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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
21-433

Trade Name:	Flovent HFA
Generic Name:	Fluticasone propionate inhalation aerosol
Sponsor:	Lilly Research Laboratories
Approval Date:	April 14, 2004
Indications:	Provides for the use of Flovent HFA (fluticasone propionate HFA) Inhalation Aerosol for maintenance treatment of asthma as prophylactic therapy in adults and adolescent patients 12 years of age and older.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-433

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Statistical Review(s)	X
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-433

APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-433

GlaxoSmithKline
P. O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Dawn Watson
Director, U.S. Regulatory Affairs, Respiratory

Dear Ms. Watson:

Please refer to your new drug application (NDA) dated February 26, 2002, received February 27, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flovent HFA (fluticasone propionate HFA) Inhalation Aerosol.

We acknowledge receipt of your submissions dated April 5, and 16, May 21, and 31, June 24, and 28, July 9, and 24, September 5, and 19, October 3, and December 13, 2002, August 11, and November 13, 2003, and April 2, 16, 20, 26, and 29, and May 7, 11, 12, and 13, 2004.

The November 13, 2003, submission constituted a complete response to our December 27, 2002, action letter.

This new drug application provides for the use of Flovent HFA (fluticasone propionate HFA) Inhalation Aerosol for maintenance treatment of asthma as prophylactic therapy in adults and adolescent patients 12 years of age and older.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling [text for the package insert (copy enclosed) and Patient Instructions for Use (copy enclosed) submitted on May 13, 2004, and carton and container labeling submitted on May 12, 2004]. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-433**." Approval of this submission by FDA is not required before the labeling is used.

We remind you of the following agreements.

1. (b)(4)----------issues will be addressed for fluticasone propionate and fluticasone ---------- through NDA 20-121/S-027 for FLONASE® (fluticasone propionate) Nasal Spra----------Refer to July 8, 2003, meeting minutes.)

2. Implementation of a modified cascade impactor assay, with a reduced number of actuations per assay, will occur within 18 months of product launch. (Note: the to-be-proposed method is not limited to (b)(4)--------per assay, but it should not include changes in acceptance criteria for (b)(4)---------- ----------

3. The phenomenon of atypically high results at the end of inhaler use for manual sample collection after automated discharge of waste actuations, will continue to be investigated. Any necessary changes resulting from this investigation will be appropriately submitted within 12 months of approval.

4. You will continue to re-evaluate the acceptance criteria for the concentration of the drug substance in the suspension. Any necessary changes resulting from this investigation will be appropriately submitted within 12 months of approval.

5. The robustness of the (b)(4)-- ---------- will continue to be investigated. Appropriate regulator---------- ----------onths of approval if any additional change in the method is required.

6. You will investigate the apparent drug interference with quantification of the (b)(4)---------- in the drug product compared with placebo, and then propose suitable drug pr---------- criteria for(b)(4)---------- which are based on the findings of the investigations. These will ---------- within 6 months of approval.

7. You commit to working with your supplier(b)(4)----------to re-evaluate the methodology used to measure ---------- ----------get date for the completion of this commitmen---------- --------ency's recent letter, i.e. March 2005.

8. A final specification for valve actuation force will be submitted within 6 months after approval of this NDA.

9. Submit the(b)(4)---------- during the ----------

10. Within 4 weeks of the date of approval, you will propose additional controls for (b)(4)--------- (b)(4)----------as part of the system suitability. This is an ----------lance (below) is approved. This proposal will include a detailed, tiered approach for addressing mass balance failures outside the range of (b)(4)------ of label claim.

11. You will submit a prior approval supplement to implement final acceptance criteria for quantitative mass balance within 3 months of product launch. This pertains to the specification for (b)(4using the cascade impactor.

12. (b)(4)----------

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 0 months to less than 6 months and deferring pediatric studies for ages 6 months to less than 12 years for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of asthma in pediatric patients ages 6 months to 11 years of age.

   Final Report Submission: May 14, 2007.

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitments**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Pulmonary and Allergy Drug Products, and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure (Package insert & Patient Instructions for Use)

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

/s/

Badrul Chowdhury
5/14/04 03:14:07 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-433

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-433

GlaxoSmithKline
P. O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Lorna Wilson
Director, Regulatory Affairs

Dear Ms. Wilson:

Please refer to your new drug application (NDA) dated February 26, 2002, received February 27, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flovent HFA (fluticasone propionate) Inhalation Aerosol.

We acknowledge receipt of your submissions dated April 5, and 16, May 21, and 31, June 24, and 28, July 9, and 24, September 5, and 19, and October 3, 2002.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies.

There are a number of critical problem areas for this drug product that relate to consistent drug product quality and performance, and that need to be resolved. Some of these issues have been discussed within the last few years in numerous meetings. Examples include changes in particle size distribution shortly after filling and high variability in delivered dose uniformity. In addition, heat stressed stability batches tend to have less fine particle mass than the non-heat stressed batches. Sufficient data are needed to demonstrate an extractable/leachable correlation. Furthermore, there are unresolved issues with the heat stress process. The details are outlined below.

1. The following comments pertain to the specifications for the drug substance.

   a. Modify the acceptance criteria for particle size distribution for micronized drug substance for Flovent HFA Inhalation Aerosol —

b. The acceptance criteria for the drug substance appear to be inadequate to differentiate between — and fail to provide an adequate assessment to assure consistent (batch-to-batch) quality of the micronized drug substance. Explore, develop and provide alternate method(s) or a combination of tests with supportive data to control — — , and thereby ensure consistent batch-to-batch quality of both the micronized and unmicronized drug substance.

2. The following comments pertain to the drug product composition and representative batch formulae (Section P1).

a. We note that the — — — Until this issue is satisfactorily understood and controlled, — Submit revised master batch records to reflect this change.

b. Ensure that Table 2 provides the composition per can and suspension concentration based on the — . Provide revised, clarified tables as appropriate.

c. Clarify the rationale for an —

d. The following comment pertains to your —

for this, and rectify it. Modify the master batch records as appropriate.

3. The following comments pertain to the drug product manufacturing process.

a. Update the appropriate master batch records in accordance with following comments:

(1) Provide information about the drug substance quantities, and include th·

(2) The following comments pertain to your manufacturing batch record R11165/001 (44 µg, 120 actuations) as an example.

(a) Provide an explanation of the drug product name — page 2 of the executed batch record.

(b) Explain the phrases '
which appear after the phrase "Micronized Fluticasone Propionate."

(c) Explain the term

(3) In the master batch records, clarify what is the

b. The following comments pertain to procedure:

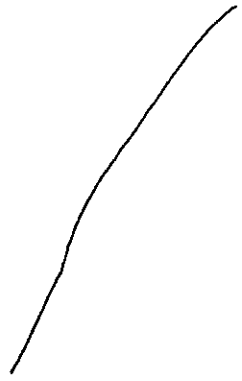
(1) You are reminded to address the remaining issues with the ' , process for the Ventolin HFA

(2) Provide the process parameters proposed for the ' process for all presentations of the drug product, and the process parameters which were used in generating the confirmatory data for the process operated at the Evreux site (Section P4.1.4, pg. 17).

(3) Explain why the , master batch record has a

(4) Provide an update of your ongoing work on the process (as mentioned on page 23 of section 2.1 of the CMC Introduction section).

4. The following comments pertain to in-process controls and tests (Section P5).

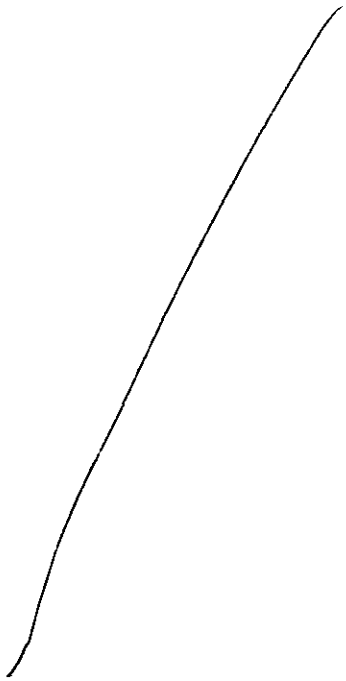


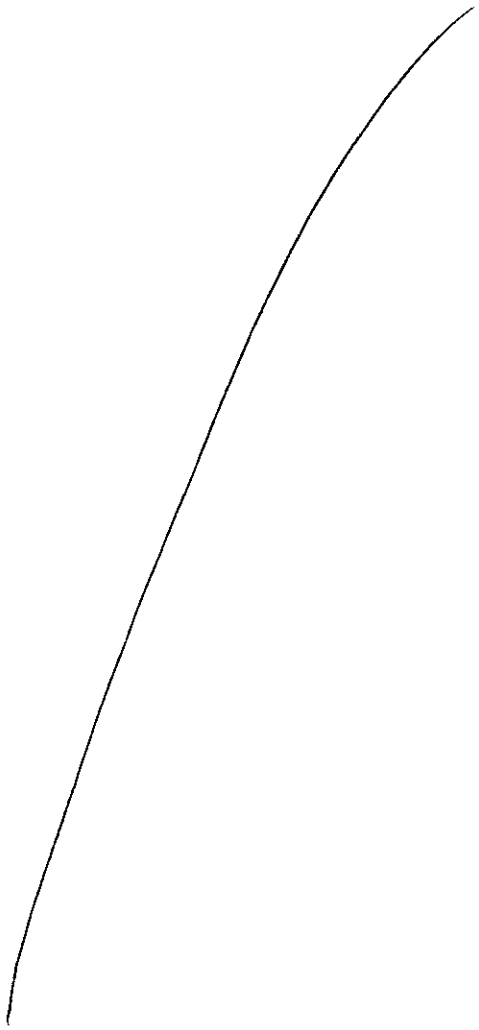
5. The following comments pertain to specifications (analytical procedures and acceptance criteria) for the drug product.

   a. These comments pertain to your general comments for the analytical methods as listed on page 308 of section P6.4 of your original NDA. Modify item #4 to indicate that these are only minor changes made to keep the — results within the stated limits. Withdraw item #6, since such changes would require a Changes Being Effected (CBE) supplement. Clarify item #7 and provide an example.

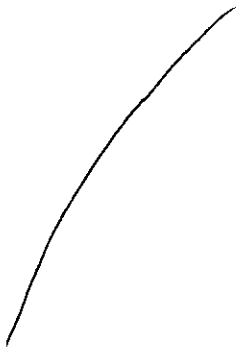
   b. —, for the determination of — impurities, test — canisters to give — results per batch at the time of release.

   c. The following comments pertain to regulatory method — and alternative method —, for determining delivered dose uniformity.





d. The following comments pertain to regulatory Method — and alternative Method — for particle size distribution by cascade impactor.



e. The following comments pertain to your method — for — impurities.

f. The following comments pertain to your methods — (regulatory) and — (alternative) for —

g.

h.

k. This comment pertains to your specification for —

6. The following comments pertain to the container closure system of the drug product.

a. Explain why the of the container closure system may change for the to-be-marketed product, and why they are specific to the Evreux, France site.

b. Modify the — acceptance criteria for —

c. We note your comment that a specification for valve actuation force will be addressed along with development efforts for Advair HFA Inhalation Aerosol. Provide a time line and a progress report for development of a method for valve actuation force, collection of data and establishment of acceptance criteria.

d. The following comments pertain to —

10 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

11. Some of the certificates of analysis are poor in legibility (e.g., see — page 80 of Appendix 4, original NDA). Submit clearer scanned images of the COAs.

12. Provide a time line for completion of the — for this drug product, and describe the current status of this effort.

13. Develop and submit a method with a reduced number of actuations per cascade impactor assay, which has been shown to be feasible for — in your preliminary studies (for all strengths). Include in your submission available data from multiple batches of — drug product.

14. Comment on differences in the

15. Update all pertinent documents as necessary in response to this letter: e.g., master batch records, specification sheets, analytical methods, and stability protocols.

16.

17. The following supporting Drug Master Files are inadequate and each DMF holder has been notified of the deficiencies: DMFs #

18. This comment pertains to the establishment of a specification for valve actuation force. You are reminded of your statement that you will address this comment along with your development efforts for Advair HFA.

19. Evaluation of the expiration dating period of the drug product is deferred pending responses to deficiencies and agreement with acceptance criteria.

20. Evaluation of — data and information are deferred pending your submission of — acceptance criteria

21. For study FLTB3048, present the safety data (including the cortisol data) for subjects using spacers separately from the non-spacer users. Resubmit an ISS excluding spacer users.

22. In addition, it will be necessary for you to submit draft labeling revised as follows. The following labeling comments are preliminary and are not inclusive.

a. Delete — in the **CLINICAL TRIALS** section.

b. Delete the paragraph that begins ' — in the CLINICAL TRIALS section,

c.

d. Replace with 440 mcg twice daily in the column "Recommended Starting Dosage" in Table 3 Recommended Dosages of FLOVENT HFA": in the DOSAGE AND ADMINISTRATION section. Leave 880 mcg BID as the highest recommended dosage.

e. Replace the Absorption paragraph under the Clinical Pharmacology section of the proposed label as follows:

Pharmacokinetics: ***Absorption:*** Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed. Systemic exposure as measured by AUC in healthy subjects (n = 24) from 8 inhalations, as a single dose, of HFA 134a-propelled fluticasone propionate using the 44-, 110-, and 220 mcg strengths increased proportionally with dose. The geometric mean (95%CI) AUC(0-24h) for the 44-, 110-, and 220-mcg strengths were 488 (362 - 657); 1,284 (904-1822); and 2,495 (1945-3200) pg*h/mL, respectively and Cmax 126 (108 -148), 254 (202-319), and 421 (338-524) pg/mL, respectively. Systemic exposure from the 220 mcg HFA 134a-propelled fluticasone propionate inhaler was 30% lower than that from the CFC 11/12-propelled fluticasone propionate inhaler, resulting in a lesser effect on cortisol. Systemic exposure in subjects with asthma from 2 inhalations of HFA 134a-propelled fluticasone propionate using the 44-mcg (n = 20), 110-mcg (n = 15), and 220-mcg (n = 17) strength inhalers twice daily for at least 4 weeks,

The geometric mean (95%CI) of AUC (0-12h) for the 44-, 110-, and 220-mcg strength were 76 (33-174), 298 (191-464), and 601 (431-838) pg*h/mL, respectively. Cmax occurred in about 1 hour and the geometric mean were 25 (18-36), 61 (46- 81), and 103 (73-145) pg/mL, respectively.

f. Revise the Pregnancy: Teratogenic Effects: Category C to read:

Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg, respectively, (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2), revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification. No teratogenicity was seen in the rat at inhalation doses up to 68.7 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2).

g. Revise the OVERDOSAGE section to read:

The oral and subcutaneous median lethal doses in rats and mice were >1000 mg/kg (approximately 4600 and 2300 times the maximum human daily inhalation dose based on mg/m^2, respectively).

When you respond to the above deficiencies, include a safety update as described in 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division, regarding the extent and format of your safety update prior to responding to this letter.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary and Allergy Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file (an) amendment, follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with The Division of Pulmonary & Allergy Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Acting Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Marianne Mann
12/27/02 11:34:32 AM