CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-433

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

Patent Information

Item 13 to NDA 21-433 Pursuant to 21 C.F.R. § 314.53:

For

FLOVENT HFA® (fluticasone propionate) Inhalation Aerosol

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	**FLOVENT HFA® (fluticasone propionate) Inhalation Aerosol**
Active Ingredient:	**fluticasone propionate**
Strengths:	**44 mcg; 110 mcg and 220 mcg / actuation**
Dosage Form:	**inhalation aerosol**
Route of Administration:	**oral inhalation**

Please add the following patents in the U.S. Department of Health and Human Services "Orange Book" of Approved Drug Products.

	US Patent Number	Expiration Date	Form of Patent Claims
1	4,335,121	Nov. 14, 2003	Drug, Drug product
2	5,658,549	Aug. 19, 2014	Drug product, method of use
3			

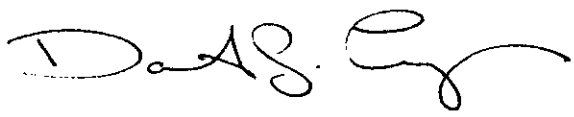
The undersigned declares the following:

1) All of the above patents are owned by Glaxo Group Limited. Glaxo Group Limited is d/b/a GlaxoSmithKline.
2) The above patents cover "the drug or a method of using the drug that is the subject of the new drug application or amendment or supplement to it 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" FLOVENT HFA® (fluticasone propionate) Inhalation Aerosol. This product is the subject of NDA 21-433.

Please address all communications regarding the patent property of this NDA to:

David J. Levy
Vice President, Intellectual Property Counsel
SmithKline Beecham Corporation d/b/a/ GlaxoSmithKline
Corporate Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
919/ 483-2723

Respectfully submitted,



Date: November 5, 2001

David J. Levy
Vice President, Intellectual Property Counsel
SmithKline Beecham Corporation d/b/a/ GlaxoSmithKline
Corporate Intellectual Property Department
Reg. 27,655

EXCLUSIVITY SUMMARY FOR NDA #21-433 _____ SUPPL #

Trade Name Flovent HFA Inhalation Aerosol_____
Generic Name fluticasone propionate_HFA_____

Applicant Name GlaxoSmithKline_____ HFD-570 #

Approval Date If Known May 14, 2004_____

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 question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_X__/ NO /___/

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 /_X__/ 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:

_____

_____

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

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

____Three years_____

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

YES /_X__/ NO /___/

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

__No_____

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 /_X__/

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 /_X__/ NO /___/

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

NDA# 20-548_Flovent Inhalation Aerosol_(CFC formulation

NDA# 20-549 Flovent Rotadiks

NDA# 20-833 Flovent Diskus

NDA# 20-770 Flovent Rotadisk (Pediatrics)

NDA# 21-077 Advair Diskus

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 NDA'S 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 /_X__/ 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 /_X__/ NO /___/

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:

(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 /_X__/

(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 /_X__/

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 /_X__/

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:

__FAP 30007, FAP 30008, FLTA 3022, FLTB 3048

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 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X_/

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 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

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"):

____FAP 30007_____ ____FLTA 3022_____

____FAP 30008_____ ____FLTB 3048_____

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?

Investigation #1 !

IND #53,502_____ YES /_X__/ ! NO /___/ Explain: _____

Investigation #2

IND #53,502____ YES /_X__/ ! NO /___/ Explain:

Investigation#3

IND 53,502 YES (X)

Investigation # 4

IND 53,502 Yes (X)

(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?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(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.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

Signature [signature] Date 5-14-04
Title: Regulatory Project Manager

Signature of Office/ See DFS. Date
Division Director

Form OGD-011347 Revised 05/10/2004

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

CONFIDENTIAL

Marketing Exclusivity

NDA 21-433

Flovent HFA (fluticasone propionate) Inhalation Aerosol

Request for Marketing Exclusivity

Pursuant to Section 505(c)(3)(D)(iii) and 505(j)(5)(D)(iii) of the Federal Food, Drug, and Cosmetic Act and Section 314.108(b)(4) of Title 21 of the Code of Federal Regulations, GlaxoSmithKline requests three years of exclusivity from the date of approval of Flovent HFA (fluticasone propionate) Inhalation Aerosol 88mcg, 220mcg, and 440mcg for maintenance treatment of asthma in patients 12 years of age and older.

GlaxoSmithKline is entitled to such exclusivity as this application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by GlaxoSmithKline. The following investigations are "essential to the approval of the application" in that the application could not be approved by FDA without the following investigations:

Indication – maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. Flovent is also indicated for patients requiring oral corticosteroid treatment for asthma.

FAP30007: A 12-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter trial to compare the efficacy and safety of FP HFA 88mcg BID, 220mcg BID, and 440mcg BID versus Placebo HFA in adolescent and adult subjects with asthma who are maintained on inhaled corticosteroid (ICS) therapy

FAP30008: A 12-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter trial to compare the efficacy and safety of FP HFA 88mcg BID, 220mcg BID, and 440mcg BID versus Placebo HFA in adolescent and adult subjects with asthma who are maintained bronchodilator therapy

FLTA3022: – A Randomized, Double-Blind, Placebo-Controlled Comparative Trial of Fluticasone Propionate 440mcg BID or 880mcg BID versus Placebo Administered via Metered-Dose Inhaler in Propellant 11/12 or GR106642X in Adolescent and Adult Oral Corticosteroid-Dependent Asthmatics

To the best of GlaxoSmithKline's knowledge, and based on a thorough literature search, there are no other published studies or publicly available reports that are relevant to the proposed formulations or conditions of use.

To the best of GlaxoSmithKline's knowledge, the above-referenced clinical investigations are "new" in that they have not been relied on by the 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 any such investigations.

The above-referenced clinical investigations were "conducted or sponsored by GlaxoSmithKline" in that GlaxoSmithKline was the sponsor of the U.S. investigational new drug application (IND 53,502) under which the studies were conducted.

Betsy J. Waldheim
Product Director, Regulatory Affairs

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-433 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: February 27, 2002 **Action Date:** May 14, 2004

HFD 570 **Trade and generic names/dosage form:** Flovent HFA (fluticasone propionate HFA) Inhalation Aerosol

Applicant: GlaxoSmithKline (GSK) **Therapeutic Class:** Respiratory

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Asthma

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

XNo: Please check all that apply: X **Partial Waiver** X **Deferred** X **Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	**kg**	**mo.** 0	**yr.**	**Tanner Stage**	
Max	**kg**	**mo.** <6	**yr.**	**Tanner Stage**	

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
Other: Difficult to diagnose the disease in children.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.** 6	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** <12	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other: GSK currently has a program underway for this population.

Date studies are due (mm/dd/yy): May 2007

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.** 12	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** Above	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: **NDA 21-433**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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
5/14/04 03:21:08 PM

DIVISION DIRECTOR'S MEMORANDUM

Date: May 14, 2004

To: NDA 21-433

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Flovent HFA 44 mcg, 110 mcg, and 220 mcg (flucitasone propionate HFA 44 mcg, 110 mcg, and 220 mcg) Inhalation Aerosol

Applicant: GlaxoSmithKline

Administrative and Introduction

GlaxoSmithKline (GSK) submitted a 505(b)(1) new drug application (NDA 21-433) on February 26, 2002, for use of fluticasone propionate HFA inhalation aerosol (Flovent HFA) in patients 12 years of age and older with asthma. The applicant proposed to market three strengths of the product, 44 mcg, 110 mcg, and 220 mcg, measured as the ex-actuator dose. Other fluticasone inhalation products, such as Flovent Inhalation Aerosol, Flovent Diskus, and Flovent Rotadisk are also approved for marketing in the United States in three similar strengths. The Flovent HFA is being developed as a replacement product for the CFC containing Flovent Aerosol, meaning that patients who are currently being treated with Flovent Aerosol can change over to Flovent HFA when the CFC containing product is phased out. The clinical program for Flovent HFA is a stand-alone program because during early preclinical development GSK determined that the in vitro performance characteristics of Flovent HFA Aerosol and Flovent CFC Aerosol were different. The original application received an approvable action on December 27, 2002, primarily due to CMC deficiencies. GSK submitted a complete response to the approvable action on November 13, 2003, which was received by the Agency on November 14, 2003. The PDUFA due date on this submission is May 14, 2004. This submission consists primarily of new CMC information. GSK also addressed other points noted in the previous action letter. The major CMC deficiencies are now resolved. Therefore, the NDA will be approved in this review cycle.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The drug substance fluticasone propionate is a well known compound that is already approved in several commercial drug products. CMC information for the drug substance is referenced to the NDA for marketed Flonase Nasal Spray, and is therefore acceptable. The final micronized form of drug substance is manufactured at GSK Operations site in United Kingdom. The drug product is a micronized suspension of fluticasone propionate in the liquefied hydrofluoroalkane propellant HFA-134a contained in an aluminum alloy can sealed with a metering valve and affixed to an actuator. There are three strengths of fluticasone propionate and HFA formulated to deliver 44 mcg, 110 mcg, and 220 mcg of

fluticasone propionate per actuation ex-actuator. All three strength products are proposed to be supplied as 120 actuations per inhaler presentation:

. Each canister will be overfilled to maintain sufficient formulation to deliver the labeled number of actuations for the full shelf life.

There were critical CMC deficiencies related to consistent drug product quality and performance that were identified during the previous review cycle. Some of those included

The critical CMC issues have now been resolved. Acceptance criteria for particle size distribution and delivered dose uniformity have been tightened to an acceptable level. The applicant proposed acceptance criterion for delivered dose uniformity that is slightly outside the range that the Agency has accepted in the past for inhaled products, but given the drug class the proposed specifications are reasonable. The drug is intended for chronic administration and is not for acute relief of symptoms; therefore, slightly higher variations between doses will not be a safety or efficacy risk. There was a question on the lack of dose proportionality among the three strengths of the product based on cascade impactor data. The three strengths of the product were not strictly dose-proportional across all stages of the cascade impactor. But the three strengths are sufficiently dose proportional when

This is sufficient to conclude that the three strengths are indeed dose proportional. There are several minor CMC issues that GSK has agreed to work on post-approval to improve product quality. These are summarized in Dr. Schroeder's CMC discipline review. These issues do not impact on the safety and efficacy of the product and therefore can be worked on post-approval. GSK has also agreed to

. All manufacturing sites related to this application have acceptable evaluation status.

Clinical and Statistical

The pivotal clinical studies submitted to the NDA included one study in patients previously maintained on bronchodilators (FAP30008), one study in patients previously maintained on inhaled corticosteroids (FAP30007), one study in patients previously maintained on oral corticosteroids (FLTA3022), and two long-term safety studies (FAP30001 and FLTB3048). In subsequent sections of this memorandum these studies are briefly reviewed. Detailed review of the studies can be found in Dr. Gilbert-McClain's Medical Officer Review from 2002. In this memorandum all doses are mentioned as the ex-actuator dose.

Study in patients previously maintained on bronchodilators:

FAP30008 was a double-blind, placebo-controlled, parallel group study conducted in patients 12 years of age and older who were previously maintained on inhaled beta-agonists only. The study was conducted in 78 centers in the United States. The study had a 2-week screening period during which patients were switched from their prescribed

short-acting beta agonist to Ventolin MDI for as needed use, followed by a 12-week double-blind treatment period during which patients were treated with Flovent HFA 440 mcg BID, 220 mcg BID, 88 mcg BID, or placebo. The primary efficacy endpoint was a mean change in pre-dose percent predicted FEV1 at endpoint (last observation) compared to pre-dose baseline. There were four key secondary endpoints – mean change in PEFR at endpoint compared to baseline, duration of participation in the study, mean change in Ventolin MDI use at endpoint compared to baseline, mean change in asthma symptom score at endpoint compared to baseline. Asthma Quality of Life Questionnaire (AQLQ) developed by Juniper and Guyatt was also administered at randomized visit and at week 12 or at the discontinuation visit. The AQLQ contains 32 items in 4 domains. The domains are activity limitation (11 items), asthma symptoms (12 items), emotional function (5 items), and environmental stimuli (4 items). The response format consists of a 7-point scale where 1 indicates maximal impairment and 7 indicates no impairment. A change of 0.5 for overall score and for individual domain score is considered to be clinically meaningful. The applicant defined a priori a reduced population comprised of subjects with an overall AQLQ score of less than or equal to 5.8 at baseline as the primary analysis population for the AQLQ. Safety variables assessed in the study included recording of adverse events, physical examination, laboratory tests, assessment of adrenal axis by 24-hour urine cortisol values, and ECG.

A total of 397 patients were randomized, approximately equally to the four treatment arms. Approximately 80% of patients completed the study, with more completers in the active treatment arms (74% to 89%) compared to the placebo arm (70%). All three doses of Flovent HFA were effective in the study. Mean FEV1 at endpoint compared to baseline increased by 0.30 L (11.2%) in the Flovent HFA 440 mcg BID arm, 0.35 L (9.8%) in the Flovent HFA 220 mcg BID arm, 0.32 L (9.0%) in the Flovent HFA 88 mcg BID arm, compared to 0.16 L (3.4%) in the placebo arm. Differences between all active treatment arms and placebo were statistically significant. Secondary endpoints were also numerically superior for active treatment arms compared to placebo. Improvements in morning PEFR were statistically significantly different for all active treatment arms compared to placebo. Duration of participation in the study was statistically significantly different than placebo for the Flovent 440 mcg BID arm, but not for Flovent 220 mcg BID and 88 mcg BID arms. Ventolin MDI use and asthma symptom score were not statistically significantly different for active treatment arms compared to placebo.

For AQLQ the primary analysis population included approximately 85% of the randomized subjects. The Flovent 440 mcg BID arm had clinically meaningful change from baseline over placebo for overall score (change of 0.66), and for the 4 domains of activity limitation (change of 0.59), asthma symptoms (change of 0.64), emotional functions (0.80), and environmental stimuli (change of 0.76). Changes for Flovent 220 mcg BID and 88 mcg BID arms did not cross the clinically meaningful threshold of 0.5 for the overall scores and for all individual domains, except for a 0.52 change for environmental stimuli for the Flovent 88 mcg BID arm.

There were no unique safety signals noted in this study. All three doses of Flovent HFA were well tolerated in the study.

Study in patients previously maintained on inhaled corticosteroids:
FAP30007 was also a double-blind, placebo-controlled, parallel group study conducted in patients 12 years of age and older. The study was conducted in 79 centers in the United States. Design and conduct of the study was similar to Study FAP3008 described above, except that the patients were previously maintained on inhaled corticosteroids. During the 2-week screening period patients were switched from their short-acting beta agonist to Ventolin MDI and their inhaled corticosteroids were continued. At the end of screening period patients whose FEV1 remained comparable to the baseline and asthma remained stable were randomized to double-blind treatment. Treatment arms were same as Study FAP3008.

A total of 415 patients were randomized, approximately equally to the four treatment arms. Approximately 70% of patients completed the study, with more completers in the active treatment arms (77% to 83%) compared to the placebo arm (38%). All three doses of Flovent HFA were effective in this study. Mean FEV1 at endpoint compared to baseline increased by 0.18 L (4.6%) in the Flovent HFA 440 mcg BID arm, 0.14 L (3.2%) in the Flovent HFA 220 mcg BID arm, 0.12 L (2.2%) in the Flovent HFA 88 mcg BID arm, compared to a 0.26 L (8.3%) decrease in the placebo arm. Differences between all active treatment arms and placebo were statistically significant. Secondary endpoints were also numerically superior for active treatment arms compared to placebo. Some of the differences reached statistical significance.

For AQLQ the primary analysis population included approximately 85% of the randomized subjects. All three doses of Flovent had clinically meaningful change from baseline over placebo for overall score (changes of 0.75 for Flovent 440 mcg BID arm, 0.79 for Flovent 220 mcg BID arm, and 0.79 Flovent 88 mcg BID arm). The scores for activity limitation, asthma symptoms, and emotional function domains also crossed the clinically meaningful threshold of 0.5 for all three doses of Flovent. The domain of environmental stimuli did not cross the clinically meaningful threshold for any of the Flovent arms.

There were no unique safety signals noted in this study. All three doses of Flovent HFA were well tolerated in the study.

Study in patients previously maintained on oral corticosteroids:
FLTA3022 was a double-blind, placebo-controlled, parallel group study conducted in patients 12 years of age and older who were previously maintained on oral corticosteroids. The study was conducted in 39 centers in the United States. The study had a 2-week screening period during which all medications including corticosteroids were continued, but their prescribed beta-agonist was switched to Ventolin MDI. After the screening period, the patients entered a 16-week double-blind treatment period where they were randomized to treatment with Flovent 880 mcg BID, 440 mcg BID, or placebo. Unlike the previous two studies, the HFA and CFC formulation of fluticasone were used in this study. There were five treatment arms – 2 treatment arms with the two doses of the Flovent HFA, 2 treatment arms with the two doses of Flovent CFC, and placebo.

During the double-blind treatment period, investigators titrated the dose of oral prednisone once-a-week according to specified criteria. The primary efficacy endpoint in the study was mean oral prednisone use during weeks 1-16. There were many secondary endpoints including the endpoints used in the studies described above. Safety variables assessed in the study included recording of adverse events, physical examination, laboratory tests, assessment of adrenal axis by Cortrosyn stimulation testing, and ECG.

A total of 168 patients were randomized, approximately equally to the five treatment arms. Approximately 67% of patients completed the study, with more completers in the active treatment arms (59% to 81%) compared to the placebo arm (33%). Both doses of Flovent of both formulations were effective in this study. Mean oral prednisone requirement at baseline ranged from 12.5 to 14.2 mg in the different treatment arms. During weeks 1-16 the mean daily prednisone use was 6.2 mg for the Flovent HFA 880 mcg BID arm, 6.4 mg for the Flovent CFC 880 mcg BID arm, 5.8 mg for the Flovent HFA 440 mcg BID arm, 4.9 mg for the Flovent 440 mcg CFC arm, compared to 14.9 mg for the placebo arms. There were no differences between the two active treatment arms; rather the lower dose appeared to be numerically better than the higher dose. Secondary efficacy variables also showed superiority of the active treatment arms compared to placebo, but there were no dose ordering. Although the overall AQLQ scores and many of the individual domains for the Flovent arms crossed the clinically significant threshold, the results are not useful because a high percentage (64%) of patients from the placebo group did not complete the study and the number of patients in the Flovent arms for AQLQ assessment ranged from only 25 to 34. The numbers are too small for any conclusion.

There were not unique safety signals noted in this study. All three doses of Flovent HFA were well tolerated in the study.

Long term safety studies:
FAP30001 was a double-blind, parallel group 6-month study of Flovent HFA 440 mcg BID and 220 mcg BID conducted in patients 12 years of age and older with asthma. The study was conducted in 18 centers in the United States. Safety variables assessed were similar to those used in the 12-week studies described above. A total of 182 patients were randomized, approximately equally to the two treatment arms. Approximately 80% of patients completed the study. Both doses of Flovent were well tolerated in this study. There were no unique safety signals noted in this study. The adverse events profile was similar to other studies. Corticosteroid related adverse events seemed to be dose related. Assessment of adrenal axis was somewhat limited because of limitation of the urinary cortisol data.

FLTB3048 was a double-blind, parallel group 12-month study of Flovent HFA 440 mcg BID and Flovent CFC 440 mcg conducted in patients 16 years of age and older with asthma. The study was conducted internationally with sites in Canada and Western European countries. Safety evaluations were similar to previous studies. A total of 325 patients were randomized, approximately equally to the two treatment arms. Approximately 90% of patients completed the study. Both formulations of Flovent were

well tolerated in this study. Interestingly, Flovent HFA patients appeared to have more asthma exacerbations in this study.

Summary efficacy conclusion, dose recommendation, and safety findings:
Various dosage regimens of Flovent HFA were studied in three different patient groups based on prior asthma therapy as reviewed above. The dosage regimen studied in patients previously maintained on inhaled beta-agonists or inhaled bronchodilators were 88 mcg BID, 220 mcg BID, and 440 mcg BID. The dosage regimen studied in patients previously maintained on oral corticosteroids were 440 mcg BID and 880 mcg BID. All doses were statistically significantly superior to placebo for the primary efficacy endpoints and the secondary efficacy endpoints tended in the same direction. The clinical program for Flovent HFA was somewhat small with the lower doses replicated in patients with differing asthma severity and the higher dose not replicated. This is acceptable because fluticasone in other formulations and in three similar dose strengths is well studied in similar spectrum of asthma severity. Three dosage strengths of fluticasone in other formulations are also approved for marketing in the United States. In the Flovent HFA program there were no clear dose responses in any of the studies. This is somewhat reminiscent of other fluticasone asthma clinical program where dose response has been difficult to demonstrate, particularly for the higher two doses. Although Flovent HFA was a stand alone program, information from other fluticasone clinical studies are relevant because the active moiety is the same and the ranges of dosages studied were similar. Based on the similarity of clinical findings across different formulations of fluticasone, the recommended dose range for Flovent HFA will be from 88 mcg BID to 880 mcg BID, although the Flovent HFA program did not show a separation between the 440 mcg BID and 800 mcg BID doses on efficacy endpoints. For patients who were previously on oral bronchodilators or inhaled corticosteroids, the recommended starting dose will be 88 mcg BID and the highest dose will be 440 mcg BID. For patients on oral corticosteroids, the recommended starting dose will be 440 mcg BID and the highest dose will be 880 mcg BID. This is similar to the recommended dose range for other orally inhaled fluticasone products approved for marketing in the United States. For Flovent HFA there will be some caveat to the 880 mcg BID dose in the label that will state that clinical studies failed to show clear advantage of the 880 mcg BID dose over the 440 mcg BID dose. It is expected that the 880 mcg BID dose will be used in rare patients who are on oral corticosteroids and are difficult to taper.

All doses of Flovent HFA studied in the pivotal efficacy and safety studies were generally well tolerated. Adverse events that occurred more frequently in the Flovent HFA treatment arms than the placebo arm were typical events seen with orally inhaled corticostoroids, such as upper respiratory tract irritation and infection, and oral candidiasis. No evidence of adrenal axis suppression was seen in clinical efficacy and safety studies and in specific pharmacodynamic studies conducted to assess the adrenal axis.

Clinical Pharmacology and Biopharmaceutics
GSK submitted results from a fairly comprehensive clinical pharmacology program with the original submission. The program addressed the key biopharmaceutics issues, such as pharmacokinetic parameters after single and multiple doses, effect of HFA propellant on systemic exposure of fluticasone, and potential clinical significance of differences in fluticasone between formulations. These studies were reviewed in detail in Dr. Kofi Kumi's review and were found to be adequate. As in other orally inhaled fluticasone products, fluticasone was systemically bioavailable from the lung. But one point of interest was the observation that the bioavailability of fluticasone appeared to be less for the HFA based product compared to the CFC based product. Following administration of 1760 mcg fluticasone using the Flovent HFA 220 mcg product in healthy volunteers, the exposure was about 30% lower compared to the same dose administered using the Flovent CFC 220 mcg product.

Pharmacology and Toxicology
GSK submitted complete preclinical general toxicology studies with the original submission. These were reviewed in detail by Dr. Lawrence Sancilio and were found to be adequate. Preclinical inhalation toxicity studies conducted with the HFA formulation did not show any unique toxicology findings. All findings were typical glucocorticoid effects and were consistent with effects seen with other formulations of fluticasone. Studies addressing the reproductive toxicity, genotoxicity, and carcinogenicity of fluticasone were submitted to the NDAs for other formulations of fluticasone and were reviewed earlier. Fluticasone was not genotoxic or mutagenic. Carcinogenicity studies with fluticasone were negative. Reproductive toxicology studies showed some known teratogenic effects of corticosteroids, such as cleft palate. There were no unique findings with fluticasone. The pregnancy category for Flovent HFA will be C, which is same as other fluticasone containing products.

Data Quality, Integrity, and Financial Disclosure
DSI audited two study sites during review of the original submission and did not identify and irregularities. During review of the original submission and subsequent submissions no irregularities that would raise concerns regarding data integrity were found. No ethical issues were present. All studies were performed in accordance with accepted clinical standards. The applicant submitted acceptable financial disclosure statements.

Pediatric Considerations
The current development program for Flovent HFA studied patients 12 years of age and older and the applicant is seeking approval for ages 12 years and above. The applicant will be asked to develop the product to a lower age because the delivery device is suitable for use in children younger than 12 years. The lower age bound for similar devices has typically been 4 years.

Linear growth suppression is a concern with all corticosteroids including orally inhaled corticosteroids. The Agency and scientific community consider linear growth

suppression in children as an important marker for systemic effect of corticosteroids. This issue was discussed at an Advisory Committee meeting held on July 30 and 31, 1998. All orally inhaled and nasal corticosteroids have a labeling language to indicate that these drugs can cause growth suppression. Flovent HFA will also have the similar labeling language. GSK did not conduct a linear growth study with Flovent HFA, but did conduct a growth study with Flovent Rotadisk and showed a positive effect. Results of the Flovent Rotakisk growth study will be included in the Flovent HFA label, because the systemic bioavalability of fluticasone from Flovent HFA is likely to be higher than that from Flovent Rotadisk. The systemic bioavailability of fluticasone from Flovent Rotadisk in healthy volunteers is about 13.5% of the nominal dose (Flovent Rotadisk Product label). The systemic bioavalability of fluticasone from Flovent CFC Inhalation Aerosol is about 30% of the ex-actuator dose (Flovent Inhalation Aerosol product label), and the systemic bioavailability of fluticasone from Flovent HFA is about 30% lower than that from Flovent CFC Inhalation Aerosol (Flovent HFA proposed product label). Although cross-study comparison has problems, at this time there are no data that directly compares systemic bioavalability between Flovent Rotadisk and Flovent HFA.

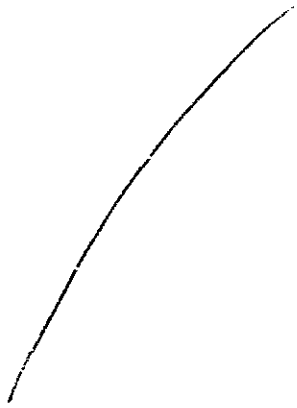
Product Name

The product name Flovent is approved and has been used by GSK for orally inhaled formulations containing fluticasone. The suffix HFA and the dose strengths are appropriate for this dosage form.

Labeling

GSK's proposed label for Flovent HFA is similar to other orally inhaled products containing fluticasone. But the proposed

. During the previous review cycle the label was not extensively reviewed because the application was approvable. During this cycle all disciplines of the Division reviewed the label. The Division and GSK have agreed on a final labeling text that adequately reflects the drug product and the clinical program. On the Division's suggestion, GSK agreed to remove or qualify



Action

The submitted data are sufficient to support the efficacy and safety of Flovent HFA 44 mcg, 110 mcg, and 220 mcg for use in patients 12 years of age and older with asthma. The major CMC deficiencies are resolved. GSK and the Division have agreed to several post-approval agreements to address outstanding CMC issues that do not impact safety and efficacy. GSK will also [redacted] at a later time. The action on this application will be APPROVAL.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Badrul Chowdhury
5/14/04 09:07:23 AM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: May 6, 2004

To: Mary Sides	**From:** Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-315-5381 483	**Fax number:** 301-827-1271
Phone number: 919-483-6464	**Phone number:** 301-827-1084
Subject: NDA 21-433	
Total no. of pages including cover: 3	

Comments: CMC comments

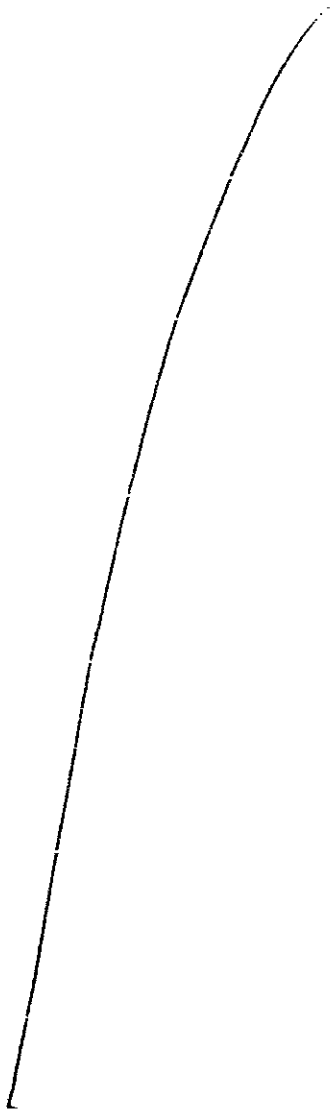
Document to be mailed: ☐ YES ☑ NO

NDA 21-433

Dear Ms. Sides:

We are reviewing your NDA for Flovent HFA Inhalation Aerosol, and have the following additional questions and requests for information. We ask that you respond to these questions by 12:00 noon on Monday May 10, 2004.

1. Based upon the following data and scientific principles, provide an agreement to propose quantitative mass balance criteria ~ variation around label claim) as part of the — specification, within 3 months of the date of approval of this NDA. This was previously requested in our facsimile transmission sent on March 23, 2004. —



1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

Initialed by: Barnes/5-6-04
Schroeder/5-6-04
Lostritto/5-6-04

Filename: N21433May04CMC comments.doc

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FACSIMILE TRANSMITTAL SHEET

DATE: April 1, 2004

To: Mary Sides	**From:** Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-483-5381	**Fax number:** 301-827-1271
Phone number: 919-483-6464	**Phone number:** 301-827-1084

Subject: NDA 21-433

Total no. of pages including cover: 3

Comments: CMC comments

Document to be mailed: • YES ☑ NO

NDA 21-433

Dear Ms. Sides:

We are reviewing your NDA resubmission dated November 13, 2003, for Flovent HFA and have the following additional comments and requests for information.

Comments below include cross references in parentheses to our approvable letter dated December 27, 2002.

1. Indicate where the new storage facility for Flovent HFA is located and when it will be operational. (Comment 10k(4))

2. The following preliminary labeling comments pertain to labeling for the carton, the immediate container and the mouthpiece, as provided in the original NDA.

   a. Clarify whether the actuator label is embossed on the actuator, or whether it will be a paper label.

   b. The colors chosen for "Flovent HFA" on the immediate container and carton labels, and the background color make the trade name difficult to read for the 44 mcg strength product. Improve the prominence of the trade name in these places.

   c. Print the words "Lot" and "Exp" on the appropriate areas of the immediate container and carton labels.

   d. Modify the established drug name in all labeling, to fit the following form: "fluticasone propionate HFA *x* mcg inhalation aerosol."

   e. Improve the prominence of the information on the side panels of the cartons.

3. Please clarify whether the data for —— (Tables 143-146) in Appendix 8 were obtained using the revised method ——

We remind you of the following agreements and request that you provide a timeline for completion of item # 1.

1.

2. Implement a revised cascade impactor method, utilizing a smaller number of actuations per cascade impactor assay, within 18 months of product launch. We are providing the following clarification. A cascade impactor method with less than — per assay is the desired goal, with no impact on acceptance criteria. (Comment 13)

I may be reached at 301-827-1084 for any questions.

Ladan Jafari, Regulatory Project Manager

Drafted by: LJ/3-31-04

Initialed by: Barnes/3-31-04
Schroeder/4-1-04
Lostritto/4-1-04

Filename: N21433April1 CMCcomments.doc

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/s/

Ladan Jafari
4/1/04 12:25:02 PM
CSO

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FACSIMILE TRANSMITTAL SHEET

DATE: March 23, 2004

To: Mary Sides	**From:** Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-483-5381	**Fax number:** 301-827-1271
Phone number: 919-483-6464	**Phone number:** 301-827-1084
Subject: NDA 21-433	
Total no. of pages including cover: 2	

Comments: CMC comments

Document to be mailed: • YES ☑ NO

NDA 21-433

Dear Ms. Sides:

We are reviewing your NDA submission dated November 13, 2003, for Flovent HFA and have the following request for information.

We have noticed that control of mass balance is not addressed in NDA 21-433 for Flovent HFA. In order to ensure appropriate control of the particle size distribution for Flovent HFA, provide for appropriate mass balance controls as an addition to the drug product specification for this test . Alternatively, you may provide an agreement to submit a prior approval supplement which provides for mass balance controls for within three months of the date of approval of this NDA.

I may be reached at 301-827-1084 for any questions.

Ladan Jafari, Regulatory Project Manager

Initialed by: Barnes/3-23-04
Schroeder/3-23-04
Lostritto/3-23-04

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/s/

Ladan Jafari
3/23/04 12:08:03 PM
CSO

Ladan Jafari
3/23/04 12:10:04 PM
CSO

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Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: March 15, 2004

To: Mary Sides	**From:** Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-483-5381	**Fax number:** 301-827-1271
Phone number: 919-483-6464	**Phone number:** 301-827-1084
Subject: NDA 21-433	
Total no. of pages including cover: 6	

Comments: CMC comments

Document to be mailed: • YES ☑ NO

NDA 21-433

Dear Ms. Sides:

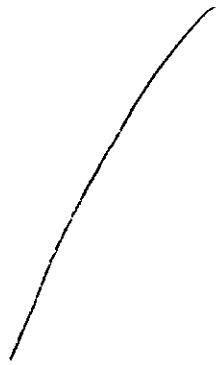
We are reviewing your submission dated November 13, 2003, and have the following requests for information.

Comments below include cross references in parentheses to our approvable letter dated December 27, 2002.

1. The following comments pertain to your — — procedures which are part of method — for determining delivered dose uniformity.

   a.

   b.



2. Specify in method — aerodynamic particle size distribution (APSD) by cascade impactor, the — that was used in the validation experiments (e.g. manufacturer and model). (Comment 5d(1))

3. Increase the number of canisters tested in your stability protocol for APSD from — — as previously requested. (Comment 5d(3)).

4. Improve method — for — impurities, t — — — or alternatively provide adequate justification with data as previously requested. (Comment 5e(3))

5. Provide an agreement to reconsider the acceptance criteria for concentration of the drug suspension, once more data are available (e.g., within 12 months after approval). (Comment 5f(3))

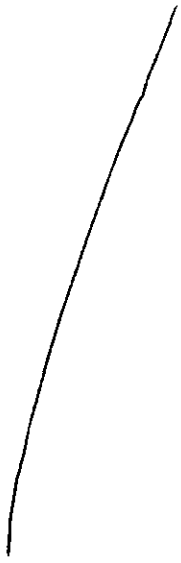
6. Provide a comparative list of the item codes of the container closure components intended for the commercial product, along with item codes assigned during development for the same components. Highlight any changes. (Comment 6a)

7. For the critical and major [redacted] acceptance criteria for the valves which both list the same defects (i.e., '[redacted], reword the different acceptance criteria so as to clarify the difference between the two. (Comment 6b)

8. As previously requested, provide a unique identifying number (or suffix) for each [redacted] test method for actuator and strapcap. The methods are diverse, and this will eliminate confusion as well as facilitate review of any future changes in any of the methods. (Comment 6g(4))

9. Indicate where [redacted] of propellant GR 106642X will be performed, since you have withdrawn the [redacted] from the NDA for this function. (Comment 6i)

10. The following comments pertain to [redacted]



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____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

14. Provide a listing of any other unsatisfied commitments made for this application not mentioned in this letter.

I may be reached at 301-827-1084 for any questions.

Ladan Jafari, Regulatory Project Manager

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Schroeder/3-15-04
Lostritto/3-15-04

Filename: N21433 CMC IR.doc

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/s/

Ladan Jafari
3/17/04 11:00:33 AM
CSO

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FACSIMILE TRANSMITTAL SHEET

DATE: August 26, 2003

To: Mary Sides	**From:** Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-483-5381	**Fax number:** 301-827-1271
Phone number: 919-483-6464	**Phone number:** 301-827-1084
Subject: NDA 21-433	
Total no. of pages including cover: 2	

Comments: CMC comments

Document to be mailed: ☐ YES ☑ NO

NDA 21-433

Dear Ms. Sides:

In response to your recent proposal dated August 11, 2003, regarding the number of cans for Cascade Impaction Testing, we have the following comments.

The [redacted] to the specification is a separate issue from the number of canisters tested, and we have no objections to a [redacted].

The following are our recommendations:

1. Test - canisters for particle size distribution, as a better representation of the batch.

2 [redacted]

3. We cannot evaluate specific numerical limits at this time; that will be done during the review of your complete response, along with all of the data.

I may be reached at 301-827-1084 for any questions or comments.

Ladan Jafari, Regulatory Project Manager

Initialed by: Barnes/8-26-03
Schroeder/8-26-03
Poochikian/8-26-03

Filename: N21433CMCcomments.doc

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FACSIMILE TRANSMITTAL SHEET

DATE: July 18, 2003

To: Michael Golden	**From:** Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-483-5381	**Fax number:** 301-827-1271
Phone number: 919-483-3692	**Phone number:** 301-827-1084
Subject: NDA 21-433	
Total no. of pages including cover: 10	

Comments: Meeting minutes

Document to be mailed: YES ☑ NO

NDA 21-433
Drug: Flovent HFA
Applicant: GSK
Meeting Date: July 8, 2003
IMTS: 10609

GSK Representatives:

Ian Ashurst, Ph.D.	Director, New Product Supply
Maurice Boles, Ph.D.	Manager/Flovent HFA, Inhalation Product Development
Alan Cripps, Ph.D.	Director, MDI Development, UK
Michael Golden	Director, CMC Regulatory Affairs
Charles Mader, Ph.D.	Director, Head Inhalation Products Development, USA
Ray Ormiston, Ph.D.	Manager, CMC Regulatory Affairs
Mary Sides	Manager, CMC Regulatory Affairs
Patrick Turlier	Director, New Product Supply/Regulatory

Division of Pulmonary & Allergy Drug Products (DPADP) Representatives:

Lydia Gilbert-McClain, M.D., Acting Medical Team Leader
Marianne Mann, M.D., Deputy Director
Badrul Chowdhury, M.D., Ph.D., Director
Alan Schroeder, Ph.D., CMC Reviewer
Guirag Poochikian, Ph.D., CMC Team Leader
Ladan Jafari, Regulatory Project Manager

Office of New Drug Chemistry:

Eric Duffy, Ph.D., Division Director

Background: GSK submitted a meeting request dated April 14, 2003, to discuss a few deficiencies cited in the approvable letter for Flovent HFA application dated December 27, 2002. GSK also met with the Division on March 4, 2003, to get clarification on some of the points of the approvable letter. GSK believes that this would be the last meeting before a complete response to the Flovent HFA application is submitted. The Division's responses to GSK questions are listed below.

The following comments are in response to the introduction section of the briefing package.

Comment 9c:

This pertains, in part, to our request for updated stability summary data for stability batches. GSK has indicated that 18 months of data have already been provided for the — stability batches and no additional data will be provided for these studies. The Division asks that GSK provide summary data for individual cascade impactor stages, as requested, for the — stability batches as well as for the — stability batches.

- GSK indicated that they plan to provide the requested data to the Division.

Comment 1b:

Comment 9d:

Comment 5.d(3):

This comment pertains to the Division's request for testing more than — canisters for particle size distribution, and for providing tightened acceptance criteria for individual canisters and for means of the multiple canisters tested for particle size distribution.

The test for particle size distribution should routinely include more thar —canisters. This is to insure that the data are reliable for this important parameter, and to make it consistent with the Division's approach.

- GSK asked how many canisters should be tested for this purpose and the Division responded that at least —would be optimum. GSK indicated that they can only test a maximum of — canisters a day for Flovent HFA. GSK asked if they could develop a — or the acceptance criteria, —

  —. The Division asked that GSK send a proposal before submission of their complete response and we would discuss it internally before agreeing on any particular number. The Division asked that GSK send this proposal well in advance of the resubmission.

Comment 6.h.(1):

This pertains to providing a more accurate method and acceptance criterion for —

Comment 9e:

The Division began by asking for clarification for how, in general, data are rounded relative to acceptance criteria (e.g., if raw data have more significant figures than the number of significant figures in the acceptance criteria).

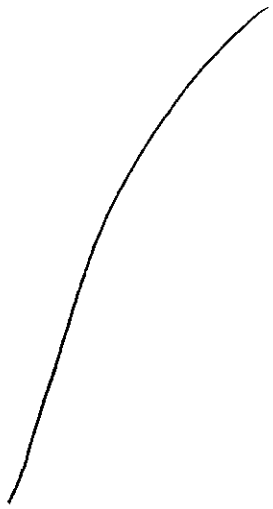
- GSK indicated that if acceptance criteria are less than 0.3% and the data is 0.27%, this would be rounded to 0.3%.

Comment 9e requested tighter acceptance criteria for — impurities as well as for total impurities (based on the drug product data).

GSK had indicated that the proposed acceptance criteria for — impurities for Flovent HFA are identical to the approved limits (for micronized fluticasone propionate) for their marketed products for oral and nasal inhalation.

The Division stated that GSK's proposal is acceptable.

Comment 9j:



Comment 10a:

This pertains to the re-priming period and data supporting it.

The drug per actuation should — after priming or re-priming. Additional data points are needed for the profile. As the Division originally requested, provide data with several time periods — days of non-use after priming.

There was considerable discussion on this issue, to clarify what the Division was looking for. The Division noted that the data are limited — days of non-use after priming, and these data suggest that re-priming may be indicated — days of non-use.

- GSK indicated that they believed that they did not need to re-prime if individual values were within — and the mean was within — GSK raised concerns that the patient may lose a lot of the drug product if this approach is not acceptable.

- The Division responded that just being within the acceptance criteria is not adequate. Data should demonstrate that re-priming has been achieved, and that the drug product is delivering the amount of drug specified in the label claim, or —

- The Division indicated that we need to see more data points than — days, and more batches tested at these time points in order to determine a proper interval for re-priming.

Comment 13:

This comment requests development of a cascade impactor method for particle size distribution with a reduced number of actuations (e.g., — in preliminary studies).

GSK has agreed to submit such a method, with their other responses in late summer. GSK has suggested that such a method be implemented as a Phase 4 commitment within 18 months of product launch.

- The Division stated that formal stability data may not be needed to demonstrate method comparability. GSK should provide the data as they become available. Batches currently available may be tested, using drug products of various ages. The issue here is one of demonstrating methods to be comparable, not demonstrating stability.

- GSK indicated that they have generated data and they will provide those data to the Division in their response. These data indicate that there is a shift as they go from __ — . GSK still has not completed the validation of the modified method. GSK asked if they could get an agreement on providing stability data in a Phase 4 commitment.

- The Division indicated that we would rather resolve all issues pre-approval and avoid any Phase 4 commitments. The Division asked that GSK provide the method with data and we would have to discuss it internally before we can decide on this.

Comment 15:

This pertains to updating of pertinent documents in response to the Division's letter. GSK has agreed to provide the following updated documents with their response: specifications, analytical methods and stability protocols. GSK proposed to provide updated master batch records just prior to approval (when it is confirmed that GSK responses are acceptable).

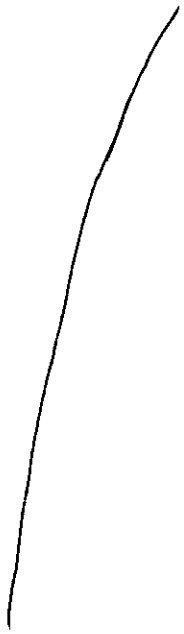
The Division indicated that this may be acceptable provided that GSK include a list of all changes, including cross-references to letter date and comment number. We would like to remind GSK that revised batch records will need adequate time for review prior to a final favorable action.

- GSK clarified that the basis of their request was the amount of time that it requires to revise the master batch records, and they would prefer to not have to do this multiple times.

- The Division acknowledged that for GSK's proposal, the Division would need to provide feedback to GSK that they have satisfied our concerns and should provide revised master batch records.

- GSK asked if it would be helpful if they provided a single revised batch record for one strength in advance of providing all of the revised batch records. The Division responded that it this may facilitate the review process.

Comment 16:



The Division also gave a Brief summary of our major outstanding concerns, which were not discussed at today's meeting.

Issues discussed in the March 4, 2003, meeting include modifying the targets for various drug product specifications, and various — issues.

The following significant issues were discussed in the Division's December 27, 2002, approvable letter. This list may not be not all-inclusive.

Dose Content Uniformity: the proposed acceptance criteria are too wide. [e.g., see comment 5c (9) in our December 27, 2002, letter]

Dose Proportionality: —
— [e.g., see comments 9c and 10f]

The method and acceptance criteria for — are inadequate [e.g., see comment 5j].

e

Action: GSK indicated that as a result of the discussions today, they may delay sending the response for Flovent HFA application until later this year.

Drafted by: LJ/7-11-03

Initialed by: Schroeder/7-15-03
Poochikian/7-15-03
Duffy/7-11-03
Chowdhury/4-16-03

Filename: GSK Flovent HFA.doc

6 Page(s) Withheld

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____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

Deputy Director Memorandum

NDA:	21,433
Product:	Flovent HFA Inhalation Aerosol
Indication:	Maintenance Treatment of Asthma
Date:	December 23, 2002
Reviewer:	Marianne Mann, M.D.

This application is for Flovent HFA Inhalation Aerosol delivered via metered dose inhaler (MDI) for the maintenance treatment of asthma. The drug substance, fluticasone propionate, has been marketed since 1996, and is available as a CFC Inhalation Aerosol delivered via MDI, as well as via a dry powder (Flovent Rotadisk and Flovent Diskus).

The applicant seeks approval for Flovent HFA in three dosage strengths: 44 mcg, 110 mcg, and 220 mcg, which is identical to the three dosage strengths of Flovent CFC that are currently available. The applicant seeks approval for doses of 88 mcg BID, 220 mcg BID, 440 mcg BID, and 880 mcg BID, with labeling similar to that noted for the Flovent CFC product.

This application is considered approvable due to numerous chemistry deficiencies related to drug product quality and performance.

There were no preclinical concerns raised in this NDA review since fluticasone is a well-known moiety, and since the HFA formulation raises no new concerns. There were also no biopharmaceutical concerns raised in this NDA review. The most notable pharmacokinetic study demonstrated that the systemic exposure to Flovent HFA versus Flovent CFC was lower (30-35% lower) comparing comparable doses of each product in healthy volunteers. Although comparative data of the HFA and CFC formulations in asthmatic subjects is not available, this information suggests that Flovent HFA is less systemically bioavailable than Flovent CFC, and may therefore have less systemic toxicity.

The clinical program for this application was a "stand-alone" application, relying solely on data with the Flovent HFA product versus placebo for approval. There were two pivotal 12-week clinical trials (one in asthmatics previously taking ICS and one in presumably milder asthmatics taking only inhaled bronchodilators) which each supported efficacy of Flovent HFA 88 mcg BID, Flovent HFA 220 mcg BID, and Flovent 440 mcg BID versus placebo. A modest trend for dose response was noted in each of these trials. Safety results from these 12-week trials revealed the usual incidence of anticipated adverse events for an inhaled corticosteroid such as throat irritation, hoarseness, dysphonia, and upper respiratory inflammation. These were also noted to occur in a dose-related fashion, and can be described adequately in product labeling. I agree with

both the primary and secondary medical reviewers that the approval of these doses of Flovent HFA is supported.

The major area of concern raised in this application was the approvability of Flovent 880 mcg BID which was supported by study FLTA3022.

FLTA3022 was a 16-week, randomized, double-blind, placebo-controlled, comparative trial of Flovent HFA (440 and 880 mcg dosed twice daily), Flovent CFC (440 and 880 mcg dosed twice daily) and placebo. This trial was performed in patients taking oral corticosteroids, and the primary endpoint was the mean oral predisone use during the 16-weeks of active treatment. Efficacy results are shown below.

Mean Oral Daily Prednisone Use (mg)

	Placebo N=32	Flovent HFA 440 mcg bid n=32	Flovent HFA 880 mcg bid n=32	Flovent CFC 440 mcg bid n=36	Flovent CFC 880 mcg bid n=33
Baseline	14.2	12.5	12.7	13.0	14.3
Weeks 1-16	14.9	5.8	6.2	4.9	6.4

Efficacy was no different with the higher dose of Flovent HFA and Flovent CFC versus the lower dose. In addition, there were some safety concerns raised with the higher dose of Flovent HFA in that three serious adverse events of pneumonia were noted in this arm. The usual steroid-related adverse events of candidiasis of the mouth and throat, throat irritation, and pharyngitis were also more common in the higher dose Flovent HFA treatment arm (but not at significantly different rates that the comparable Flovent CFC arm). Thus, the medical team leader felt that Flovent HFA 880 mcg BID should not be approved.

I agree that there is concern about approving Flovent HFA 880 mcg BID, but I do not feel labeling should absolutely preclude the use of the 880 mcg BID dose in patients who are taking oral corticosteroids. Flovent CFC recommends dosing of 880 mcg BID for all patients who are oral corticosteroid dependent. Flovent HFA appears to be less systemically bioavailable, and should therefore be as safe as Flovent CFC at this dose. The fact that Flovent HFA failed to show dose-response in this study is notable, but concerns about this are somewhat lessened by the fact that Flovent CFC also failed to show dose-response.

I agree with the primary reviewer that the recommended dose of Flovent HFA for patients who are taking oral corticosteroids should be 440 mcg, although I believe that labeling can also describe the use of doses up to 880 mcg for use in this patient population.

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/s/

Marianne Mann
12/23/02 12:24:25 PM
MEDICAL OFFICER

Badrul Chowdhury
12/23/02 12:54:37 PM
MEDICAL OFFICER
Deputy Div Dir and Div Dir Memo

5 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

February 18, 2002

GlaxoSmithKline

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709
Tel. 919 483 2100
www.gsk.com

Mellon Bank
Food and Drug Administration
Mellon Independence Center
701 Market Street
Philadelphia, PA 19106

Re: NDA 21-433; FLOVENT® HFA (fluticasone propionate) Inhalation Aerosol
User Fee: With Clinical Data; User Fee # 4299

Please find enclosed GlaxoSmithKline check number 00901881 in the amount of $313,320.00. This is 100% of the application fee for the New Drug Application for Maintenance Treatment of Asthma in Patients 12 Years of Age and Older. This application will be submitted to the Division of Pulmonary and Allergy Drug Products, Center for Drug Evaluation and Research, FDA.

Please find below requested information regarding this application.

Type of Application:	New Drug Application with Clinical Data	X
	New Drug Application without Clincial Data	
	Supplemental New Drug Application with Clinical Data	

Should you have any questions, please contact me at (919) 483-5121.

Sincerely,

Lorna C. Wilson

Lorna C. Wilson
Director
Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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 CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

2. TELEPHONE NUMBER *(Include Area Code)*

(919) 483-2100

3. PRODUCT NAME

Flovent HFA (fluticasone propionate) Inhalation Aerosol

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-433

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☐ 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:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4299

7. 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 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

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
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Lorna C. Wilson Lorna C. Wilson	Director Regulatory Affairs	18 February, 2002

FORM FDA 3397 (4/01)

GLAXOSMITHKLINE
FP0825
P.O. BOX 13681
PHILADELPHIA PA 19101-3681

gsk GlaxoSmithKline

MELLON BANK FOOD AND DRUG ADMIN
MELLON IDEPENDENCE CENTER
701 MARKET STREET
PHILADELPHIA PA 19106

PAYMENT DATE 02/01/02
Page 1 of 1

STATEMENT OF REMITTANCE

VOUCHER NO.	INVOICE NUMBER/REMARKS	INVOICE DATE	GROSS	DISCOUNT	NET
02282494	CR31332000 User Fee-Flovent / HP x33949	01/31/02	313,320.00		313,320.00

VENDOR NO.
00468590

$313,320.00

ETACH AND RETAIN THIS STUB FOR YOUR RECORDS.

CHECK # 00901881 ATTACHED BELOW

THIS PANTOGRAPH AREA OF THE DOCUMENT CHANGES COLOR GRADUALLY AND EVENLY FROM DARK TO LIGHT WITH DARKER AREAS BOTH TOP AND BOTTOM

gsk GlaxoSmithKline

GLAXOSMITHKLINE
FP0825
P.O. BOX 13681
PHILADELPHIA PA 19101-3681

VENDOR NO.
00468590

62-20
311

No. 00901881

02/01/02

PAY TO THE ORDER OF
MELLON BANK FOOD AND DRUG ADMIN
MELLON IDEPENDENCE CENTER
701 MARKET STREET
PHILADELPHIA PA 19106

*********$313,320.00

VOID AFTER 180 DAYS

Three hundred thirteen thousand three hundred twenty and 00/100 Dollars

TIBANK DELAWARE, A SUBSIDIARY OF CITICORP
NF ⁻⁻NN'S WAY, NEW CASTLE, DE 19720

Charles F. Kelly Jr.

⑈00901881⑈ ⑆031100209⑆ 3910465 9⑈

NDA 21-433

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 22, 2002

To: MS. Mary Sides	**From: Ladan Jafari** Division of Pulmonary and Allergy Drug Products
Company: GSK	
Fax number: 919-483-5381	**Fax number:** 301-827-1271
Phone number: 919-483-6464	**Phone number:** 301-827-1084
Subject: NDA 21-433	
Total no. of pages including cover: 2	

Document to be mailed: ☐ YES ☑ NO

We are reviewing your NDA submission for Flovent HFA and have the following request for information.

Provide a report of development efforts so far, directed at [redacted]

If you have any questions, please contact me at 301-8247-1084.

Ladan Jafari, Regulatory Project Manager

Initialed by: Barnes/7-19-02
Bertha/7-19-02

Filename: N21433cmcinforequest.doc

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/s/

Ladan Jafari
7/22/02 02:41:52 PM
CSO

NDA 21-433
Drug: Flovent HFA (fluticasone propionate) Inhalation Aerosol
Applicant: GSK

Division of Pulmonary & Allergy Drug Products

NDA Administrative Review

Application number: 21-433

Drug Name: Flovent HFA (fluticasone propionate) Inhalation Aerosol

Aplicant: GlaxoSmithKline (GSK)

Indication: Maintenance treatment of asthma in adolescents and adults 12 years of age and older.

Submission Date: February 26, 2002

Receipt Date: February 27, 2002 (electronic submission)

The following completed documents were submitted by GSK.

1. Form FDA 356h.
2. Form FDA 3397 (User Fee Cover Sheet)
3. Cross-reference
4. Index to the Application
    - Table of Contents for each volume to include lists of tables and figures
5. Patent Information
6. Debarment Certification
7. Application Summary:
    a. Labels and Labeling Summary
    b. Chemistry, Manufacturing, and Controls
    c. NonClinical Pharmacology & Toxicology
    d. Human Pharmacology & Biovailability/Bioequivalence
    e. Statisitical

f. Clinical, including Case Report Forms and Case Report Tabulations

The application is administratively filable.

Ladan Jafari, Regulatory Project Manager

Filename: N21433adminreview

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/s/

Ladan Jafari
4/23/02 03:02:29 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 19, 2001

To: Ms. Betsy Waldheim	**From: Ladan Jafari**
Company: GlaxoSmithkline	Division of Pulmonary and Allergy Drug Products
Fax number: 919-483-5756	**Fax number:** 301-827-1271
Phone number: 919-483-5319	**Phone number:** 301-827-5584
Subject: PreNDA meeting minutes for IND 53,502	
Total no. of pages including cover: 23	
Comments:	

Document to be mailed: ☐ YES ☑ NO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 19, 2001

APPLICATION: IND 53,502 (fluticasone propionate HFA)

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1. Don Collier	Project Manager, IT	Division of Pulmonary & Allergy Drug Products (DPADP) (HFD-570)
2. Emmanuel Fadiran	Clinical Pharmacology & Biopharmaceutics Team Leader	DPADP
3. Ladan Jafari	Project Manager	DPADP
4. Lisa Kammerman	Biometrics Team Leader	DPADP
5. Charles Lee	Medical Reviewer	DPADP
6. Robert Meyer	Director	DPADP
7. Mary Purucker	Medical Team Leader	DPADP
8. Larry Sancilio	Preclinical Reviewer	DPADP
9. Sandra Suarez	Clinical Pharmacology & Biopharmaceutics Reviewer	DPADP
10. Joe Sun	Supervisory Pharmacologist	DPADP

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Discipline	Sponsor/Firm Name
1. Frank Barnhart	Clinical	GlaxoSmithKline
2. Courtney Crim	Medical Affairs	GlaxoSmithKline
3. Gill Dines	Toxicology	GlaxoSmithKline
4. Susan Duke	Statistics	GlaxoSmithKline
5. Nancy Herje	Medical Affairs	GlaxoSmithKline
6. Shuyen Ho	Statistics	GlaxoSmithKline
7. Elaine Jones	Regulatory Affairs	GlaxoSmithKline
8. Steve Shrewbury	Medical	GlaxoSmithKline
9. Betsy Waldheim	Regulatory Affairs	GlaxoSmithKline

Background: GSK requested a Pre-NDA with the Division to discuss the development status of their fluticasone propionate HFA program. GSK also submitted a briefing package dated April 13, 2001, which contained a list of questions to be discussed at the meeting. See attachment 1 for Dr. Lee's overhead slides, attachment 2 for Dr. Suarez' overhead slides, attachment 3 for Dr. Kammerman's overhead slides.

1. *Question 1 of the briefing package.*

   - The Division agreed that they would review a fully electronic NDA submission.

2. *Question 2 of the briefing package.*

   - The Division stated that they would accept the hyperlink in the ISE and ISS.

3. *Question 3 of the briefing package.*

   - The Division stated that the font sizes would be acceptable.

4. *Question 4 of the briefing package.*

   - The Division found the proposal for BA studies, acceptable, however, stated that the relevance of the data would be a review issue.

5. *Question 5 of the briefing package.*

   - The Division agreed that GSK need not submit curriculum vitae for the principal investigators for supporting studies FLIT92, FLIT93, FLTB3047, FLTB4008, and long-term study FLIT94.

6a. *Question 6 of the briefing package.*

   - The Division stated that combining data from FAP30007, FAP30008 with data from FLTA3020 is acceptable.

6b *Question of the briefing package.*

   - The Division agreed that integrating the data from FAP30001 and FLTB3048 for the only first six months, is acceptable.

6c. *Question of the briefing package.*

- The Division stated that the proposal was acceptable.

6d. Question of the briefing package.

- The Division found the proposal acceptable.

6e. Question of the briefing package.

- The Division found the proposal not acceptable, and stated that the assessment should include trials FLIT92, FLIT 93, FLIT94, FLIT96, FLTB3047, FLTB4008, and FAS30009.

  - GSK indicated that the above data were already submitted to the Division for review in September of 1997, and inquired if they had to resubmit. The Division stated that they should resubmit these data

6f. Question of the briefing package.

- The Division stated that GSK's submission lists pivotal clinical studies FAP30007 and FPA30008, and supplemental pediatric study FAS30009 as being ongoing. Pivotal clinical studies FAP30007 and FAP30008 must be completed and a complete study report for each of these studies should be submitted with the NDA. Blinded listing for reports of deaths, serious adverse events may be submitted for supplemental pediatric study FAS30009. Reports for pregnancies would not be expected from this study.

6g. Question of the briefing package.

- The Division found the proposal acceptable.

6h. Question of the briefing package.

- The Division agreed with the proposal, however, requested that case report forms be included for all deaths, serious adverse events, and withdrawals in all clinical pharmacology and clinical studies in the NDA submission.

Question 7 of the briefing package.

1. Acceptable from a statistical perspective.

2. Risks for sponsor and for drug approval.

   (1) Violation of assumption:
   Response to study drug increases monotonically from Placebo to FP 440mcg BID.

Example: Active Treatment versus Placebo

Comparison(versus Placebo)		p-value
440mcg (BID)		.10
220mcg (BID)		.03
88mcg (BID)		.04

   (2) Must conclude "no statistically significant differences among the four treatment groups", even if some nominal p-values are less than 0.05.

   Example: Active Treatment versus Placebo

   - 440mcg is not statistically different from Placebo.

   Cannot conclude treatment is significantly different from Placebo, although the nominal p-values for the comparisons 220mcg versus Placebo and 88mcg versus Placebo are less than 0.05.

   (3) Potentially inconsistent conclusions from the studies, because method relies on p-values only.

   Example:
   - Study 1 conclusion: no differences among treatment groups.
   - Study 2 conclusion: differences among all treatment groups.
   - Confidence intervals around the treatment effects cannot be done.

- Consider using Dunnett's test.

3. Only results from the closed testing procedure will be considered.

4 All results from analyses of primary and secondary endpoints must be reported.

5 Submit multiplicity plan as amendments to the protocols.

Question 8 of the briefing package.

Acceptability of proposed statistical reviewer's aid

- The Division found GSK's proposal acceptable, and requested that GSK submit a copy to the Electronic Document Room as well.

Question 9 of the briefing package.

The Division requested that GSK provide the data listings with their NDA submission.

The Division also provided the following additional comments

1. The Division inquired if the data analysis methods contained in the protocols are also the final data analysis plans. GSK stated that they have additional information that they will submit for review.

2. When considering the impact of missing data on the interpretation of study results, the Division stated we would like to look at sensitivity analyses (e.g., a worst case scenario).

3. Analysis of covariance (ANCOVA) models need to reflect the stratification used at the time of randomization. Thus, Treatment by Stratification interactions are needed in the ANCOVA models.

   The sponsor indicated randomization was not stratified by center; a central randomization was used. Therefore, the ANCOVA models do not need to include treatment by center interactions.

4. Indicate the number of subjects who are expected to withdraw from study participation.

5. All statistical review comments above are based on the pre-NDA package and selected

sections from the study protocols that were faxed to the Division the day before the pre-NDA meeting. Comments were not based on reviews of the study protocols. The Division also stated that any labeling comments would be a review issue and would not be discussed at this time. The Division did point out, however, that we do not include p-values in labeling as we used to in the past.

Question 10 of the briefing package.

- The Division agreed that waiving the study requirements for Flovent Diskus in children under 4 years of age is appropriate since an inspiratory flow-driven device is not suitable for children in this age range.

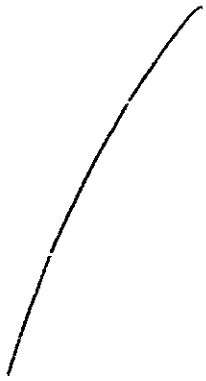
- The Division explained that the regulatory requirements for sponsors to fulfill the Pediatric Rule, or to answer a Written Request for Pediatric Studies, would be different from the requirements necessary to support a full pediatric indication.

- GSK stated that they are only seeking to fulfill the requirements of the Pediatric Rule, and at this time do not plan to seek an indication for children under the age of 4 years.

Question 11 of the briefing package.

The Division stated that GSK would not be able to make an in vitro link between the spacing devices with such a study. The Division explained that since the devices are very different, many CMC issues would arise. The Division indicated that each MDIs may behave differently with different spacers, and therefore, a clinical study or studies would be necessary to link such data.

Question 12 of the briefing package.



.nt

14 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

Question 8

Acceptability of proposed statistical reviewer's aid

1. Acceptable
2. Submit a copy to the Electronic Document Room

Question 9

Data listings

Please clarify "data listings"

Additional comments

1. Are the data analysis methods contained in the protocols also the final data analysis plans?

2. Analysis of covariance (ANCOVA) models need to reflect the stratification used at the time of randomization. Thus, the following terms are needed in the ANCOVA models:
   - Treatment by Center interactions
   - *Treatment by Other Stratification interactions*

3. *Indicate the number of subjects who are expected to withdraw from study participation.*

4. *Comment on the need for a LOCF imputation, which equates to comparisons of study treatments at the time of discontinuation. Because the study objective is to assess the efficacy at the end of 12 weeks – not at study discontinuation – consider "sensitivity" analyses to assess the impact of missing data on the interpretation of results at 12 weeks.*

5. All comments above are based on the pre-NDA package and selected sections from the study protocols. I may have additional comments after reviewing the protocols.

cc: Original
HFD-570/Div. Files
HFD-570/Jafari
HFD-570/Lee
HFD-570/Purucker
HFD-570/Suarez
HFD-570/Fadiran
HFD-570/Sancilio
HFD-570/Sun
HFD-570/Kammerman

Drafted by: LJ/6-29-01

Initialed by: Lee/7-3-01
Purucker/7-3-01
Suarez/7-9-01
Fadiran/7-9-01
Kammerman/7-18-01
Meyer/7-18-01

Filename: I53502PreNDAmtgminutes

MEETING MINUTES

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
7/19/01 09:49:27 AM

IND 53,502

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: June 19, 2001

To: Mr. Wayne Talton	**From: Ladan Jafari** Division of Pulmonary and Allergy Drug Products
Company: GlaxoSmithkline	
Fax number: 919-483-7473	**Fax number:** 301-827-1271
Phone number: 919-483-5381	**Phone number:** 301-827-5584
Subject: CMC meeting minutes	
Total no. of pages including cover: 11	
Comments:	

Document to be mailed: ☐ YES ☑ NO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 31, 2001

APPLICATION: IND 53,502 (fluticasone propionate HFA)

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1. Ladan Jafari	Regulatory Project Manager	Division of Pulmonary & Allergy Drug Products (DPADP) (HFD-570)
2. Robert Meyer	Director	DPADP
3. Guirag Poochikian	Chemistry Team Leader	DPADP
4. Mary Purucker	Clinical Team Leader	DPADP
5. Brian Rogers	Chemistry Reviewer	DPADP

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
1. Maurice Boles	Head, Inhaled Product Strategy	GlaxoSmithKline
2. Rosemary Leak	Head, International Inhalation Product Development	GlaxoSmithKline
3. John Morgan	Head, Respiratory New Submissions	GlaxoSmithKline
4. Ray Ormiston	Regulatory Affairs Project Manager, CMC New Submission	GlaxoSmithKline
5. Michael Riebe	New Product Supply Leader, Respiratory MDIs	GlaxoSmithKline
6. Satinder Sethi	Head, Inhaled Product Safety	GlaxoSmithKline
7. Wayne Talton	Associate Director, Regulatory Affairs, CMC New Submissions	GlaxoSmithKline

BACKGROUND: GlaxoSmithKline requested this meeting to discuss the development status of fluticasone propionate HFA. A briefing package detailing all the questions to be discussed at the meeting was submitted on April 24, 2001. An additional document containing a core protocol for NDA stability batches and a core protocol for the — NDA stability batches of fluticasone propionate was also submitted on May 18, 2001. The questions raised in the briefing package are printed in Italics below, followed by discussions.

- GlaxoSmithKline initiated the meeting by stating that they plan to submit the NDA for fluticasone propionate HFA in February 2002. The Division inquired as to when GlaxoSmithKline would transition to the new HFA formulation and GlaxoSmithKline responded that they plan to have it available for the United States market as quickly as possible after approval. GlaxoSmithKline indicated that they currently have fluticasone propionate HFA approved, launched and transitioned in several countries.

- The Division indicated that the inclusions of various tables , — — as well as the references to the guidance documents were useful tools in reviewing the briefing package and encouraged GlaxoSmithKline to follow the same format at the time of the NDA submission. The Division also requested that GlaxoSmithKline elaborate on the historical precedents, and include them in the NDA submission.

1. *Does the Agency agree that the data on — product, described above, to be included in the NDA submission are adequate to accept the NDA for filing?*

   Does the Agency agree that the additional data (i.e. — data for three batches of each product) to be supplied as a stability update during review will be adequate both with regard to content and timing to allow the Agency to complete its review by the action date?

The Division had the following comments:

- The extent of data proposed is acceptable for filing.
- The extent of data proposed is adequate to allow completion of review by the action date.
- The quality of the — batch data may have a large effect on both the approvability and on the length of time justified for the expiration-dating period.

- GlaxoSmithKline indicated that the first batch of — from Evreux, France will be

available in June 2001, and stated that all of these batches will be over-wrapped. GlaxoSmithKline added that the original batch size was [redacted] which is equivalent to 50-60% of commercial scale. The second batch produced in June, would be [redacted], which is equivalent to the full commercial scale of [redacted] inhalers.

- GlaxoSmithKline indicated that the NDA stability data planned for February 2002, would be comprised of primary [redacted] batches containing a [redacted] data, followed by an 18-month updated data set. The [redacted] batches would have [redacted] months supportive data from the [redacted] facility, followed by a [redacted] updated data from their Evreux facility. GlaxoSmithKline stated that they plan to establish expiry based on the [redacted] and inquired if that was acceptable.

  - The Division agreed that the concept was acceptable, however, the decision would be based upon the comparability of the [redacted] data. The Division indicated that they would look at accelerated data, data on [redacted] prior to making any final decisions.

  - The Division reminded GlaxoSmithKline that they should document and submit in the application [redacted]

2. *We would like to obtain feedback from the Agency on the acceptability of these data proposals to support the incorporation of [redacted] drug substance, micronized at either [redacted] Evreux, into the original NDA.*

The Division had the following comments:

- The proposal is at least partially unacceptable. Additional in-use stability storage data is necessary (p. 5 of 5/18/01 amendment). Data for evaluation of the performance must include sufficient points of measurement to permit evaluation of the [redacted] (e.g., additional testing should be done at [redacted]. Also, the omitted [redacted] test points should be re-instituted).

  Based upon the proposed 18-month expiration dating period, GlaxoSmithKline needs to perform in-use studies at [redacted] on batches of drug product that are manufactured and [redacted] at Evreux.

  The purpose of this study is to evaluate the steady-state performance when unprotected (if this condition can be reached), the rate of change of performance during exposure to

the exposed storage conditions, and determination of the exposure time necessary to reach this condition.

In the NDA, provide direct comparisons of all combinations of sites and functions separately. These comparisons need to demonstrate acceptable comparability between all possible manufacturing scenarios.

- GlaxoSmithKline indicated that they wished to discuss the possibility of dropping the — facility and adding it as a new manufacturing facility by means of a CBE supplement after approval of the NDA.

  ➢ The Division stated that dropping one facility at the time of NDA submission, would significantly cut down on the review time, and agreed that as long as the — site is an approved site, then it can be added as a new manufacturing facility in a CBE supplement post approval.

- GlaxoSmithKline indicated that their proposal for submission o — testing data for the Evreux facility would consist of — batches per strength per pack size. Out of the — batches, they propose to have — batches (one for each strength plus one for the sample) to be placed on full stability and the other — would have data provided only at release.

  ➢ The Division advised GlaxoSmithKline against the above proposal where — — would be placed in their stability testing program. The Division then stated that in our opinion, they should have a minimum of — from each strength/size placed in their stability testing program, and strongly recommended — of each. The Division requested that GlaxoSmithKline provide the stability data in the form of Excel spreadsheets, and indicated that this request was not a requirement, but would be a helpful tool in reviewing the application.

3. *A revised core stability protocol to be applied to — NDA stability batches is provided herein (Table 1). We would like to obtain Agency feedback on this stability protocol (Question 3 of the pre-NDA briefing document).*

APPEARS THIS WAY ON ORIGINAL

The core stability protocol which was currently being applied to our primary stability batches (i.e., — was presented in Table 14, Page 35, of our briefing

document. We are currently at the — time point of this protocol. This protocol has been revised from the — time point forwards, in line with Agency feedback on — . This amended protocol is provided herein (Table 2). We would like to obtain Agency feedback on this amended protocol to be applied to the ongoing stability batches

The Division had the following comments:

- The protocol is partially acceptable. Objections to its structure are as follow:

When there is no — data, the testing under — needs to be conducted at earlier time points such as — and possibly earlier depending upon the results of the accelerated studies.

- GlaxoSmithKline discussed the core protocol for the — NDA stability batches of fluticasone propionate (see amendment dated May 18, 2001), as well as the effect of storage at — on the mean content of fluticasone propionate — . They believed that the data demonstrate no overall trend in mean content of fluticasone propionate for any of the — for either inverted or upright orientation.

- The Division reminded GlaxoSmithKline that evaluating the storage conditions — — could impose problems, and that — they need to consider various time points.

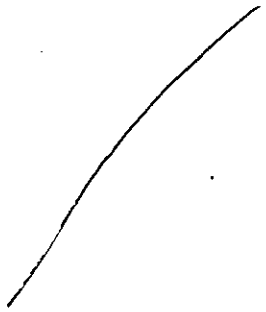
Particle size distribution and Dose Content Uniformity measurements must be done using the same number of priming actuations as that to be recommended in the labeling.

Particle size distribution data must include —

accomplished. We are purposefully withholding comments on the — until thorough evaluation and review of the stability data can be accomplished. Your proposed — must be recognized as being only tentative and are subject to change to provide tight control on the — particle sizes.

GlaxoSmithKline needs to minimized the number of actuations used in the CI for PSD measurements. It is desirable to have the quantity of fluticasone propionate deposited on the CI be set to as low a level as possible and kept constant for all strengths of drug product. The

number of actuations in each strength should then be adjusted accordingly to provide this quantity.



For each presentation individually, Dose Content Uniformity measurements must be made using the minimum actuations per dose as permitted on the labeling.

- GlaxoSmtihKline agreed and indicated that their NDA supports only 2 actuations per dose.

The acceptance criteria for particle size distribution will include

The stability protocol must be comprehensive to expedite the review process. This information is necessary for historical reference and review.

The acceptance criteria for

4. *A revised in-use stability protocol to be used for all future testing is provided herein (Table 3). We would like to obtain Agency Feedback on this single in-use protocol to be applied for all future testing (Question 4 of pre-NDA briefing document).*

3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

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MEETING MINUTES

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/s/

Ladan Jafari
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