
    - *Your internal postmarketing pharmacovigilance database*
    - *FDA Adverse Event Reporting System (AERS) database*
    - *World Health Organization's (WHO) International Drug Monitoring Program*
    - *Overdose data from the National Poison Data System (NPDS) from American Association of Poison Control Centers (AAPCC)*
    - *Drug Abuse Warning Network (DAWN)*

    Search results from each data source should be described and analyzed independently.

3. *Provide targeted analyses for the following safety issues:*
    - *HPA axis suppression*
    - *Effect on growth*
    - *Effect on bone metabolism*
    - *Effect on glucose metabolism*

- *Potential drug-drug interactions (with CYP3A4 inhibitors including but not limited to protease inhibitors and azole antifungals)*
- *Bacterial rhinosinusitis*
- *Local adverse events such as perforation of nasal septum*
- *Any other safety concerns you consider to be of clinical relevance.*

4. *You should conduct a world wide literature search focused on all publicly available safety data on fluticasone propionate nasal spray. References and complete copies of all articles from the literature search will need to be provided, as well as your analysis of the literature. For any articles originally published in a foreign language, a complete English translation must be included.*

5. *If fluticasone propionate is internationally marketed as a nonprescription drug, the NDA submission should provide the indications(s), dose(s), and a targeted analysis of the adverse event data for that nonprescription use. These nonprescription labels should be provided (and translated if not in English) to assess whether there is additional safety information identified in other countries that warrants inclusion in the Drug Facts label.*

6. *The NDA must contain an integrated summary and analysis of safety based on data contained in items 1 to 4 above. Refer to 21 CFR 314.50 for NDA requirements.*

Your proposal for an OTC switch of intranasal fluticasone propionate appears reasonable; however, the suitability of the product for OTC use will be a review issue. We note that, if approved, fluticasone propionate would be the first nonprescription intranasal corticosteroid drug product. Thus, it is likely that we will seek input from outside experts at an Advisory Committee Meeting to discuss the important issues raised by this NDA.

Discussion:
GSKCH agreed to the requested content of the safety database. However, they stated that they have more than 50 Phase II/III studies with Flonase and proposed that they recode and pool data for the most relevant studies that support OTC Flonase use and submit that to the Agency with rationale. The Agency agreed, but added that studies not considered pertinent in supporting OTC use should still be listed and summarized in the NDA. GSKCH agreed.

3. Draft Label
GSKCH requests Agency comments on the content within each of the following Drug Facts sections of the proposed OTC label (Sections 11.4 and 11.5). GSKCH recognizes that the exact language is subject to further testing to demonstrate whether it accomplishes the intended goal of guiding consumers on appropriate use.

FDA preliminary response:
These labeling comments and recommendations below are based on a preliminary review of the Drug Facts content as provided in this submission. The comments are intended to help you to develop a draft label suitable for label comprehension testing. Further label changes may be

necessary based on the results of consumer studies. Note that the contents of the final label will be a review issue.

In general, bolding in Drug Facts is used for the headings and subheadings (see 21 CFR 201.66(d)(3)), or certain warnings required by regulation to be bolded (e.g. "Keep out of reach of children" warning under 21 CFR 330.1(g) [§ 201.66(c)(5)(x)]). A statement that requires greater prominence can be bolded although we recommend avoiding excessive bolding so as not to detract from the other information on the Drug Facts label (see the Guidance for Industry: Labeling OTC Human Drug Products - Questions and Answers (December 2008)).

We note that the Drug Facts panel omits the risk of nasal septal perforation and other rare but serious adverse events. While you contend that the risk of septal perforation is minimal, inclusion of this risk in labeling may be warranted and will be a review issue.

Uses
Question 4. Does the Agency agree with the language used to describe the indications for use as an OTC product?

FDA preliminary response:
The proposed OTC indication cites relief of symptoms of nasal allergies (b) (4) *" Since the efficacy of Flonase for managing allergic rhinitis caused by specific allergens has not been specifically studied, it appears that a list of specific allergens is not warranted.*

Do not use
Question 5. Does the Agency agree that the language in this section identifies those contraindications representing an absolute prohibition on use of this product?

FDA preliminary response:
No, we do not agree. As stated in our previous meeting response dated May 2, 2001, we recommend that you add bulleted statements advising consumers not to use this drug product to treat sinus infection, asthma, or cold symptoms. The bulleted statement " (b) (4) *" should be moved to the* ***Do not use*** *sub-section. The words "* (b) (4) *" should be removed from the beginning of this statement as this wording is reserved for ingredients with a known potential for anaphylactic reactions.*

Discussion:
GSKCH stated that they understand the rationale to test whether consumers think it is appropriate to use the drug product to treat asthma, sinus, and/or cold symptoms. The Agency recommended that this also be tested in the actual use study. GSKCH agreed.

Ask a doctor before use if you have
Question 6. Based on the information presented in Section 6.3 concerning the safe use according to the proposed label, GSKCH believes that there are only two situations where consumers

should not use the product unless first consulting with their doctor. Does the Agency agree with the proposed list of preexisting conditions where consumers should not use the product unless first consulting with a doctor?

FDA preliminary response:
We note that the prescription label has precautionary language pertaining to (b) (4) *s these risks are not reflected in your proposed OTC label, you will need to justify their omission.*

The following symptoms should be addressed in your label in this section: (b) (4) *Any warning pertaining to these symptoms should also be included in a bulleted statement under the "ask a doctor before use if" section and tested in the label comprehension/self-selection studies.*

Discussion:
GSKCH inquired about the rationale for including (b) (4) In response, FDA clarified that its intention is not to require the translation of all Rx (b) (4) into a Drug Facts label. Rather, FDA expressed that systemic safety concerns have not been sufficiently mitigated by information provided in the current briefing package. FDA cited the safety synopsis included in the briefing material, which included 42 unexplained AERS reports of (b) (4) associated with fluticasone propionate nasal spray. The relevance of any systemic effects from (b) (4) labeling for this switch proposal thus depends on whether the totality of the safety data, once reviewed, is adequate to allay systemic safety concerns. GSKCH agreed to provide a comprehensive safety review in the NDA submission.

With respect to the local effects of concern such as (b) (4), GSKCH proposed the language be provided on the consumer labeling instructing users to stop use and ask a doctor if 'your symptoms do not improve in (b) (4) days.' The rationale to support this language is based on data from GSKCH's own studies as well as current clinical practice guidelines, which suggest that use of Flonase for a (b) (4) day period will not worsen infection or compromise treatment. GSKCH pointed out that clinical guidelines encourage providers to (b) (4)

(b) (4)

(b) (4) FDA advised that the current Rx label suggests the product should be used with caution, if at all, in the presence of a variety of infections ((b) (4)). If this is not the case, data should be presented in the nonprescription NDA to justify the Drug Facts labeling.

Ask a doctor or pharmacist before use if you are taking
Question 7. Does the Agency agree that ketoconazole is the only drug-drug interaction to be included in this section?

FDA preliminary response:
No, we do not agree. As stated in our previous meeting response dated May 2, 2001, we recommend that you add a bulleted statement advising consumers who are taking (b) (4) *to ask their doctor or pharmacist before using this product. This statement should also be included as one of the primary communication objectives and tested in the label comprehension study.*

We note that the prescription label advises caution and warning with concomitant use of (b) (4) *inhibitors that is not limited to ketoconazole alone.* (b) (4) *We recommend that you address this issue in your application and/or label.*

Discussion:
GSKCH sought advice regarding the first paragraph of this response, which requests GSKCH to adequately address concomitant medication (b) (4). The Agency stated that, as with the response to Question 6 above, the comment is intended to inform GSKCH that they must adequately address systemic side effects of (b) (4) use. GSKCH pointed out (b) (4)

(b) (4) GSKCH agreed and stated specifically that they are planning to include the warning language related to ritonavir.

When using this product
Question 8. Does the Agency agree with the proposed list of side effects that a consumer may experience, and activities to avoid when using the product?

FDA preliminary response:
We note that you include [redacted] *in your proposed list of side effects. It is unclear to us why you choose to* [redacted] *above other adverse events* [redacted]

Stop use and ask a doctor if
Question 9. Does the Agency agree with the proposed text listed in this section?

FDA preliminary response:
We suggest adding cautionary language about the onset of new symptoms such as facial [redacted] *pain* [redacted].

Discussion:
GSKCH agreed to add cautionary language, such as [redacted] although they would prefer not to explicitly state specific symptoms. The Agency cautioned that if no specific symptoms are stated, GSKCH should find out what these statements may mean to consumers. For example, [redacted] GSKCH agreed to test such proposed nonprescription labeling statements for comprehension.

Directions
Question 10. Does the Agency agree with the format and language of dosage instructions for use in an OTC setting for our proposed indication and identified target population?

FDA preliminary response:
With respect to dosing regimen:
Provide justification for the omission of the [redacted]. *The proposed OTC dosing does not include all the dosing regimens recommended in the approved package insert for Flonase. The proposed OTC label recommends use of 2 sprays in each nostril once daily (50 mcg/spray; 200 mcg total daily dose) for the first week, followed by 1 or 2 sprays in each nostril daily (100 or 200 mcg total daily dose) "as needed to treat your symptoms" from Week 2 onwards. The approved Flonase dosing also allows for an alternative dosing regimen of 1 spray in each nostril* [redacted] *(200 mcg total daily dose).*

[redacted]

We recommend that bullets appear before or after, not before and after, the Directions table (see Guidance for Industry: Labeling OTC Human Drug Products, May 2009).

Discussion:
See discussion under 2A.

Question 11. Does the Agency agree that the information in this section is appropriate and should not be located in another section of the Drug Facts label? Does the Agency have any suggestions for additional information to be included?

FDA preliminary response:
No, we do not agree. The first bulleted statement (b) (4) *should be removed.*

We also have the following preliminary comments about the OTC User's Guide:

- *Revise the fifth step by adding "with* (b) (4) *clean tissue" after the word "nozzle" and* (b) (4) *so the step now reads: "wipe the nozzle with a clean tissue and replace the* (b) (4) *cover after each use."*
- *Include a section that instructs consumers how to clean the pump spray, similar to the instructions that are in the current prescription patient package insert.*

Development Program
4A. Label Comprehension
Question 12. Label development will follow an iterative process that will include both qualitative and quantitative testing. An outline of our proposed label comprehension trial is included in this meeting package.

Does the Agency have any comments on the proposed primary communication objectives to be tested in the label comprehension study?

FDA preliminary response:
The primary communication objectives should include: ask a doctor or pharmacist before use if you are using any oral or inhaled product containing a steroid. 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.[1] 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.*

[1] 2007 Report: National Center for Education Statistics, Institute of Education Science, Literacy in Everyday Life-Results From the 2003 National Assessment of Adult Literacy (NAAL)

- *The exclusion criteria should exclude participants who have participated in research studies in the past 12 months (not 6 months).*

For additional information, we refer you to the Guidance for Industry: Label Comprehension Studies for Nonprescription Drug Products (August 2010) at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM143834.pdf

These are preliminary comments based on the information in the protocol outline; additional comments will be provided when the full protocol is submitted for our review prior to conducting the study.

Discussion:
GSKCH stated that they agreed with the Agency's comments and that rationale for proposed target threshold will be provided. There was back and forth discussion regarding the different methodology of literacy assessment between REALM and NAAL in identifying low literate subjects. However, further discussion led to agreement that with REALM, the study population can be enriched with sufficient number of low literate subjects to ensure that 30% of the study population is low literate.

4B. Self-Selection
Question 13. Given the long history of OTC allergy labeling, the ability of consumers to self-recognize allergies is well established. Therefore, the selection study outlined in this meeting package targets consumers who have the highest risk of serious consequences if they do not consult their physician prior to using Flonase-OTC.

Does the Agency have any comments on the proposed design of the self-selection study?

FDA preliminary response:
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.*

These are preliminary comments based on the information in the protocol outline; additional comments will be provided when the full protocol is submitted for our review prior to conducting the study.

4C. Actual Use

Question 14. The safe use of Flonase-OTC without medical supervision will be assessed through the conduct of two actual use studies to measure compliance with label elements that we believe are necessary for the safe use of the product. The first study will focus on when to stop use and seek medical attention. The second study will focus on dosing and duration of use. Both studies will also track safety consequences of OTC product use (i.e., adverse events).

Does the Agency have any comments on the overall design and objectives of these two studies as a basis for demonstrating consumer understanding and safe use of the product in an OTC setting?

FDA preliminary response:

We recommend you submit the full protocol for the actual use 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 studies:

The two-week study:

- *All-comers with nasal allergies should be allowed to enter the study; however, those with contraindications (those who with unhealed nasal injury and allergy to product ingredients) should not be allowed to purchase the study medication. The number of subjects with contraindications who attempt to purchase the study medication should be collected. Their reasons for not heeding the warnings should be solicited.*
- *Provide a justification for your proposed target threshold.*
- *The exclusion criteria should exclude participants who have participated in research studies in the past 12 months.*
- *Subjects who develop fever or facial/sinus pain during the study should be asked whether they stopped taking the study product.*

The 4-month study:

- *The study should enroll two groups of subjects - those who have never used Flonase Nasal Spray and others who have previously used Flonase Nasal Spray intermittently or chronically. Subgroup analysis should be provided in the final study report.*
- *All-comers with nasal allergies should be allowed to enter the study; however, those with contraindications (those who have allergies to product ingredients and unhealed nasal injury) should not be allowed to purchase the study medication. The number of subjects with contraindications who attempt to purchase the study medication should be collected. Their reasons for not heeding the warnings should be solicited.*
- *You will need to provide a justification for your proposed target threshold.*
- *The exclusion criteria should exclude participants who have participated in research studies in the past 12 months.*
- *Subjects who develop fever or facial/sinus pain during the study should be asked whether they stopped taking the study product.*
- *Your proposed study duration of four months duration may be too short to assess the pattern of use. We are open to developing a better understanding of your rationale for choosing to study subjects only for four months but we think that a more appropriate*

duration for the Actual Use study would be six months, to allow better assessment of usage patterns.

Please specify for review in a Statistical Analysis Plan:

- *what the primary endpoint measuring compliance is*
- *how it is derived from the diary data and phone calls*

We recommend that testing be done with a significance level of 2.5% for one sided tests.

These are preliminary comments based on the information in the protocol outlines; additional comments will be provided when the full protocols are submitted for our review prior to conducting the study.

Discussion:
GSKCH agreed to provide separate analyses of Flonase-experienced and Flonase-naïve users. Furthermore, at least 20% of the study population would be Flonase-experienced users.

GSKCH then inquired about the Agency's recommendation for a 6-month versus a 4-month actual use study. GSKCH explained their rationale for selecting the 4-month timeframe as it being sufficient to allow assessment of behavior beyond the proposed (b) (4) months of product use. The Agency stated that a 6-month duration may allow for identification of more adverse events that may emerge with extended use of the product. Nevertheless, should GSKCH decide not to conduct the actual use study for 6 months, GSKCH should provide justification for such decision. GSKCH agreed that justification for its decision would be provided.

4D. Overall Development Program

Question 15. Does the Agency have any comments on the overall development program outlined in the meeting package (label comprehension, self-selection and actual use) in terms of its ability to provide information sufficient to evaluate the ability of consumers to safely and appropriately use the product without the supervision of a health care professional?

FDA preliminary response:
In addition to the studies you proposed in your meeting package, we highly recommend that you test the comprehension of the OTC User's Guide describing the proper steps for using the pump spray. You should also test the ability of consumers to actually follow those steps.

Discussion
The Agency inquired whether GSKCH would test the (b) (4) and GSKCH stated that they agreed with the comment and would test the (b) (4).

Additional Administrative Comments:

Comments shared with you today are based upon the contents of the meeting package, which is considered to be an informational aid to facilitate the meeting discussion. As this meeting is a

Pre-IND meeting, the comments from the Agency serve as guidance to you at this preliminary stage. The comments are not meant to be viewed as commitments from the Agency. Review of the information submitted to the IND might identify additional comments or information requests.

For applications submitted after February 2, 1999, applicants are required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

Depending on your development program, we encourage you to request and attend, at a minimum, a pre-NDA meeting prior to submitting a new application to discuss the content and format of your application.

We encourage you to submit your requests for FDA review of your proposed proprietary name during the IND phase of your drug development program. The content requirements for such a submission can be found in the draft Guidance for Industry entitled, "Contents of a Complete Submission for the Evaluation of Proprietary Names" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf). Please note that such a request can be made as early as at the end of phase 2 of the IND review process.

Your pre-IND has been assigned #109805. Please reference this number on all submissions and correspondence. Please note, studies in humans may not be conducted under this PIND. Before you may conduct studies in humans, you must submit an Investigational New Drug Application (IND, see 21 CFR Part 312).

3.0 SUMMARY OF DISCUSSION AND ACTION ITEMS

- GSKCH will provide data and clinical rationale to address the corticosteroid class effects as presented on the Drug Facts labeling.
- GSKCH will consider current practice in the prescription setting as they develop the proposed nonprescription labeling.
- GSKCH will address drug-drug interactions with known CYP3A4 inhibitors.
- Findings from the label comprehension study will be incorporated in the revised Drug Facts labeling by GSKCH.
- GSKCH will ensure that subjects selected for the label comprehension study will encompass those from the general population. Enrichment of the study population with a low literacy cohort will ensure 30% of the subjects are low literate.
- GSKCH will provide justification for a 4-month vs. a 6-month actual use study to assess longer-term compliance.
- GSKCH will reassess its internal safety database and provide full safety reports for findings relevant to the OTC switch proposal. Furthermore, a comprehensive Integrated Summary of Safety will be provided in the NDA. GSKCH will select the appropriate studies to integrate.

- GSKCH will provide data with a justification/rationale for proposing OTC Flonase be used for those (b) (4) years of age and older.
- GSKCH will test the OTC User's Guide to ensure consumers comprehend the instructions.

4.0 ATTACHMENTS AND HANDOUTS

The presentation, "Flonase Switch Challenges" was provided at this meeting by GSKCH and is attached.

5.0 POST-MEETING ADDENDUM

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/s/

ANDREA LEONARD SEGAL
03/14/2011

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Division of Pulmonary and Allergy Drug Products

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To:

Name: Patricia Marie

Organization Name/Dept: GSK

CC:

Phone number: 919-483-7650

Fax number: 919-315-0033

From: Ladan Jafari

FAX: 301 – 827 – 1271

Phone: 301 – 827 – 1050

- ☐ Urgent
- ☐ For Review
- ☐ Please Comment
- ☐ Please Reply
- ☐ OTHER:

Date sent: 2.26.03

Number of pages including cover page: 3

Message:

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MEMORANDUM OF TELECON

DATE: February 26, 2003

APPLICATION NUMBER: NDA 20-548/S-018, Flovent (fluticasone propionate) Inhalation Aerosol

BETWEEN:

Name: Patrick Wire, Product Director
Phone: 919-483-7650
Representing: GlaxoSmithKline (GSK)

AND

Name: Ladan Jafari, Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: Pediatric Exclusivity

GSK submitted the above supplemental NDA on December 13, 2002. The supplement contained final study reports for pediatric studies conducted in accordance with Section 505A of the FD&C Act and Written Request issued (b) (4)

The Division of Pulmonary and Allergy Drug Products compared these study reports against the terms of the Written Request and its amendments and determined that the terms of the Written Requests and its amendments have been met. This finding was confirmed with the CDER Pediatric Exclusivity Board on February 25, 2003.

With the Board's decision, I contacted Dr. Patrick Wire, Product Director, Respiratory Group, on February 26, 2003, and informed him that pediatric exclusivity has been granted for fluticasone propionate by meeting the terms of the Written Request and its amendments. I informed him that notice of this additional exclusivity award should appear on the CDER Pediatric Internet web site within a few days and will also appear in the next supplemental printing of the Orange Book.

Ladan Jafari
Regulatory Project Manager

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

/s/

Ladan Jafari
2/26/03 02:48:46 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND (b) (4)
NDA 19-957
NDA 20-121
NDA 20-548
NDA 20-549
NDA (b) (4)
NDA 20-833

Glaxo Wellcome, Inc.
Attention: Joy E. Ferrell, Director, Regulatory Affairs
P.O. Box 13398
Five Moore Drive
Research Triangle Park, North Carolina 27709

Dear Ms. Ferrell:

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IND (b) (4)
NDA 19-957
NDA 20-121
NDA 21-548
NDA 20-549
NDA (b) (4)
NDA 20-833

If you have any questions, contact David Hilfiker, Project Manager, at 301-827-1050, or Millie Wright, Project Manager, at 301 827-2020.

Sincerely yours,

Robert J. DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

John K. Jenkins, M.D., F.C.C.P.
Director
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