

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-833

**ADMINISTRATIVE DOCUMENTS AND
CORRESPONDENCE**

Patent Information

Pursuant to 21 C.F.R. § 314.53

for

FLOVENT® DISKUS®,

fluticasone propionate inhalation powder 50mcg

fluticasone propionate inhalation powder 100mcg

fluticasone propionate inhalation powder 250mcg

Amendment to Item 13 of NDA 20-833

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

Trade Name: Flovent® Diskus®

Active Ingredient: fluticasone propionate

Strengths: fluticasone propionate inhalation powder 50mcg
fluticasone propionate inhalation powder 100mcg
fluticasone propionate inhalation powder 250mcg

Dosage Form: inhalation powder

	US Patent Number	Expiration Date	Form of Patent Claims
1	4,335,121	14 November, 2003	Fluticasone Propionate per se, compositions, processes for preparation and various methods of use
2	5,590,645	1 March, 2011	Product administration system
3	D 342,994	4 January, 2008	Product administration system
4	5,860,419	1 March, 2011	Product administration system
5	5,873,360	23 February, 2016	Product administration system

The undersigned declares the following:

- 1) All of the above patents are owned by Glaxo Group Limited.
- 2) The United States Agent for all the above patents is Glaxo Wellcome Inc.

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

David J. Levy
Vice President, Intellectual Property Counsel
Glaxo Wellcome Inc.
Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-2723

Respectfully submitted,



Date: 15 March, 1999

Charles Dadswell
Assistant Intellectual Property Counsel
Glaxo Wellcome Inc.
Registered Patent Attorney
Registration No. 35,851

APPEARS THIS WAY
ON ORIGINAL

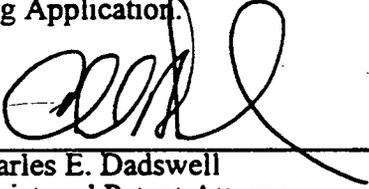
ITEM 13
Patent Information for
FLOVENT® DISKUS® Inhalation Powder
NDA 20-833

Active Ingredient:	Fluticasone Propionate
Strength of Drug Product:	50, 100 and 250 micrograms per inhalation
Dosage Form:	Inhalation powder
Route of Administration:	Oral inhalation
Applicant Firm Name:	Glaxo Wellcome Inc.
Patent Number:	4,335,121
Coverage:	Fluticasone Propionate per se, compositions, processes for preparation and various methods of use
Issue Date:	June 15, 1982
Expiration Date:	November 14, 2003
Patent Term Extension:	1,004 days
Expiration Date:	November 14, 2003
Patent Number:	5,590,645
Coverage:	Product administration system
Issue Date:	January 7, 1997
Expiration Date:	March 1, 2011

Patent Number: Des. 342,994
Coverage: Product administration system
Issue Date: January 4, 1994
Expiration Date: January 4, 2008

The Undersigned certifies to the best of his knowledge and belief the above listed patents are valid patents, claiming fluticasone propionate or its administration system, the subject of a New Drug Application.

07/02/97
Date


Charles E. Dadswell
Registered Patent Attorney
United States Registration No. 35,851

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ON ORIGINAL

Trade Name Flovent Diskus Generic Name fluticasone dipropionate

Applicant Name GLaxoWellcome HFD # 570

Approval Date If Known 9/29/00

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA?
YES / / NO / /

b) Is it an effectiveness supplement?
YES / / NO / /

If yes, what type? (SE1, SE2, etc.) _____

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

YES / / NO / /

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

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

d) Did the applicant request exclusivity?

YES / / NO / /

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

3 years

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

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW-CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES / / NO / /

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

NDA# 20-121 Flonase _____ NDA # 20-549 Flovent Rotadisk

NDA# 19-958 Cutivate _____ NDA 19-957 Cutivate _____

NDA# 20-548 Flovent Inhalation Aerosol _____

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. 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 / / NO / /

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

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

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

YES / / NO / /

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 / /

APPEARS THIS WAY
ON ORIGINAL

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

YES / / NO / /

If yes, explain: _____

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

YES / / NO / /

If yes, explain: _____

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

FLTA 2001, FLTA 2002, FLTA 2003, FLTA 2004, FLTA 2005, FLTA 2006, FLTA 2007,
FLTA2008

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.

**APPEARS THIS WAY
ON ORIGINAL**

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 -8

YES / /

NO / /

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

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

Investigation #1 - 8

YES / /

NO / /

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

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

FLTA 2001, FLTA 2002, FLTA 2003, FLTA 2004, FLTA 2005, FLTA 2006, FLTA 2007, FLTA2008

**APPEARS THIS WAY
ON ORIGINAL**

(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: _____

/S/
Signature
Title: CPMS
9/29/00
Date

/S/
Signature of Office/
Division Director
9/29/00
Date

cc: Original NDA

Division File

HFD-93 Mary Ann Holovac

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-833

Flovent™ (Fluticasone Propionate) Diskus™
Inhalation Powder

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.



8 APR 98

Charles E. Mueller
Head, International Compliance Services
World Wide Compliance

Date

.....
The list of Glaxo Wellcome Principal Investigators for the above titled submission has been compared with the 12Nov97 Food and Drug Administration Debarment List and the 22Aug97 Disqualified, Restricted, and Given Assurances lists.



8 Apr 98

Jeanne Kistler/Terri Cronan
Compliance Services Coordinator
World Wide Compliance

Date

Division Director's Memorandum (Addendum)

Date: Friday, September 29, 2000
NDA: 20-833
Sponsor: Glaxo Wellcome
Proprietary Name: Flovent Diskus (fluticasone propionate inhalation powder).

Introduction: This is a further resubmission of an NDA for the Flovent Diskus at dosage strengths of 50, 100 and 250 mcg per blister. The original approvable action for this drug was taken on March 31, 1999, and the second cycle action was taken on December 8th, 1999. The failure to approve in both cycles was largely due to many remaining CMC concerns.

Chemistry/Manufacturing and Controls: The CMC issues have been resolved, with an in-use period of 6 weeks of the 50 and 100 mcg products, with the 250 mcg product having a 2 month in-use period.

Clinical / Statistical: See Dr. Purucker's addendum review of the safety update. The sponsor has removed any present claims for once-daily dosing, due to FDA's uncertainty of effectiveness for doses below 500 mcg daily and FDA's concern that we were not clear if the data provided showed 500 mcg would be even as effective as much lower doses given BID (as low as 100 mcg). We therefore did not feel we could appropriately label for 500 mcg QD. Essentially, except for some revisions to the labeling (particularly to add _____ and _____ to the "_____ " discussion), there are no remaining clinical issues.

Conclusions: This NDA will be approved with no clinical phase 4 commitments.

JSI

Robert J. Meyer, MD
Director,
Division of Pulmonary and Allergy Drug Products.

GlaxoWellcome

DUPLICATE

AC

ORIG AMENDMENT

September 27, 2000

Sandra Barnes, Project Manager
Division of Pulmonary Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Food and Drug Administration
HFD-570, Room 10B-03
5600 Fishers Lane
Rockville, MD 20857



**Re: NDA 20-833; FLOVENT® DISKUS® (fluticasone propionate inhalation powder)
Response to FDA Request/Comment: CMC: Response to Draft FDA CMC
Comments Dated September 26, 2000**

Dear Ms. Barnes:

The purpose of this submission is to provide responses to the draft CMC comments received from the Agency on September 26, 2000 for Flovent Diskus and to respond to the request for an updated Environmental Assessment. This submission includes complete responses to comments 1-5 and appendices for the updated lactose specifications with reference to our commitment to develop a specification and test for Appendix 1); the updated method validation package (Appendix 2); the updated master batch record (Appendix 3); and the updated Environmental Assessment that includes the calculations used to support the categorical exclusion.

This submission is provided in duplicate, with a desk copy for Dr. Koble submitted under separate cover. If you have any questions regarding this submission, please contact me at (919) 483-3692 or send a page to (888) 361-4834.

Sincerely,

A handwritten signature in black ink, appearing to read "Michael Golden".

Michael Golden
Product Director
Regulatory Affairs

Job # US00163R

Glaxo Wellcome Inc.

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

Telephone
919 483 2100

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338.
Expiration Date: April 30, 2000.
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

Glaxo Wellcome Inc.

DATE OF SUBMISSION

September 27, 2000

TELEPHONE NO. (Include Area Code)

(919) 483-2100

FACSIMILE (FAX) Number (Include Area Code)

(919) 483-5381

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code
and U.S. License number if previously issued):

Five Moore Drive
Research Triangle Park, NC 27709

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State,
ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)

NDA 20-833

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Fluticasone Propionate

PROPRIETARY NAME (trade name) IF ANY

Flovent ® Diskus® (fluticasone propionate inhalation powder)

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

S-(fluoromethyl)6 α ,9 α -difluoro-11 β , 17-dihydroxy-16 α -methyl-3-oxoandrosta-
1,4-diene-17 β -carbotnioate, 17-propionate

CODE NAME (if any)

CCI18781

DOSAGE FORM:

Inhaler

STRENGTHS:

50, 100, 250mcg

ROUTE OF ADMINISTRATION:

Oral Inhalation

(PROPOSED) INDICATION(S) FOR USE

Maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older.

APPLICATION INFORMATION

APPLICATION TYPE

(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b) (1)

505 (b) (2)

507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug

Holder of Approved Application

TYPE OF SUBMISSION

(check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

SUPAC SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

REASON FOR SUBMISSION

Response to FDA Request/Comment: CMC: Response to Draft FDA CMC
Comments Dated September 26, 2000

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)	
<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input checked="" type="checkbox"/>	4. Chemistry section
<input checked="" type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods Validation Package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2), 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3), 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (21 CFR 314.50 (d) (4))
<input type="checkbox"/>	8. Clinical data section (21 CFR 314.50 (d) (5))
<input type="checkbox"/>	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (21 CFR 314.50 (d) (6), 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (21 CFR 314.50 (f) (1), 21 CFR 601.2)
<input type="checkbox"/>	12. Case reports forms (21 CFR 314.50 (f) (2), 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.5 (K) (3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. OTHER (Specify) Response to FDA Request/Comment: CMC: Response to Draft FDA CMC Comments Dated September 26, 2000

CERTIFICATION

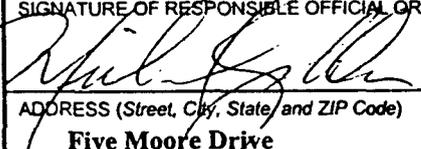
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biologic product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99 and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Michael Golden Product Director, Regulatory Affairs	DATE September 27, 2000
--	--	-----------------------------------

ADDRESS (Street, City, State, and ZIP Code) Five Moore Drive Research Triangle Park, NC 27709	Telephone Number (919) 483-3692
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Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer Paperwork Reduction Project (0910-0338) Hubert H. Humphrey Building, Room 531-H 100 Independence Avenue, S.W. Washington, DC 20201	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.
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Please **DO NOT RETURN** this form to this address.

Division Director's Memorandum

Date: Wednesday, December 08, 1999
NDA: 20-833
Sponsor: Glaxo Wellcome
Proprietary Name: Flovent Diskus (fluticasone propionate inhalation powder).

Introduction: This is resubmission of an NDA for the Flovent Diskus at dosage strengths of 50, 100 and 250 mcg per blister. Flovent (fluticasone propionate) is already approved both as an MDI formulation with CFC propellants (at 44, 110 and 220 mcg strengths ex-actuator) and as an inhalation powder for the Diskhaler (at the same strengths as the Diskus). The Diskus represents a more patient-friendly DPI than the approved Diskhaler in that it is not patient loaded and contains 60 doses per device rather than 4 per disk. The original approvable action for this drug was taken on March 31, 1999. The failure to approve at that time was largely due to many remaining CMC concerns, although there were significant clinical issues related to the proposed once-daily dosing.

Chemistry/Manufacturing and Controls: While many of the CMC issues have been resolved, there are remaining issues that preclude approval this cycle. One issue of clinical note is that the

_____ It appears at this point that an in-use period of more than _____ cannot be justified. The 250 mcg product appears more stable and it appears like a 2 month in-use period is acceptable.

Clinical / Statistical: See Dr. Purucker's addendum primary review and Dr. Gebert's addendum statistical reviews for details. The sponsor provided reanalyses and additional rationale to try to support once-daily dosing. The Division finds these analyses and rationale to be insufficient for once-daily doses below 500 mcg. While the 500 mcg product has been demonstrated to be effective, cross-study comparisons would place its effect size as similar to 100 mcg BID (i.e., less than 1/2 the daily nominal dose). Adequate comparative safety of the 500 mcg QD dosing and lower doses given twice daily are not available.

Labeling: There will still need to be significant revisions to the labeling prior to this product being approved, but given the outstanding clinical and CMC issues, these revisions should be left until the entire application is approvable. However, the Division is trying to achieve final comments on the container closure labeling per the company's request.

Conclusions: This NDA is approvable, pending resolution of the CMC issues and the revision of the proposed labeling (including removing the once-daily indication). It is

anticipated that the remaining issues, though significant, can be resolved in a reasonable time frame as the CMC issues do not appear to necessitate further data generation.

ISI

Robert J. Meyer, MD / 12/8/99
Director,
Division of Pulmonary and Allergy Drug Products.

**APPEARS THIS WAY
ON ORIGINAL**

4 Page(s) Withheld

Cobbs
SEP 13 1999

TELECONFERENCE

IMTS# 4788

Representing Glaxo Wellcome:

Kathy Prodan, Director, Regulatory Affairs
Stuart Harding, Clinical Research
Karen House, Clinical Research
Patrick Wire, Clinical Research
Jill Wolford, Clinical Research
Susan Duke, Biostatistics
Dell Mather, Global Health Outcomes
Mary Sides, Regulatory Affairs

Representing the Division of Pulmonary Drug Products:

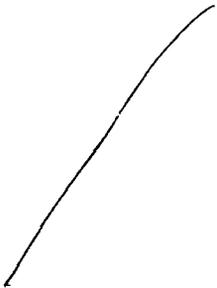
Lindsay Cobbs, Project Manager
Bob Meyer, Acting Director, DPDP
Mary Purucker, Clinical Reviewer
Jim Gebert, Statistical Reviewer

Background: This teleconference was requested to discuss the clarifications for several comments from the AE letter dated March 31, 1999. Please see the telephone facsimile dated April 15, 1999, for details.

1. The Division asked Glaxo which once daily doses they believed were supported by data provided. _____
 - a. Glaxo stated that they believed the data supported' _____
 - b. The Division agreed that the 500 mcg once daily dose was supported in adults but that the 200 mcg dose did not achieve statistical significance for the primary endpoint in three studies. _____

M

1 Page(s) Withheld

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2. **Glaxo requested clarification of the Division's proposal to add the statement "Because individual responses may vary, children previously maintained on the Rotadisk 50 or 100 mcg twice daily may require dosage adjustments upon transfer to Flovent Diskus" to the labeling.**
 - a. **The results of study FLTA2007 indicate that the 50 mcg twice daily dose did not achieve statistical significance on the primary endpoint which implies that the Diskus formulation may be less efficacious in children than the Rotadisk.**
 - b. **The pediatric pharmacokinetic data indicated lower levels of systemic exposure with the Diskus formulation compared to the Rotadisk.**

 3. **Glaxo requested the Division's rationale for removal of the claims from the labeling.**
- 
- 

- c. Glaxo requested clarification of the definition of cosyntropin stimulation testing abnormality in the labeling.
- The Division noted the change in the labeling was based on the definition of an abnormality in the cosyntropin labeling and referred Glaxo to comment 16.c.(i) of the approvable letter. The Division also agreed to revisit this part of the labeling if Glaxo provided their rationale for their proposal that Glaxo indicated was based on data with the MDI and Rotadisk formulations.
- d. Glaxo inquired about the Division's decision that there was
4. Glaxo stated that the response to the approvable letter would be submitted by June 8, 1999.

APPEARS THIS WAY
ON ORIGINAL

NDA 20-833
Flovent Diskus
May3, 1999
Page 5

cc:

Original NDA 20-833
HFD-570/PURUCKER/9-13-99
HFD-570/GEBERT
HFD-570/MEYER
HFD-570/COBBS

Drafte by:JLCobbs/August 18, 1999

MY DOCUMENTS/FLOVENTTEL.DOC

**APPEARS THIS WAY
ON ORIGINAL**

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

REQUEST FOR CONSULTATION

TO: (Division/Office) DPADP/pharmacology/toxicology

FROM: Dale Koble

1/2/99	IND NO.	NDA NO. 20-833	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT June 7, 1999
NAME OF DRUG Flovent Diskus		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG 3S	DESIRED COMPLETION DATE 11/16/99
NAME OF FIRM: Glaxo Wellcome				

15/1/99

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input checked="" type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (Specify below) |
| <input type="checkbox"/> MEETING PLANNED BY _____ | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> IER	<input type="checkbox"/> CHEMISTRY <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO MAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

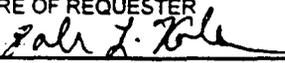
CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary)

In response to Question 5b of the approvable letter dated March 31, 1999, the applicant provides information concerning the safety qualification for the _____ . Please review the information provided and provide a recommendation concerning the safety qualification

of the _____
cc:
Orig NDA # 20-833
HFD-570/Div. File
-570/DKoble/GPoochikian/LSancilio/LCobbs

SIGNATURE OF REQUESTER 	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

GlaxoWellcome Fax

To Lindsay Cobbs Fax 301-827-1271

From Kathy Prodan Date 4/15/99

Telephone 919-483-5110 Total Pages 2

Fax 919-315-0033

Mission

Glaxo Wellcome is a research-based company whose people are committed to fighting disease by bringing innovative medicines and services to patients throughout the world and to the healthcare providers who serve them.

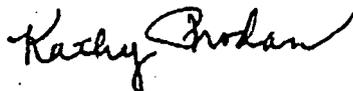
Values

- High Standards
- Valuing Customers
- Valuing People
- Teamwork
- Embracing Change
- Achievement
- Corporate Citizenship

Dear Lindsay,

As we discussed, attached is the list of clinical comments for NDA 20-833 that we would like to discuss with the medical reviewer. Also, as mentioned, Stuart Harding and I will be at the Agency next Wednesday (the 21st) for another meeting with the Division, if there would be any time to meet that day. Thanks for your help in setting this up.

Regards,



**APPEARS THIS WAY
ON ORIGINAL**

The information contained in these documents is confidential and may also be privileged and is intended for the exclusive use of the addressee designated above. If you are not the addressee any disclosures, reproduction, distribution, or any other dissemination or use of this communication is strictly prohibited. If you have received this transmission in error please contact us immediately by telephone so that we can arrange for its return.

Glaxo Wellcome Inc.

Five Moore Drive
PO Box 3398
Research Triangle Park, NC
27709-3398

Telephone

Fax

CONFIDENTIAL

We would like to discuss the following comments related to the medical review for Flovent Diskus:

1. Comment 1 of the approvable letter noted that the available data related to the once daily dosing recommendation are insufficient to support a claim, but with requests to

2. We would like clarification of the basis for Comment 16.g which requested inclusion of a statement to the effect that children transferring from Flovent Rotadisk to Diskus may require dosage adjustments. The results of FLTA2006 indicated little difference between the Rotadisk and Diskus treatment groups. *not let*

3. The comments on the marked-up package insert deleted

BEST POSSIBLE COPY

MEMORANDUM

DATE: March 31, 1999

FROM: John K. Jenkins, M.D.
Director, Division of Pulmonary Drug Products

TO: NDA 20-833

SUBJECT: Overview of NDA Review Issues

[Handwritten signature]
/S/
3/31/99

Administrative:

NDA 20-833 for Flovent Diskus 50, 100, and 250 mcg (fluticasone propionate inhalation powder) was submitted by GlaxoWellcome on March 31, 1998. Flovent Diskus is a multi-dose dry powder inhaler (DPI) presentation of fluticasone. Fluticasone is currently approved in the US for oral inhalation in Flovent 44, 110, and 222 mcg Inhalation Aerosol (a CFC-based MDI) and in Flovent Rotadisk 50, 100, and 250 mcg Inhalation Powder for Diskhaler. The Division reviewed the NDA as a standard application. The user fee goal date for this application is March 31, 1999.

Clinical:

The proposed indication for Flovent Diskus is for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older and in patients requiring oral corticosteroid therapy for asthma, many of whom may be able to reduce or eliminate their requirement for oral corticosteroids over time. This is the same indication that is currently approved for other Flovent NDAs and is the same indication that was adopted by the Division as part of class labeling for orally inhaled corticosteroids. In support of the proposed indication for Flovent Diskus, the sponsor submitted the results of nine Phase 3 trials in patients 4 years of age and older with asthma of varying degrees of severity requiring varying levels of medical treatment at study entry. For a complete review of the studies submitted in support of this application, please refer to the Medical Officer Review prepared by Drs. Purucker and Meyer and the Medical Team Leader Memorandum prepared by Dr. Meyer.

I concur with Dr. Purucker and that Meyer that the sponsor has provided adequate data to support the safety and efficacy of Flovent Diskus over the proposed dosages and indications when used as twice daily therapy. I also concur with the medical reviewers that the clinical data in support of the proposed once daily dosing schedule is inadequate. The generally non-supportive clinical data coupled with _____, makes the once daily dosing strategy not approvable. There are still unanswered questions regarding the relationship between the different dosage strengths of Flovent Diskus

proposed for marketing (i.e., dose proportionality of effect). However, these are not issues that preclude approval and can be addressed by labeling comments as suggested by Drs. Purucker and Meyer (this approach is consistent with the Division's approach for other multi-strength products where the dose proportionality has not been clearly established). In general, the clinical effect of Flovent Diskus in adults and adolescents appears to be comparable to that seen with Flovent Diskhaler when they are administered at the same nominal daily dose and dosing regimen. This observation is supported by the generally comparable pharmacokinetic data seen in this age group (see below). There is some suggestion, however, from the clinical data that the effect of the Diskus may be slightly less than that seen with Diskhaler in children 4-11 years of age. This difference is also consistent with the pharmacokinetic results seen in this age group (see below). The reason(s) for these disparate findings in adults and children are not clear and warrant further investigation by the sponsor, though such data are not required prior to approval. These findings will be reflected in the labeling to help physicians when switching patients from one DPI formulation to another.

From a safety perspective, there is no significant signal of new safety concerns related to Flovent Diskus compared to other approved formulations of fluticasone that arise from the NDA database. It is noteworthy that cases of eosinophilic vasculitis, including Churg-Struass Syndrome, were observed in the clinical trials database. These events have also been reported in association with Flovent from postmarketing adverse event reports, however, a causal association has not been established. The occurrence of Churg-Strauss Syndrome is already included in the labeling for the approved Flovent products.

The NDA is approvable from a clinical standpoint for twice daily dosing with appropriate labeling. The sponsor will be provided with general labeling comments in the action letter and these comments will generally parallel the labeling of approved Flovent products.

Pharmacology/Toxicology:

The pharmacology/toxicology of inhaled fluticasone propionate have been well established by previous NDAs. The sponsor did not submit any new pharmacology/toxicology data to this NDA and none is needed.

The application is approvable from a pharmacology/toxicology standpoint with adequate labeling. Detailed revisions of the draft package insert will be provided in the action letter.

Clinical Pharmacology and Biopharmaceutics:

Please refer to the review prepared by Dr. Chen for a full review of the clinical pharmacology and biopharmaceutics data submitted in support of this NDA. Based on data collected in one of the pivotal phase 3 trials in adults, the pharmacokinetics of fluticasone following administration of Flovent Diskus 500 mcg twice daily in adults and

adolescents (2X250 mcg twice daily) was comparable to Flovent Diskhaler at the same daily dose and regimen. These data are consistent with the generally comparable clinical effect of the two products when dosed at the same total daily dose (see above). Conversely, data obtained in children 4-11 years of age at doses of 50 and 100 mcg twice daily suggest that the systemic exposure to fluticasone is less following dosing with the Diskus than with the Diskhaler. Again, this is consistent with the clinical data for the two products in children (see above).

The application is approvable from a clinical pharmacology and biopharmaceutics standpoint with appropriate labeling. Labeling comments will be included in the action letter.

Chemistry, Manufacturing, and Controls:

The Diskus is currently approved for delivery of salmeterol in the Serevent Diskus device. Please see the CMC review prepared by Dr. Koble for a detailed review of the CMC data submitted in support of this application. There are numerous outstanding CMC deficiencies that must be adequately addressed prior to approval of this application. One area of particular concern is the

The application is not approvable from a CMC standpoint. Numerous CMC deficiencies will be included in the action letter.

Data Integrity:

The Division of Scientific Investigations was not asked to conduct audits of any clinical sites involved in the clinical studies submitted in support of this NDA. There are no indications from the limited auditing done by the clinical and statistical reviewers of any issues that would lead to questions regarding the integrity of the clinical database.

Labeling:

The proposed trade name, Flovent Diskus 50, 100, and 250 mcg, is acceptable. The sponsor will be provided comments regarding the draft labeling in the action letter.

Recommendation:

Overall this application is approvable for twice daily dosing, however, there are numerous CMC and labeling deficiencies that must be adequately addressed before this

application can be approved. The proposed once daily dosing indication is not approvable due to the limitations of the available clinical data in support of this dosing strategy and

the sponsor should receive an APPROVABLE letter listing the outstanding deficiencies.

cc:

NDA 20-833
HFD-570/Division File
HFD-570/Jenkins
HFD-570/Cobbs
HFD-570/Meyer

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Team Leader Review Memorandum

Memorandum to: NDA 20-833 file
Product: Flovent Diskus (fluticasone propionate inhalation powder)
Memo date: 3-31-99
Memo from: Robert J. Meyer, MD Medical Team Leader, DPDP

THIS MEMORANDUM IS TO DOCUMENT THE SECONDARY REVIEW CONCLUSIONS ON THE NDA FOR FLOVENT DISKUS FOR THE TREATMENT OF ASTHMA IN PATIENTS AGED 4 YEARS AND ABOVE.

OVERVIEW:

FLOVENT INHALATION POWDER IS THE SUBJECT OF AN APPROVED NDA, 20-549, IN THE FORM OF THE ROTADISK PRODUCT FOR DELIVERY THROUGH THE DISKHALER (AND THE SUBSTANCE HAD PREVIOUSLY BEEN APPROVED AS A PART OF THE FLOVENT INHALATION AEROSOL MDI NDA 20-548). FLOVENT DISKUS DIFFERS SOMEWHAT IN FORMULATION FROM THE ROTADISK (12.5 MCG TOTAL BLISTER WEIGHT INSTEAD OF 25 MCG), BUT MOSTLY IN DEVICE - THE DISKUS MULTIDOSE DRY POWDER INHALER THAT HOLDS 60 DOSES/DEVICE. THE DISKUS DEVICE ITSELF HAS BEEN REVIEWED PREVIOUSLY FOR THE SEREVENT DISKUS NDA, 20-692, WHICH WAS APPROVED IN 1997. THEREFORE, THIS PRODUCT REPRESENTS A DRUG PRODUCT UTILIZING A FORMULATION VERY SIMILAR TO AN APPROVED FORMULATION DELIVERED BY A DEVICE THAT HAS PREVIOUSLY BEEN REVIEWED. ALTHOUGH GLAXO-WELLCOME PERFORMED A FULL CLINICAL DEVELOPMENT PROGRAM, THIS REVIEW IN MANY WAYS IS ANALOGOUS TO A "SWITCH" PROGRAM.

EFFICACY:

THE EFFICACY DATA FOR THIS NDA STEM FROM MULTIPLE PHASE 3 TRIALS, INCLUDING AN ORAL CORTICOSTEROID SPARING STUDY (2002), 3 PEDIATRIC TRIALS DOWN TO AGE 4 AND 5 ADULT TRIALS. BESIDES THE USUAL GLAXO WELLCOME ASTHMA STUDY DESIGNS, MANY OF THESE TRIALS INCLUDED ONCE DAILY DOSING ARMS FOR PURPOSES OF SUPPORTING LABELING FOR ONCE DAILY DOSING.

THE SPONSOR HAS WELL ESTABLISHED THE EFFICACY OF THIS PRODUCT IN CHILDREN AGES 4 AND UP, AS WELL AS ADULTS. THE EFFICACY IN ADULTS INCLUDES A DEMONSTRATION OF THE ORAL CORTICOSTEROID SPARING EFFECT OF DOSES OF 500 AND 1000 MCG/DAY. THE TWICE DAILY REGIMEN IS EFFECTIVE IN PATIENTS EITHER ENTERING THE TRIALS ON INHALED CORTICOSTEROIDS, AND IN PATIENTS PREVIOUSLY ONLY ON BRONCHODILATORS. NONE OF THE TRIALS DEMONSTRATED A CONVINCING DOSE RESPONSE, HOWEVER, WHICH IS TYPICAL FOR SUCH INHALED CORTICOSTEROID TRIALS. THE CLINICAL DATA SUPPORTING THE ONCE DAILY DOSING IS UNCONVINCING, AND SHOWS CLEAR, MARKED INFERIORITY OF THIS DOSING REGIMEN COMPARED TO BID, EVEN AT CONSIDERABLY HIGHER DAILY DOSES GIVEN QD. VERY OFTEN, THE QD DOSING GROUPS FAILED ON THE PRIMARY AND SECONDARY ENDPOINTS. WHILE THE 500 MCG QD DOSING APPEARED TO BE EFFECTIVE IN 2 TRIALS, THERE ARE INADEQUATE DATA TO LABEL THE PRODUCT FOR THIS DOSE (E.G.,

FURTHER, THERE WAS NO SAFETY ADVANTAGE TO THE ONCE DAILY DOSING IDENTIFIED. FINALLY, THE

THE EFFICACY DATA COMPARING THE DISKUS TO THE ROTADISK PRODUCTS APPEARS TO SHOW

GOOD COMPARABILITY IN ADULTS (CONFIRMED BY REASONABLY SIMILAR PK FOR FLUTICASONE, A DRUG THAT IS ALMOST EXCLUSIVELY SYSTEMICALLY AVAILABLE DUE TO LUNG DELIVERY). HOWEVER, THE EXISTING DATA IN 4 - 11 YEAR OLDS OFFERS NUMERICAL SUGGESTION THAT THE DISKUS IS SOMEWHAT LESS EFFICACIOUS, AGAIN CORROBORATED BY PK DATA, WITH THE ROTADISK FLUTICASONE EXPOSURE APPEARING TO BE GREATER THAN THE DISKUS IN THIS AGE RANGE.

SAFETY:

THE SAFETY DATA FOR THIS SUBSTANCE BY THE INHALATION ROUTE IS EXTENSIVE. THIS NDA CONTAINS A LARGE AMOUNT OF DATA WITH THIS PRODUCT, BUT ADDS LITTLE NEW TO THE SAFETY PROFILE OF FLUTICASONE. IMPORTANT IN THIS REGARD IS THAT THERE WERE LITTLE DATA TO ADDRESS SYSTEMIC ISSUES SUCH AS GROWTH, BONE MINERALIZATION, OR EVEN GOOD HPA TESTING IN THIS NDA. HOWEVER, GIVEN THE PK DATA SUGGESTING COMPARABLE TO LOWER EXPOSURES TO FP FROM THE DISKUS COMPARED TO THE ROTADISK (WITH WHICH MANY SUCH STUDIES WERE DONE), IT APPEARS THAT THE PRIOR DATA ARE SUFFICIENT TO SUPPORT THE SAFETY OF THIS PRODUCT, IN COMBINATION WITH THE DATA FROM THE PRODUCT ITSELF.

OVERALL CONCLUSIONS:

I AM IN AGREEMENT WITH DR. PURUCKER'S ASSESSMENT THAT THIS APPLICATION IS APPROVABLE FROM THE CLINICAL STANDPOINT. HOWEVER, DUE TO BOTH CMC CONCERNS

AND DUE TO UNCONVINCING CLINICAL DATA, I DO NOT BELIEVE THE ONCE DAILY DOSING ALTERNATIVE SHOULD BE APPROVED. ALL REFERENCES TO THESE DATA IN THE

SECTIONS OF THE LABEL SHOULD BE REMOVED. FURTHER, I BELIEVE THAT THE LABELING SHOULD CONTAIN A STATEMENT


ROBERT J. MEYER, MD
MEDICAL TEAM LEADER
DIVISION OF PULMONARY DRUG PRODUCTS

**APPEARS THIS WAY
ON ORIGINAL**

CC: Purucker/Medical Officer/HFD-570
Cobbs/project manager/HFD-570
Division File/HFD-570
NDA #20-833

Cobbs

TELECON RECORD

Date: March 27, 1999

NDA: 20-833

Product: Flovent Diskus

FDA Participant: J. Lindsay Cobbs, Project Manager
Division of Pulmonary Drug Products

Sponsor: Kathleen Prodan
Director Regulatory Affairs

GlaxoWellcome

Background: Dr. Purucker, the reviewing Medical Officer, requested clarification of the Diskus dosing 100 mcg for Protocol FLTA2006, Tables 36, 37 and 38 of Volume 1.163 pages 199, 200 and 201 respectively.

I contacted Kathy Prodan regarding the once daily (QD) dosing for the Diskus FP100 mcg in the above tables and verified that each Table contained a typographical error. The Tables' subheadings should read Placebo, Diskus FP50mcg BID, Diskus FP100mcg BID, Diskhaler FP50mcg BID and Diskhaler FP100mcg Bid instead of the Diskus and Diskhaler FP100mcg QD.

**APPEARS THIS WAY
ON ORIGINAL**

cc: NDA 20-833
HFD-570/Division File
HFD-570/Cobbs
HFD-570/PURUCKER
HFD-570/MEYER
DRAFTED BY: LCOBBS/March 22, 1999
N:/MY DOCUMENTS/N20833tel99-03-22.DOC

151
3-21-99

NDA 20-833

Page 2

If you have any questions, contact Mr. J. Lindsay Cobbs, Project Manager, at (301)
827-1051.

Sincerely,

/s/

8/12/95

Cathie Schumaker, R.Ph.
Chief, Project Management Staff
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

NDA 20-833

Page 3

cc:

Archival NDA 20-833

HFD-570/Div. Files

HFD-570/J.L.Cobbs

DISTRICT OFFICE

Drafted by: LCobbs/August 6, 1998

Initialed by: SCHUMAKER/8-10-98

Final by: LGrimshaw/8-12-98

/S/
U 8-13-98

filename: N:\STAFF\COBBS\N20833AC.DOC

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

AUG 17 1998

NDA 20-833

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park
North Carolina 27709

Attention: Kathleen A. Prodan
Director, Regulatory Affairs

Dear Ms. Prodan:

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

Name of Drug Product: Flovent Diskus (fluticasone propionate) Inhalation Powder
Therapeutic Classification: Standard
Date of Application: March 30, 1998
Date of Receipt: March 31, 1998
Our Reference Number: NDA 20-833

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 30, 1998, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 31, 1999.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

**APPEARS THIS WAY
ON ORIGINAL**

AUG - 5 1998

Division of Pulmonary Drug Products**NDA Administrative Review**

Application number: 20-833

Name of Drug: Flovent (fluticasone propionate) Diskus Inhalation Powder
(50, 100, 250 mcg)

Sponsor: Glaxo Wellcome Inc. (GW)

Indication: Maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older.

Submission Date(s): March 30, 1998

Receipt Date: March 31, 1998

The following complete documents were submitted by GW.

1. Form FDA 356h.
2. Form FDA 3397 (User Fee Cover Sheet).
3. Cross-References.
4. Index to the application.
5. Patent Information.
6. Debarment Certification.
 - Amended April 10, 1998.
7. Application Summary:
 - a. Labels and Labeling Summary
 - Draft labeling disk provided.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-833

Glaxo Wellcome Inc.

Flovent (fluticasone propionate) Diskus Inhalation Powder

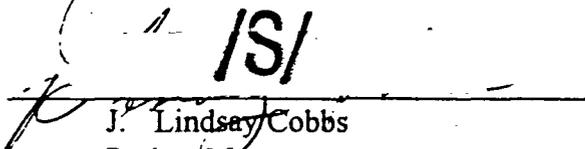
Page 2

- b. Pharmacologic class, scientific rationale, intended use and potential clinical benefits summary.
 - c. Foreign Marketing history.
 - d. Chemistry, Manufacturing and Controls Summary.
 - Statistical evaluation of the stability data for each strength provided on 3 diskettes.
 - e. Nonclinical Pharmacology and Toxicology Summary.
 - f. Human Pharmacokinetic and Bioavailability Summary.
 - Data for 3 studies provided on diskette.
 - g. Clinical Data Summary and Results of Statistical analysis.
 - Patient information and efficacy and safety data from the 9 pivotal studies and the patient information and safety data from the 6 supporting studies are provided on diskette (ASCII and SAS).
 - h. Benefit/Risk Relationship and Proposed Postmarketing studies.
8. Case Report Tabulations.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-833
Glaxo Wellcome Inc.
Flovent (fluticasone propionate) Diskus Inhalation Powder
Page 3

The application is administratively fileable.

ISI


J. Lindsay Cobbs
Project Manager

August 3, 1998

Date

CC ORIGINAL NDA 20-833
HFD-570/DIVISION FILE
HFD-570/Cobbs

Initialed by: Schumaker/

ISI
8/5/98

N:\My Documents\n20833AdminRev.doc

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>20-833/SE</u>	
Drug <u>Florent Diskus</u>	Applicant <u>Glaxo Wellcome</u>
RPM <u>Barnes</u>	Phone <u>7-1055</u>
<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Reference listed drug _____	
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rolling Review
Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P	
Pivotal IND(s) _____	
Application classifications: Chem Class <u>3</u> Other (e.g., orphan, OTC) _____	PDUFA Goal Dates: Primary <u>Sept 29, 2000</u> Secondary _____

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- ◆ User Fee Information: User Fee Paid
 User Fee Waiver (attach waiver notification letter)
 User Fee Exemption

- ◆ Action Letter..... AP AE NA

- ◆ Labeling & Labels
 - FDA revised labeling and reviews..... _____
 - Original proposed labeling (package insert, patient package insert) X
 - Other labeling in class (most recent 3) or class labeling..... N/A
 - Has DDMAC reviewed the labeling? Yes (include review) No
 - Immediate container and carton labels _____
 - Nomenclature review N/A

- ◆ Application Integrity Policy (AIP) Applicant is on the AIP. This application is is not on the AIP.
 - Exception for review (Center Director's memo)..... N/A
 - OC Clearance for approval..... N/A

- ◆ Status of advertising (if AP action) Reviewed (for Subpart H – attach review) Materials requested in AP letter.

- ◆ Post-marketing Commitments
 - Agency request for Phase 4 Commitments.....
 - Copy of Applicant's commitments

- ◆ Was Press Office notified of action (for approval action only)?..... Yes No
 - Copy of Press Release or Talk Paper.....

- ◆ Patent
 - Information [505(b)(1)] X
 - Patent Certification [505(b)(2)]..... N/A
 - Copy of notification to patent holder [21 CFR 314.50 (i)(4)]..... N/A

- ◆ Exclusivity Summary

- ◆ Debarment Statement

- ◆ Financial Disclosure
 - No disclosable information Pre 1998
 - Disclosable information – indicate where review is located

- ◆ Correspondence/Memoranda/Faxes

- ◆ Minutes of Meetings

 - Date of EOP2 Meeting N/A
 - Date of pre NDA Meeting N/A
 - Date of pre-AP Safety Conference N/A

- ◆ Advisory Committee Meeting

 - Date of Meeting N/A
 - Questions considered by the committee
 - Minutes or 48-hour alert or pertinent section of transcript

- ◆ Federal Register Notices, DESI documents

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo)

- ◆ Clinical review(s) and memoranda X

- ◆ Safety Update review(s) _____
- ◆ Pediatric Information
 - Waiver/partial waiver (Indicate location of rationale for waiver) Deferred Pediatric Page..... _____
 - Pediatric Exclusivity requested? Denied Granted Not Applicable
- ◆ Statistical review(s) and memoranda X
- ◆ Biopharmaceutical review(s) and memoranda..... X
- ◆ Abuse Liability review(s) N/A
 Recommendation for scheduling N/A
- ◆ Microbiology (efficacy) review(s) and memoranda N/A
- ◆ DSI Audits None Requested
 - Clinical studies bioequivalence studies _____

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ CMC review(s) and memoranda X
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability X
- ◆ DMF review(s) N/A
- ◆ Environmental Assessment review/FONSI/Categorical exemption In CMC Rev
- ◆ Micro (validation of sterilization) review(s) and memoranda N/A
- ◆ Facilities Inspection (include EES report)
 Date completed _____ Acceptable Not Acceptable
- ◆ Methods Validation Completed Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Pharm/Tox review(s) and memoranda X
- ◆ Memo from DSI regarding GLP inspection (if any) N/A

- ◆ Statistical review(s) of carcinogenicity studies N/A
- ◆ CAC/ECAC report N/A

**APPEARS THIS WAY
ON ORIGINAL**

65 Draft Labeling Page(s) Withheld