CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-077

ADMINISTRATIVE DOCUMENTS

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-077 SE
Drug ADVAIR DISKUS _____ Applicant Glaxo Wellcome
RPM Parinda Jani Phone (3010 827-1064
☒505(b)(1)
☐505(b)(2) Reference listed drug
☐Fast Track ☐Rolling Review Review priority: ☒ S ☐P
Pivotal IND(s) ———
Application classifications: PDUFA Goal Dates:

Chem Class 4S Primary August 25, 2000
Other (e.g., orphan, OTC) _____ 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..... X
  - Original proposed labeling (package insert, patient package insert) X
  - Other labeling in class (most recent 3) or class labeling.....
  - Has DDMAC reviewed the labeling? ..... ☒ Yes (include review) ☐ No
  - Immediate container and carton labels X
  - Nomenclature review X
- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☒ is not on the AIP.
  - Exception for review (Center Director's memo).....
  - OC Clearance for approval.....

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 X
- Was Press Office notified of action (for approval action only)?..... ☒ Yes ☐ No
  - Copy of Press Release or Talk Paper.....None.....
- Patent
  - Information [505(b)(1)] X
  - Patent Certification [505(b)(2)].....
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....

Exclusivity Summary X
Debarment Statement X

♦ Financial Disclosure	X
No disclosable information	X
Disclosable information – indicate where review is located	
Correspondence/Memoranda/Faxes	X
♦ Minutes of Meetings	X
Date of EOP2 Meeting	
Date of pre NDA Meeting	
Date of pre-AP Safety Conference	
♦ Advisory Committee Meeting	
Date of Meeting	November 23, 1999
Questions considered by the committee	X
Minutes or 48-hour alert or pertinent section of transcript	X
♦ 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)	X
Clinical review(s) and memoranda	X
Safety Update review(s) ...(included in the clinical review)	X
♦ 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)	
Recommendation for scheduling	N/A
Microbiology (efficacy) review(s) and memoranda	N/A
♦ DSI Audits	X
☐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)	
Environmental Assessment review/FONSI/Categorical exemption	Categorical Exclusion
Micro (validation of sterilization) review(s) and memoranda	N/A

- Facilities Inspection (include EES report)
  Date completed May 5, 2000 ..... ☐ 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)	
Statistical review(s) of carcinogenicity studies	
◆ CAC/ECAC report	

APPEARS THIS WAY
ON ORIGINAL

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 19, 2000

NDA NUMBER: 21-077

NAME OF DRUG: Advair™ Diskus® ——— (salmeterol xinafoate/fluticasone propionate inhalation powder)

NDA HOLDER: Glaxo Wellcome, Inc.
Research Triangle Park, NC 27709

I. INTRODUCTION

This consult was written in response to a request from the Division of Pulmonary and Allergy Drug Products (HFD-570) for assessment of the tradenames Advair Diskus ——, Advair Diskus ——— and Advair Diskus ——. *In particular, the Division expressed a need for information on how to identify the salmeterol component in the tradename and to express ——— in the tradename.* The sponsor has proposed to include ——— in the tradename, since the salmeterol component is the same in all three formulations (e.g., 50 mcg) and the fluticasone component varies (e.g., 100mcg, 250mcg, and 500mcg).

A previous consult had been requested regarding the name "Advair Diskus ——— and completed by the LNC on August 9, 1999. The conclusion of the LNC at that time was as follows:

"[The names] Advil (OTC) and Advera (OTC) [are considered to be] look-alike, sound-alike [names]; strength of only one ingredient is misleading. Sponsor should re-do explanation of potency to include both ingredients; [this name is considered to be] acceptable."

Advair Diskus is a combination product consisting of two active ingredients: salmeterol xinafoate and fluticasone propionate. Three strengths will be available: salmeterol xinafoate 50 mcg in combination with fluticasone propionate 100 mcg, 250 mcg or 500 mcg. This product is indicated for the maintenance treatment of asthma ——— in patients 12 years of age and older. Advair Diskus comes supplied with a disposable inhaler device that contains either 28 or 60 blisters of the active drug combination. There is no propellant in the DISKUS products. The device punctures the blister to load the drug powder for inhalation into a chamber and the patient then inhales the powder when ready. This manufacturer currently holds NDAs for other products that utilize the DISKUS® delivery device (e.g., Serevent Diskus, Flovent Diskus, ———.

II. SAFETY AND RISK ASSESSMENT

A. Product name search, product availability and dosing comparison, and focus group

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or look alike to Advair Diskus to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. An internal focus group discussion was conducted to review all findings from the searches.

A number of product names were identified in the OPDRA focus group that were thought to have potential for confusion. These products included Advil (ibuprofen tablets 50mg, 100mg, 200mg, concentrated drops, oral suspension), Advera (liquid nutritional supplement for HIV/AIDS patients, Arava (leflunomide 10mg, 20mg, 100mg oral tablets), Avandia (rosaglitazone 2mg, 4mg, 8mg oral tablets), Avita (tretinoin topical gel), Maxair (pirbuterol inhalers).

Of these products, Advil was considered to be the most likely product to be confused with Advair, This seems particularly likely if only one ingredient strength is included in the Advair proprietary name and the designation "mcg" is included as well. For example, "Advair ——— ;" could be confused with "Advil 100mg" in verbal or written prescriptions, as could the other strengths of Advair. It also seems unlikely that physicians will include the additional dosage form name "Diskus" in communicating prescriptions, as no other dosage forms of Advair are currently available in the U.S.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In reviewing the draft labeling for Advair Diskus, OPDRA has attempted to focus on safety issues relating to potential medication errors. Many of the items discussed in this consult involve issues normally reviewed by the chemist and medical officer.

We reviewed the draft product labeling for Advair Diskus and identified several labeling, packaging, and safety concerns.

A. CONTAINER AND CARTON LABELING (50mcg/100mcg, 50mcg/250mcg, 50mcg/500mcg products)

1. The established name printed on the round front device label must be at least 50% of the size of the proprietary name (see 21 CFR 201.10).

---

[i] MICROMEDEX Healthcare Intranet Series, 1999, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 1999).

[ii] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

[iii] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[iv] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-99, and the electronic online version of the FDA Orange Book.

[v] WWW location http://www.uspto.gov/tmdb/index.html.

2. We recognize that the Agency has previously requested that the applicant holder revise their established name. However, the Description section of the package insert states that each blister contains salmeterol xinafoate equivalent to salmeterol 50 mcg. If this is true, then all other labels and labeling should be revised accordingly, since the product ~~has been~~ erroneously and perhaps inadvertently labeled as having 50 mcg of salmeterol xinafoate. *Per USP/NF standards,* we suggest that the statement [redacted]

3. We would recommend that the strength of each active ingredient [redacted] as indicated in brackets below. We suggest the following, although there may be other alternatives to this suggested format:

[redacted]

4. We would recommend that the usual dosage statement be revised, as recommended by 21 CFR 201.100(b)(2) to the following: USUAL DOSAGE: [redacted]

5. We understand that this is a DISKUS product, similar in design and labeling to Serevent Diskus. However, this combination drug product will be difficult to prescribe with the additional modifiers of DISKUS and the numerical representation of the three strengths of Advair. For simplicity, we would ask the sponsor to consider one of the following alternative naming schemes:

[redacted]

-or-

[redacted]

6. We note that the primary color scheme for the round device label and carton is different for each strength of the product (e.g., 50/100 blue, 50/250 purple, 50/500 gray). However, the square label for the foil overwrap is purple for all strengths. Although large, background reverse print of "100", "250" and "500" is included on each foil overwrap, we have some concern that the 50/100 and 50/500 strength products may be mistaken for the 50/250 products. We suggest that these overwraps either bear a color consistent for each strength or be absent of color (e.g., white).

B. PACKAGE INSERT and PATIENT MEDICATION GUIDE

See changes as recommended above.

IV. DISCUSSION

In reviewing this proprietary name, several names were identified that had some sound-alike and look-alike qualities. One product in particular, Advil, seems most likely to be confused verbally with Advair in communicating and interpreting prescriptions for either product. Although Advil is an over-

the-counter product, written or verbal inpatient or outpatient prescription orders for OTC products are not rare. However, due to the short time provided for this review, we were unable to conduct our normal handwritten and verbal prescription studies.

We also agree with the previous decision of the LNC that inclusion of the [redacted] in the proprietary name is misleading and may be confusing; it gives the appearance that the product contains only [redacted] It would be highly undesirable for a patient to receive or continue to use a second inhaler that contained salmeterol, given the nature of this drug and the need for strict compliance with the currently FDA-approved twice-daily dosing schedule for salmeterol products. Inclusion of [redacted] after Advair would also seem to increase the likelihood of misinterpretation of a prescription for Advair with Advil (ibuprofen), or vice versa. Advil is now available in multiple strengths, for use not only adults but also in pediatrics, in which dosing tends to be based on weight and age and thus not uniform. Advil and other NSAIDS also have precautions for use in patients with asthma, as they may have an increased risk of bronchospasm with their use.

We have suggested alternatives in which numerical suffixes would be added to the name: [redacted]

Note that either naming scheme does not include "mcg" after the numerical suffix. We believe that inclusion of "mcg" will increase the likelihood of medication errors in which Advair is mistaken for a sound-alike or look-alike drug and also give a stronger impression that Advair contains only one ingredient.

V. RECOMMENDATIONS

A. OPDRA has no objections to the use of the proprietary name Advair, without inclusion of the delivery device name "DISKUS". We disagree with the concept of including only the [redacted] in the name.

We suggest the following alternative formats for distinguishing among the three strengths of this product:

[redacted]

-or-

[redacted]

B. OPDRA recommends that the Labeling and Nomenclature Committee be advised of our comments concerning the established name of the product.

C. OPDRA recommends the above labeling revisions to minimize potential errors with the use of this product.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

APPEARS THIS WAY
ON ORIGINAL

/S/

Carol Pamer, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

APPEARS THIS WAY
ON ORIGINAL

Concur:

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

cc: NDA 21-077
HFD-570; Division Files/Parinda Jani, Project Manager
HFD-570; Robert J. Meyer, Division Director
HFD-400; Min Chen, Team Leader, OPDRA
HFD-400; Claudia Karwoski, Safety Evaluator, OPDRA
HFD-400; Carol Pamer, Safety Evaluator, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Deputy Director, OPDRA
HFD-002; Murray Lumpkin, Acting Director, OPDRA

APPEARS THIS WAY
ON ORIGINAL

P. 01

TRANSACTION REPORT

AUG-24-2000 THU 05:46 PM

DATE	START	RECEIVER	TX TIME	PAGES	TYPE	NOTE	M#	DP
AUG-24	05:44 PM	919193158940	1'50"	4	SEND	OK	286	

TOTAL : 1M 50S PAGES: 4

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-077

AUG 24 2000

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

Attention: Joy E. Farrell
Director, Regulatory Affairs

Dear Ms. Farrell:

Please refer to your new drug application (NDA) dated March 24, 1999, received March 25, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ADVAIR DISKUS 100/50 (fluticasone propionate 100 mcg and salmeterol xinafoate 50 mcg inhalation powder), ADVAIR DISKUS 250/50 (fluticasone propionate 250 mcg and salmeterol xinafoate 50 mcg inhalation powder) and ADVAIR DISKUS 500/50 (fluticasone propionate 500 mcg and salmeterol xinafoate 50 mcg inhalation powder).

We acknowledge receipt of your submissions dated May 28, June 30, July 16, August 30, September 23 and 29, October 13 and 22, and December 6, 1999, January 13, February 25,

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-077

Food and Drug Administration
Rockville MD 20857

AUG 24 2000

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

Attention: Joy E. Farrell
Director, Regulatory Affairs

Dear Ms. Farrell:

Please refer to your new drug application (NDA) dated March 24, 1999, received March 25, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ADVAIR DISKUS 100/50 (fluticasone propionate 100 mcg and salmeterol xinafoate 50 mcg inhalation powder), ADVAIR DISKUS 250/50 (fluticasone propionate 250 mcg and salmeterol xinafoate 50 mcg inhalation powder) and ADVAIR DISKUS 500/50 (fluticasone propionate 500 mcg and salmeterol xinafoate 50 mcg inhalation powder).

We acknowledge receipt of your submissions dated May 28, June 30, July 16, August 30, September 23 and 29, October 13 and 22, and December 6, 1999, January 13, February 25, March 15, April 18, July 17, 25, and 26, August 14, 18, 22, 23, and 24, 2000. Your submission of February 25, 2000, constituted a complete response to our January 27, 2000, action letter.

This new drug application provides for the use of ADVAIR DISKUS (fluticasone propionate and salmeterol xinafoate) inhalation powder for the long-term, twice-daily, maintenance treatment of asthma in patients 12 years of age and older.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert and Patient's Instruction for Use leaflet submitted August 24, 2000, and immediate container and carton labels submitted August 23, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 21-077." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your submission dated August 24, 2000. This commitment, along with completion date agreed upon, is listed below.

> Glaxo Wellcome will provide a summary of the existing pharmacokinetics and pharmacodynamic data on fluticasone propionate in patients with asthma to place in context the apparent gender effects that were observed in the study SFCB3019. In the event the available data are inadequate to determine if a gender effect does or does not exist, Glaxo Wellcome will conduct a clinical pharmacology trial to examine the pharmacokinetics and pharmacodynamic effect of fluticasone propionate administration to male and female asthma patients in an attempt to definitively assess for gender effects. These data will be provided to the Agency by February 2002.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitment, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of the commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, 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 (63 *FR* 66632). We note that you have fulfilled the requirements of 21 CFR 314.55 (or 601.27) for pediatric patients 12 years of age and above. However, you have not fulfilled the requirements for pediatric patients under 12 years of age. We are deferring submission of the further required pediatric studies until August 2002.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your request whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division 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, Maryland 20857

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

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Ms. Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

/S/

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	1202a	HFD# 570	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION:	Parinda Jani		Advair Diskus	salmeterol xinafoate 50 mcg and fluticasone propionate 100 mcg inhalation powder
RE:	NDA/IND #	21-077		

A. Look-alike/Sound-alike

	Potential for confusion:		
ADVIL (OTC)	XXX Low	____ Medium	____ High
ADVERA (OTC)	XXX Low	____ Medium	____ High
	____ Low	____ Medium	____ High
	____ Low	____ Medium	____ High
	____ Low	____ Medium	____ High

B. Misleading Aspects:

_____ is misleading.
Sponsor should re-do expression of potency to include both ingredients.

C. Other Concerns:

D. Established Name

____ Satisfactory
____ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ____ UNACCEPTABLE

F. Signature of Chair/Date (S) 8/9/99

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #: 12025 HFD#: 570	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION: Parinda Jani	Advair Diskus	salmeterol xinafoate 50 mcg and fluticasone propionate 250 mcg inhalation powder
RE: NDA/IND # 21-077		

A. Look-alike/Sound-alike

	Potential for confusion:
ADVIL (OTC)	XXX Low ____ Medium ____ High
ADVERA (OTC)	XXX Low ____ Medium ____ High
	____ Low ____ Medium ____ High
	____ Low ____ Medium ____ High
	____ Low ____ Medium ____ High

B. Misleading Aspects:

[redacted] is misleading.
Sponsor should re-do expression of potency to include both ingredients.

C. Other Concerns:

D. Established Name

____ Satisfactory
____ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ____ UNACCEPTABLE

F. Signature of Chair/Date

/S/ 8/9/99

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	1202c	HFD# 570	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION:	Parinda Jani		Advair Diskus	salmeterol xinafoate 50 mcg and fluticasone propionate 500 mcg inhalation powder
RE:	NDA/IND #	21-077		

A. Look-alike/Sound-alike

	Potential for confusion:		
ADVIL (OTC)	XXX Low	___ Medium	___ High
ADVERA (OTC)	XXX Low	___ Medium	___ High
	___ Low	___ Medium	___ High
	___ Low	___ Medium	___ High
	___ Low	___ Medium	___ High

B. Misleading Aspects:

[redacted] is misleading.
Sponsor should re-do expression of potency to include both ingredients.

C. Other Concerns:

D. Established Name

___ Satisfactory
___ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ___ UNACCEPTABLE

F. Signature of Chair/Date

/S/ 8/9/99

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Pulmonary Drug Products		**HFD-570**
Attention: Parinda Jani	**Phone:** (301) 827-1064	
Date: May 20, 1999		
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product		
Proposed Trademark: ADVAIR DISKUS —— ADVAIR DISKUS —— ADVAIR DISKUS ——	**NDA/ANDA#** NDA 21-077	

Established name, including dosage form:
Salmeterol xinafoate 50 mcg and fluticasone propionate 100 mcg inhalation powder
Salmeterol xinafoate 50 mcg and fluticasone propionate 250 mcg inhalation powder
Salmeterol xinafoate 50 mcg and fluticasone propionate 500 mcg inhalation powder

Other trademarks by the same firm for companion products: Serevent Diskus/NDA 20-692/AP 9-19-97, Flovent Diskus/NDA 20-833/AE 3-31-99, ——————

Indications for Use (may be a summary if proposed statement is lengthy):
For the maintenance treatment of asthma —————— in patients 12 years of age and older.

Initial Comments from the submitter (concerns, observations, etc.):
ADVAIR is a combination product of salmeterol xinafoate and fluticasone propionate. It will be available in 3 different strengths, in which the amount of salmeterol xinafoate will be same (50 mcg), and the amount of fluticasone propionate will be varied (100 mcg, 250 mcg and 500 mcg).

APPEARS THIS WAY
ON ORIGINAL

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original NDA 21-077; HFD-570/division file; HFD-570/Schumaker, Poochikian, Koble

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION**	
TO *(Division/Office)*: Dan Boring/ HFD 530			FROM: Parinda Jani/HFD 570	
DATE 5-20-99	IND NO.	NDA NO. 21-077	TYPE OF DOCUMENT Proposed name	DATE OF DOCUMENT 3-24-99
NAME OF DRUG ADVAIR DISKSUS	PRIORITY CONSIDERATION S		CLASSIFICATION OF DRUG	DESIRED COMPLETION I July 20, 1999
NAME OF FIRM: Glaxo Wellcome				

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL	PRE--NDA MEETING	RESPONSE TO DEFICIENCY LETTER
PROGRESS REPORT	END OF PHASE II MEETING	FINAL PRINTED LABELING
NEW CORRESPONDENCE	RESUBMISSION	LABELING REVISION
DRUG ADVERTISING	SAFETY/EFFICACY	ORIGINAL NEW CORRESPONDENCE
ADVERSE REACTION REPORT	PAPER NDA	FORMULATIVE REVIEW
MANUFACTURING CHANGE/ADDITION	CONTROL SUPPLEMENT	x OTHER *(SPECIFY BELOW)*:
MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW	CHEMISTRY REVIEW
END OF PHASE II MEETING	PHARMACOLOGY
CONTROLLED STUDIES	BIOPHARMACEUTICS
PROTOCOL REVIEW	OTHER (SPECIFY BELOW):
OTHER (SPECIFY BELOW):	

III. BIOPHARMACEUTICS

DISSOLUTION	DEFICIENCY LETTER RESPONSE
BIOAVAILABILTY STUDIES	PROTOCOL-BIOPHARMACEUTICS
PHASE IV STUDIES	IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFE
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	SUMMARY OF ADVERSE EXPERIENCE
CASE REPORTS OF SPECIFIC REACTIONS (List below)	POISON RICK ANALYSIS
COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

The due date for this NDA is January 25, 2000
Please call Parinda Jani at 7-1064 or Cathie Schumaker at 7-1050 for additional information.

Thanks

cc:
orig nda 21-077/div file HFD-570/ HFD-570 Schumaker, Poochikian, Koble, Jani

SIGNATURE OF REQUESTER /S/ 5-21-99	METHOD OF DELIVERY (Check one) MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER 5/24/99

/S/

S

JAN 27 2000

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: January 11, 2000	DUE DATE: January 21, 2000	OPDRA CONSULT #: 00-010

TO: Robert J. Meyer, M.D.
Director, Division of Pulmonary and Allergy Drug Products
HFD-570

PRODUCT NAME: Advair™ Diskus® (salmeterol xinafoate/fluticasone propionate inhalation powder) NDA #: 21-077	MANUFACTURER: Glaxo Wellcome, Inc. Research Triangle Park, NC 27709

CASE REPORT NUMBER(S): Not applicable.

SUMMARY: In response to a consult from the Division of Pulmonary and Allergy Drug Products (HFD-570), OPDRA conducted a reassessment of the proposed proprietary name "Advair Diskus" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: From a safety perspective, OPDRA does not object to the use of the name Advair, with a specific recommendation for designation of multiple strengths of this combination product. The established name of this product should be revised to comply with the USP/NF standards. We also have made a number of recommendations for labeling revisions to minimize potential errors with the use of this product.

/S/ 1/21/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

/S/ 1/27/00

Peter Honig, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:		FROM:	
Jerry Phillips/OPDRA HFD-400 15B03		Parinda Jani/HFD 570	
DATE: 1-11-00	IND NO.:	NDA NO.: 21-077	TYPE OF DOCUMENT: Proposed name
DATE OF DOCUMENT: 3-24-99			
NAME OF DRUG: ADVAIR DISKSUS	PRIORITY CONSIDERATION: P	CLASSIFICATION OF DRUG:	DESIRED COMPLETION: January 21, 2000

NAME OF FIRM: Glaxo Wellcome

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL	PRE-NDA MEETING	RESPONSE TO DEFICIENCY LETTER
PROGRESS REPORT	END OF PHASE II MEETING	FINAL PRINTED LABELING
NEW CORRESPONDENCE	RESUBMISSION	LABELING REVISION
DRUG ADVERTISING	SAFETY/EFFICACY	ORIGINAL NEW CORRESPONDENCE
ADVERSE REACTION REPORT	PAPER NDA	FORMULATIVE REVIEW
MANUFACTURING CHANGE/ADDITION	CONTROL SUPPLEMENT	x OTHER *(SPECIFY BELOW)*:
MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW	CHEMISTRY REVIEW
END OF PHASE II MEETING	PHARMACOLOGY
CONTROLLED STUDIES	BIOPHARMACEUTICS
PROTOCOL REVIEW	OTHER (SPECIFY BELOW):
OTHER (SPECIFY BELOW):	

III. BIOPHARMACEUTICS

DISSOLUTION	DEFICIENCY LETTER RESPONSE
BIOAVAILABILTY STUDIES	PROTOCOL-BIOPHARMACEUTICS
PHASE IV STUDIES	IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SA
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	SUMMARY OF ADVERSE EXPERIENCE
CASE REPORTS OF SPECIFIC REACTIONS (List below)	POISON RICK ANALYSIS
COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

The due date for this NDA is January 25, 2000
Please call Parinda Jani at 7-1064.
Thanks

cc:
orig nda 21-077/div file HFD-570/ HFD-570 Poochikian, Koble, Jani

SIGNATURE OF REQUESTER	1/11/00	METHOD OF DELIVERY (Check one) MAIL HAND
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER

GlaxoWellcome FACSIMILE

DATE	AUGUST 24, 2000	**TOTAL PAGES**	
TO	Ms. Parinda Jani Food and Drug Administration	**FAX** **PHONE**	(301) 480-5683 (301) 827-1064
FROM	Ms. Joy E. Ferrell	**FAX** **PHONE**	(919) 315 0033 (919) 483-5211

Re: **NDA 21-077; ADVAIR™ DISKUS® (fluticasone propionate/salmeterol inhalation powder) 100/50 mcg, 250/50 mcg and 500/50 mcg**
Response to FDA Request/Comment

Parinda,

Phase IV Commitment

The following is provided in reference to our teleconference on August 16, and follow-up conversation on August 23, 2000.

Glaxo Wellcome agrees to a Phase IV commitment to provide the Agency a summary of the existing pharmacokinetics and pharmacodynamic data on fluticasone propionate in patients with asthma to place in context the apparent gender effects that were observed in the Study SECB3019. In the event the available data are inadequate to determine if a gender effect does or does not exist, Glaxo Wellcome agrees to conduct a clinical pharmacology trial to examine the pharmacokinetics and pharmacodynamic effect of fluticasone propionate administration to male and female asthma patients in an attempt to more definitively assess for gender effects. We will discuss protocol design with the Division prior to initiation of the trial. In the event we need to conduct a study, we anticipate it will take 18-24 months to complete this commitment.

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park, NC
27709-3398

U. S. Regulatory Affairs
Phone 919-483-2100

Patent Information

Amendment to Item 13 of NDA 21-077
Pursuant to 21 C.F.R. § 314.53
for
ADVAIR™ DISKUS® Inhalation Powder

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

Trade Name: ADVAIR™ Diskus®

Active Ingredient: salmeterol xinafoate/fluticasone propionate

Strengths: salmeterol xinafoate/fluticasone propionate 50mcg/100mcg
salmeterol xinafoate/fluticasone propionate 50mcg/250mcg
salmeterol xinafoate/fluticasone propionate 50mcg/500mcg

Dosage Form: inhalation powder

Route of Administration: oral inhalation

Please do not list the following (previously submitted) 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	5,380,922	10 January, 2012	Drug Product/Process of Production
2	D 342,994	4 January, 2008	Product Administration System
3	5,860,419	1 March, 2011	Product Administration System
4	5,590,645	1 March, 2011	Product Administration System
5	5,873,360	23 February, 2016	Product Administration System

Please list 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	4,992,474	12 February, 2008	Drug Substance Method of Use
2	5,225,445	12 February, 2008	Method of Use
3	5,126,375	12 February, 2008	Drug Substance Drug Product
4	4,335,121	14 November, 2003	Drug Substance
5	5,270,305	7 September, 2010	Drug Substance

The undersigned declares the following:

1) All of the above patents are owned by Glaxo Group Limited.
2) The United States Agent for Glaxo Group Limited is Glaxo Wellcome Inc.
3) The above Patents (4,335,121; 4,992,474; 5,225,445; 5,126,375 and 5,270,305) are required to be the subject of a submission of information pursuant to 21 C.F.R. §314.53(b), and meet the criteria for submission therein.
4) The above Patents (4,335,121; 4,992,474; 5,225,445; 5,126,375 and 5,270,305) cover the formulation, composition, and/or method of use of ADVAIR™ DISKUS®.

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: 30 November, 1999

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

APPEARS THIS WAY
ON ORIGINAL

Patent Information

Pursuant to 21 C.F.R. § 314.53

for

ADVAIR™ Diskus® Inhalation Powder
ADVAIR™ Diskus® inhalation powder 50mcg/100mcg
ADVAIR™ Diskus® inhalation powder 50mcg/250mcg
ADVAIR™ Diskus® inhalation powder 50mcg/500mcg

Item 13 of NDA 21-077

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

Trade Name: ADVAIR™ Diskus®

Active Ingredient: salmeterol xinafoate/fluticasone propionate

Strengths: salmeterol xinafoate/fluticasone propionate 50mcg/100mcg
salmeterol xinafoate/fluticasone propionate 50mcg/250mcg
salmeterol xinafoate/fluticasone propionate 50mcg/500mcg

Dosage Form: inhalation powder

	US Patent Number	Expiration Date	Form of Patent Claims
1	4,992,474	12 February, 2008	Drug Product/Methods of Use
2	5,225,445	12 February, 2008	Methods of Use
3	5,380,922	10 January, 2012	Drug Product/Process of Production
4	5,126,375	12 February, 2008	Drug Product and Compositions Thereof
5	D 342,994	4 January, 2008	Product Administration System
6	4,335,121	14 November, 2003	Drug Product
7	5,270,305	7 September, 2010	Drug Product
8	5,860,419	1 March 2011	Product Administration System
9	5,590,645	1 March, 2011	Product Administration System
10	5,873,360	23 February, 2016	Product Administration System

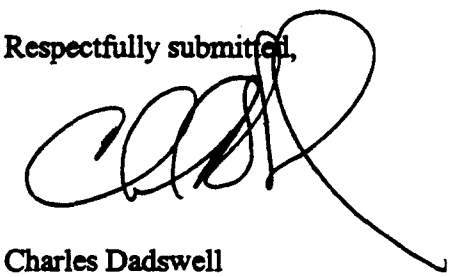
The undersigned declares the following:

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: 23 March, 1999

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

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY FOR NDA # 21-077 SUPPL #_____

Trade Name: ADVAIR DISKUS 100/50, 250/50 and 500/50
Generic Name: fluticasone propionate 100 mcg and salmeterol 50 mcg
fluticasone propionate 250 mcg and salmeterol 50 mcg
fluticasone propionate 500 mcg and salmeterol 50 mcg

Applicant Name Glaxo Wellcome HFD # 570

Approval Date If Known August 25, 2000

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 / X / NO / ___ /

b) Is it an effectiveness supplement?

YES / ___ / NO / X /

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 / 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?
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 /_X_/

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 /_X_/

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# _____ _____

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 / X / NO /___/

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

NDA# 20-236 Serevent Inhalation Aerosol

NDA# 20-692 Serevent Diskus

NDA# 19-957 Cutivate Cream

NDA# 19-958 Cutivate Ointment

NDA# 20-121 Flonase Nasal Spray

NDA# 20-548 Flovent Inhalation Aerosol

NDA# 20-549 Flovent Rotadisk

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 /_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:

Studies SFCA 3002, SFCA 3003 and SFCB 3019

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 Study SFCA 3002 YES /___/ NO /_X_/

Investigation #2 Study SFCA 3003 YES /___/ NO /_X_/

Investigation #3 Study SFCB 3019 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 Study SFCA 3002 YES /___/ NO /_X_/

Investigation #2 Study SFCA 3003 YES /___/ NO /_X_/

Investigation #3 Study SFCB 3019 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"):

SFCA 3002 SFCA 3003

SFCB 3019 _____

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 # _____ YES /_X_/ NO /___/
Explain:_____

Investigation #2

IND # _____ YES /_X_/ NO /___/
Explain:_____

Investigation #3

IND # _____ YES /_X_/ NO /___/
Explain: _____

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

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: _____

/S/ Project Manager, 8/22/00

Signature/ Title/Date

/S/ Director, DPADP 8/23/00

Signature of Office/Division Director/Date

CC:
Original NDA/21-077
Division File/HFD-570
HFD-570/Jani
HFD-93/Mary Ann Holovac

III. Marketing Exclusivity

NDA 21-077

Salmeterol/Fluticasone propionate Diskus Inhalation Powder

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, Glaxo Wellcome Inc. requests three years of exclusivity from the date of approval of salmeterol/fluticasone propionate Diskus inhalation powder 50/100mcg, 50/250mcg, and 50/500mcg for the maintenance treatment of asthma [redacted] in patients 12 years of age and older.

Glaxo Wellcome Inc. 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 Glaxo Wellcome Inc. 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 [redacted] in patients 12 years of age and older

RM1997/00600/02. A Randomized, Double-Blind, Parallel-Group Trial Evaluating the Safety and Efficacy of Salmeterol 50mcg BID and Fluticasone Propionate 100mcg BID Individually and in Combination and Placebo in Subjects with Asthma (Study No. SFCA3002)

RM1997/00624/02. A Randomized, Double-Blind, Parallel-Group Trial Evaluating the Safety and Efficacy of Salmeterol 50mcg BID and Fluticasone Propionate 250mcg BID Individually and in Combination and Placebo in Subjects with Asthma (Study No. SFCA3003)

GM1998/00018/00. A Multicenter, Randomized, Double-Blind, Double-Dummy, Parallel-Group Comparison of the Salmeterol/Fluticasone Propionate Combination Product (50/500mcg strength) BD via one Diskus/Accuhaler Inhaler with Salmeterol 50mcg BD via one Diskus/Accuhaler Inhaler and Fluticasone Propionate 500mcg BD via another Diskus/Accuhaler Inhaler and with Fluticasone Propionate 500mcg BD via one Diskus/Accuhaler Inhaler in Adolescents and Adults with Reversible Airways Obstruction (Study No. SFCB3019)

To the best of Glaxo Wellcome Inc.'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 Glaxo Wellcome Inc.'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 Glaxo Wellcome Inc." in that Glaxo Wellcome Inc. was either the sponsor of the US investigational new drug application (IND —— under which the studies were conducted (SFCA3002 and SFCA3003) or was, in the case of one study (SFCB3019) conducted outside the United States, under common ownership and control with the Glaxo Wellcome affiliated company that conducted and sponsored the study.

/S/

C. Elaine Jones, Ph.D
Product Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

NDA 21-077

Salmeterol/fluticasone propionate Diskus Inhaler

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 of the Federal Food, Drug and Cosmetic Act in connection with this application.

23 FEB 99

Charles E. Mueller
Head, Clinical Compliance
World Wide Compliance

Date

APPEARS THIS WAY
ON ORIGINAL

FINANCIAL DISLCOSURE AS TO CLINICAL INVESTIGATORS

Salmeterol/Fluticasone Propionate Diskus Inhalation Powder

NDA 21-077

In compliance with the Final Rule on Financial Disclosure by Clinical Investigators published on February 2, 1998 (63 *FR* 5233), as subsequently revised by publication on December 31, 1998 (63 *FR* 72171) (hereafter collectively referred to as the "rule"), financial interest information is provided for clinical investigators participating in studies covered by this Final Rule included in New Drug Application 21-077 for Salmeterol/Fluticasone Propionate Discus Inhalation Powder for the maintenance treatment of asthma ——————— in patients 12 years of age and older. The following synopsis includes a description of methods used for the collection and reporting of the investigator financial disclosure information. Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and supporting tables can be found in Item 19 (Vol. 175, Page 1).

The following is the list of "covered clinical studies" for purposes of the rule; as to each, Glaxo Wellcome was the sponsor:

APPEARS THIS WAY
ON ORIGINAL

PROTOCOL NO.	PROTOCOL TITLE	STUDY START DATE	STOP DATE
SFCA3002	A Randomized, Double-Blind, Parallel-Group Trial Evaluating the Safety and Efficacy of Salmeterol 50mcg BID and Fluticasone Propionate 100mcg BID Individually and in Combination and Placebo in Subjects with Asthma	06AUG96	15JUL97
SFCA3003	A Randomized, Double-Blind, Parallel-Group Trial Evaluating the Safety and Efficacy of Salmeterol 50mcg BID and Fluticasone Propionate 250mcg BID Individually and in Combination and Placebo in Subjects with Asthma	06AUG96	15JUL97
SFCB3017	A Multicenter, Randomized, Double-Blind, Double-Dummy, Parallel-Group Comparison of the Salmeterol/Fluticasone Propionate Combination Product (50/100mcg strength) BD via one Diskus/Accuhaler Inhaler with Salmeterol 50mcg BD via one Diskus/Accuhaler Inhaler and Fluticasone Propionate 100mcg BD via a Second Diskus/Accuhaler Inhaler in Adolescent and Adults with Reversible Airways Obstruction	17JUL96	09MAY97
SFCB3018	A Multicenter, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Six Month Comparison of the Salmeterol/Fluticasone Propionate Combination Product (50/250mcg strength) BD via one Diskus/Accuhaler Inhaler with Salmeterol 50mcg BD via one Diskus/Accuhaler Inhaler and Fluticasone Propionate 250mcg BD via a Second Diskus/Accuhaler Inhaler in Adolescents and Adults with Reversible Airways Obstruction	03JUL96	23JUL97
SFCB3019	A Multicenter, Randomized, Double-Blind, Double-Dummy, Parallel-Group Comparison of the Salmeterol/Fluticasone Propionate Combination Product (50/500mcg strength) BD via one Diskus/Accuhaler Inhaler with Salmeterol 50mcg BD via one Diskus/Accuhaler Inhaler and Fluticasone Propionate 500mcg BD via another Diskus/Accuhaler Inhaler and with Fluticasone Propionate 500mcg BD via one Diskus/Accuhaler Inhaler in Adolescents and Adults with Reversible Airways Obstruction	31MAY96	10NOV97
SFCB3020	A Multicentre, Randomized, Double-Blind, Double-Dummy, Parallel-Group Comparison of the Salmeterol/Fluticasone Propionate Combination Product (50/100mcg strength) BD via One Diskus/Accuhaler Inhaler with Salmeterol 50mcg BD via One Diskus/Accuhaler Inhaler and Fluticasone Propionate 100mcg BD via a Second Diskus/Accuhaler Inhaler in Children Aged 4-11 Years With Reversible Airways Obstruction	11NOV96	10SEP97
SFCB1001	A Study to Evaluate the Safety, Tolerability and Systemic Pharmacodynamic Effects of Salmeterol in the Salmeterol/Fluticasone Propionate Diskus Inhaler	10APR95	23MAY95
SFCB1002	A Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Systemic Pharmacodynamic Effects of Fluticasone Propionate in the Salmeterol/Fluticasone Propionate Diskus Inhaler	26APR95	07JUN95
SFCB1004	The Systemic Pharmacodynamic Effects and Pharmacokinetics of Salmeterol and Fluticasone Propionate When Given Alone and in Combination, After Repeat Dosing from Diskus Inhalers in Healthy Volunteers	04MAY96	08AUG96
SFCB1005	The Systemic Pharmacodynamic Effects and Pharmacokinetics of Salmeterol and Fluticasone Propionate When Given Together from Either a Single or Two Separate Diskus Inhalers, in Single Doses	31OCT96	04DEC96
C92-029	A Study to Evaluate the Safety, Tolerability and Systemic Pharmacodynamic Effects of Salmeterol in the Salmeterol/Fluticasone Propionate ——— Inhaler	03NOV93	21DEC93

Note: To arrive at the above-noted study "start" and "stop" dates, Glaxo Wellcome has defined the duration of the clinical study as the time period beginning with the first patient entered into the clinical study until the last patient assessment at the last site.

WITHHOLD 1 PAGE (S)

Division Director's Memorandum
Addendum

Date: Wednesday, August 23, 2000
NDA: 21-077
Sponsor: Glaxo Wellcome
Proprietary Name: ADVAIR Diskus (fluticasone propionate and salmeterol xinaphoate inhalation powder).

Introduction: This action is taken on a resubmission by GlaxoWellcome in response to an approvable letter of January 27, 2000. The sponsor has satisfactorily answered the concerns and information requests contained in that letter and the NDA will now be approved, once final labeling and documentation are received from the company.

Administrative: The resubmission by GlaxoWellcome was received on February 25, 2000 and, as a substantive, class II resubmission, has a 6-month PDUFA due date of August 25, 2000. Note that although not included in the last Director's Memo, there are no financial disclosure issues with this NDA, as the sponsor has certified that all covered studies were completed prior to Feb. 2, 1999.

Chemistry/Manufacturing and Controls: See Dr. Koble's additional review for details. The CMC issues raised in our previous action letter were satisfactorily addressed and the product will be approved. [redacted] the out-of-pouch stability appears to be 1 month – which is the expected usage time for any single Diskus device (i.e., 60 doses, with dosing = 1 actuation inhaled twice daily, lasting for 30 days).

Pharmacology/Toxicology: No substantive issues (apart from labeling) have been raised in this review cycle.

Biopharmaceutics: One issue that came out of the labeling review is that the PK data provided to investigate the presence or absence of a PK drug-drug interaction between fluticasone and salmeterol showed an apparent gender effect for fluticasone in all arms of the study (i.e., fluticasone alone, and in the combination/concurrent arms). These studies involved a relatively small number of women and stand in contradistinction to all other fluticasone studies, which have not shown such an effect. The sponsor will be asked for a phase 4 commitment to provide further formal data in patients to define whether a gender effect does exist with fluticasone.

Clinical / Statistical: Dr. Johnson's primary review of the safety update does not reveal any new concerns about the safety of this product. Additionally, an accounting of device robustness in actual use shows a very small consumer complaint rate for this product in countries where it is approved, supporting the ruggedness of the device.

EER: There are acceptable EERs for all the sites involved in the production and testing of this product and its components, with acceptable recommendations generated from June 1999 – January of 2000, and reconfirmed in this review cycle.

Labeling/Nomenclature: OPDRA consultation was received in the last cycle and their comments were reflected in the previous letter and subsequent labeling negotiations

Otherwise, acceptable labeling has been achieved. The indication has been made more general and in line with other asthma maintenance therapies, with the details of the appropriate population discussed in the Dosage and Administration Section. The sponsor wanted explicit recommendations for [redacted] but have not provided data to support these patients [redacted] therapy, so this wording was not allowed.

Conclusions: This NDA should be approved once all administrative and review issues are finalized (we are awaiting final Master Batch Records, final labeling and carton/container labeling). The sole phase 4 commitment from a clinical standpoint is to resolve the gender interaction issue for fluticasone.

/S/

Robert J Meyer, MD 8/23/00
Director,
Division of Pulmonary and Allergy Drug Products.

APPEARS THIS WAY
ON ORIGINAL

Division Director's Memorandum

Date: Thursday, January 27, 2000
NDA: 21-077
Sponsor: Glaxo Wellcome
Proprietary Name: ADVAIR Diskus (fluticasone propionate/salmeterol xinaphoate inhalation powder).

Introduction: This is a new NDA submitted on March 25th, 1999 to support a line of combination inhalers (Diskus devices – a 60-dose dry powder inhaler) that provide salmeterol xinaphoate 50 mcg (expressed as the base) and either 100, 250 or 500 mcg of fluticasone proprionate in a lactose [redacted] While the Flovent Diskus is approvable and the Serevent Diskus is approved, this is a novel product, being the first fixed-dose combination inhalation product for asthma, combining a long-acting bronchodilator and an inhaled corticosteroid for US marketing.

The division had extensive discussions with the company on the development of this line of related products [redacted] DPADP expressed a number of concerns for such a combination. These concerns included there would need to be a showing for a new combination drug product that it meets the combination regulations (i.e., that both components add to the overall safety and/or efficacy of the combination in a meaningful way). Specific to this line of products and asthma therapy, DPADP expressed concerns about the medical rationale for a fixed combination product for that includes a medication that is commonly and correctly titrated (fluticasone). As a part of developmental discussions, DPADP encouraged the sponsor to submit the 500 mcg product for approval, even though it has no 1:1 fluticasone counterpart and no US studies to support it, to allow more prescribing flexibility to the care-giver in assuring that patient needs are met. It should be noted that since the division did not feel like the long-term safety of the combination products was of particular concern (due to the combination product containing two approved moieties and utilizing lactose and an approved device), the program did not include a long-term, open-label safety study.

Administrative: Three issues bear noting. First, the sponsor asked for a "priority" review status for this application. Since the combination product offers nothing that is not currently obtainable in the U.S. market (i.e., both substances are in currently approved US products) and since the sponsor did not provide evidence to substantiate that there would be better compliance with the combination product, this request was denied by the division with Office concurrence (Dr. Jenkins). Secondly, this application was discussed at a meeting of the Pulmonary and Allergy Drugs Advisory Committee in November 1999, due to the novel nature of this combination product. The committee recommended approval and, despite some advice on labeling particulars and other issues, did not express any substantive concerns about the potential misuse or misunderstanding of this product in general clinical use. Thirdly, this application's 10-month PDUFA goal date was January 25, 2000. However, due to a government shutdown on January 25th and 26th due to inclement weather, the action was delayed until the 27th. It is expected,

however, that due to the unavoidable loss of two days, the action will still be counted as a "10-month" action for PDUFA tracking purposes.

Chemistry/Manufacturing and Controls: See Dr. Koble's review for details. There are remaining CMC issues that preclude approval this cycle, although many appear to be resolvable in the near-term. Not surprisingly, many of these issues are common to other Diskus products, particularly the Flovent Diskus products that are not yet approved again due mainly to CMC considerations.

Pharmacology/Toxicology: Due to this product containing two approved drug substances in a combination that is fairly common clinically (albeit separately administered), there are relatively few unique toxicology issues for this product. The sponsor has satisfactorily addressed the specific combination preclinically and, except for some changes to the proposed package insert, the product is approvable from the Pharm/Tox standpoint.

Biopharmaceutics: The main thrust of the biopharmaceutics program for this product was to assure that the two drugs given together did not significantly interact. The data provided suggest that there is no significant change in the ADME of either drug substance due to the concomitant presence of the other. While not a strict interaction concern, study 3019 did show that the FP exposure from the ADVAIR product (50/500) was somewhat less than that of the Flovent product alone. However, this was not accompanied by any perceivable decrease in efficacy, as the numerical trends favored the combination product on many efficacy measures. There was an apparent gender effect in this same study (males with lower FP exposures than females) but this may well be due to disparate baseline lung function. The sponsor has previously shown that FP exposure from the Flovent products is related to lung function (higher exposures in normals than asthmatics) and the males in 3019 had lower mean baseline FEV1s.

Clinical / Statistical: See Dr. Johnson's primary review and Dr. Elashoff's primary statistical reviews for details. Two of the three most important studies were conducted in the US (Studies 3002 and 3003) and one of them was conducted outside the US (3019). The US studies examined the 50/100 (salmeterol/FP) product and the 50/250 product against each of their respective components administered alone (i.e., Flovent Diskus at the relevant dose and Serevent Diskus) as well as placebo. This design allowed for an assessment of ADVAIR over each component given alone. The replication of the "combination policy" was provided by these two studies. The third study – 3019 – was performed outside the US and compared the 50/500 product against the two single components given together (i.e., Flovent Diskus AND Serevent Diskus), as well as Flovent alone. It did not examine the safety and efficacy of this strength product against salmeterol alone and, given the severity of asthma in these subjects, that is justifiable.

Studies 3002 (in relatively mild-moderate asthmatics) and study 3003 (in somewhat more severe patients) were designed to have a different primary endpoints for the superiority assessment of the combination over each single component comparator (serial FEV_1 against Flovent alone and a.m.trough FEV_1 against salmeterol alone), along with the study "survival" analysis. While it was expected that separate endpoints would be needed for each comparison (e.g., FP vs. Advair, Salmeterol vs. Advair), it turned out that the combination was by and large superior against both single moiety products on *all*

of the endpoints. Therefore, the combination of salmeterol and fluticasone in a single product looked more effective than either component given alone on a variety of primary and secondary endpoints. However, in a post-hoc exploratory analysis, it did not appear that patients who came into study 3002 on salmeterol alone did any better on ADVAIR 50/100 than they did "switching" to Flovent 100 mcg alone. This lends some credence to the concern over what population these products should be indicated for treating (e.g., should patients on beta agonists alone be started on Advair?). Study 3019 showed that the combination product worked similarly to the two single moiety products administered concomitantly (with only a slight numerical advantage to the combination product), but in a superior manner to Flovent 500 mcg alone. In none of the studies was there a signal that the safety profile of the combination product was importantly different from the single moiety products. Overall, these studies supported the safety and efficacy of the three dosage strengths of ADVAIR, with the two US studies offering substantial evidence to meet the combination policy of the FDA.

What the program either didn't address, or to some degree couldn't address, was the putative adherence/compliance advantage of the combination products over the single moiety products prescribed concomitantly. Again, study 3019 showed no advantage in a controlled trial of the combination product over concomitant therapy, but since it is a controlled-trial, this was not a study of real world use. In addition, the program did not really address issues of how to best titrate the medication in the face of changing asthma status, particularly how or when to downward titrate. This is an important issue as 500 mcg twice daily of Flovent (as in the highest dose ADVAIR product) can be suppressive of HPA axis function in some individuals.

Nomenclature: The sponsor proposed trade names that [redacted] (i.e., ADVAIR → Diskus is used for the product containing 50 mcg salmeterol base and 100 mcg of fluticasone propionate). The established name would include a discussion of the dose per blister of each component. While the trade name of ADVAIR is acceptable to both the division and CDER's nomenclature consultants, there is agency concern over the lack of the [redacted] being described in the proposed tradename. Disclosing the [redacted] in the tradename is important for practitioners and patients so that they are aware of the [redacted] and don't simply double the dose of ADVAIR rather than switch to a higher strength should more fluticasone be needed. Our action letter should express that concern and ask for alternative proposals from the sponsor.

EER: There are acceptable EERs for all the sites involved in the production and testing of this product and its components, with acceptable recommendations generated from June 1999 – January of 2000.

Labeling: There will still need to be significant revisions to the labeling prior to this product being approved, but there are a few labeling issues that will be included in this action – including the naming issue. The clinical trials section is lengthy and promotional in tone and will need significant revisions. DDMAC is consulting on the Patient Package Insert and their comments will be incorporated in final labeling. Further, the sponsor will be asked to achieve common labeling for all the Diskus products to the extent possible, to avoid patient confusion when they are switched from one product to another. Also important in this cycle is the DPADP request that the sponsor better state

the indication to make it less circular (i.e., currently the indication in effect states the combination is indicated for asthmatics for whom combination therapy is appropriate) and more descriptive.

Conclusions: This NDA is approvable, pending resolution of the CMC issues and revision of the proposed labeling. 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 a great deal of further data generation.

/S/

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

APPEARS THIS WAY
ON ORIGINAL

INTEROFFICE MEMO

TO: NDA 21077
FROM: C. Joseph Sun, Ph. D. /S/ Jan, 24, 2000
SUBJECT: Team Leader NDA Review Memo
Date: January 24, 2000

The pharmacology and toxicology of salmeterol xinafoate and fluticasone proprianate and the combination drug have been adequately studied and that the drug is approval from a preclinical standpoint.

Salmeterol is a beta 2 adrenergic agonist. Chronic toxicity studies were performed in rats and dogs. Hypoglycemia, ovarian cysts, leiomyoma, and hyperplasia and metaplasia of the larynx were observed in rats. Typical beta 2 adrenergic agonism effects of hypoglycemia, tarchycardia, vasodilatation and papillary fibrosis were seen in dogs. Fibrosis in the heart was also reported in mice administered orally for 18 months.

Salmeterol did not have any effects on fertility nor caused any teratogenic effects in rats. In Dutch rabbits, it produced teratogenic and developmental effects resulting form its beta-adrenergic activity; these included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw fixtures and delayed ossification of the frontal cranial. However, at a higher oral dose, it caused only delayed ossification of the frontal cranial bones in New Zealand White rabbits. It crossed the placenta in mice.

Salmeterol was not genotoxic in four mutagenicity assays (Ames test, mammalian gene mutation assay in Chinese hamster ovary cells, chromosome aberration in human lymphocytes and in vivo rat micronucleus test).

Carcinogenicity studies of salmetereol were conducted in mice (18 months by oral) and rats (24 month by oral and inhalation). In mice, it caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia and leiomyomas of the uterus and ovarian cysts. The incidence of leiomyosarcoma was not statistically significant In rats, similar findings of mesovariun leiomyomas and ovarian cysts were reported. These findings in rodents are typical for beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Fluticasone is a synthetic corticoid with anti-inflammatory activity. Chronic toxicity studies were performed in rats and dogs. Toxicity revealed in both species is typical glucocorticoid activity as evidenced by changes in thymus and adrenal and lymphoid depletion. In rats, keratitis was reported in rats in the 78-week study and 2-year carcinogencity study.

Fluticasone did not impair the fertility in rats. It was teratogenic in mice, rats and rabbits. It excreted in the milk in rats and crossed the placenta in mice, rats and rabbits.

Fluticasone was not genotoxic in four mutagenicity studies (Ames test, forward mutation assay of hamster fibroblast cells, chromosome aberration test of human lymphocytes and in vivo mouse micronucleus test).

Fluticasone demonstrated no carcinogenic potential in a 78-week mouse oral carcinogenicity study and in a 2-year rat inhalation carcinogenicity study.

No unexpected findings other than typical glucocorticoid and beta 2 adrenergic agonism activities were reported in the combination (fluticasone and salmeterol) inhalation studies in dogs and rats. Typical teratogenic effects of salmeterol and fluticasone were reported in the combination teratology studies in mice and rats.

With regarding to labeling, carcinogenesis, mutagenesis and impairment of fertility and pregnancy category C sections on the package insert should be revised as recommended in the review to incorporate the above-mentioned preclinical findings.

There is no outstanding preclinical issues.

CC: Orig. NDA
HFD-570/Division file
HFD-570/Sun
HFD-570/Jani
HFD-570/Sancilio

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21077	**Trade Name:**	ADVAIR DISKUS(SALMETEROL/FLUTICASONE PRO
Supplement Number:		**Generic Name:**	SALMETEROL/FLUTICASONE PROPIONATE INHALA
Supplement Type:		**Dosage Form:**	Powder, ——— Inhalation
Regulatory Action:	AE	**Proposed Indication:**	for the maintenance treatment of asthma ——— in patients 12 years of age and older.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)
____Infants (1-24 Months)
____Children (25 Months-12 years)
____Adolescents (13-16 Years)
_X_Other Age Groups (listed): 12 and above

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	STUDIES needed. Applicant has COMMITTED to doing them
Study Status	Protocols are under discussion. Comment attached

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

AE letter wa sent 1-27-00. Sponsor has submitted "proposed pediatric development plan" for children 4 - 11 years of age

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, PARINDA JANI

S

Signature

2-3-00

Date

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR 2 1 2000

Hugh H. Windom, M.D.
Asthma and Allergy Research Center
1775 Arlington Street
Sarasota, FL 34239

Dear Dr. Windom:

Between August 11 and August 17, 1999, Ms. Lourdes Valentin-Aponte, representing the Food and Drug Administration (FDA) inspected your conduct as the investigator of record of a clinical study (protocol #SFCA3003) of the investigational drug Advair™ Diskus® (salmeterol/fluticasone propionate inhalation powder) that you conducted for Glaxo Wellcome Inc. This inspection is part of FDA's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

At the close of the inspection, Ms. Valentin-Aponte presented her inspectional observations (Form FDA 483) and discussed these observations with you. From our evaluation of the inspection report and your oral responses to the inspectional observations, we conclude that you did not adhere to all pertinent Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. In particular, we note that you failed to maintain adequate Drug Dispensing Records for 3 subjects and adequate records regarding calibration test results for the Spirometer Pulmonary Function Test for 2 subjects.

Please ensure that corrective actions will be taken to prevent similar problems in your current and future studies.

We appreciate the cooperation shown Investigator Ms. Valentin-Aponte during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy (HFD-45)
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, MD 20855

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Paul Chervinsky, M.D.
New England Research Ctr., Inc.
49 State Road
Wattuppa Bldg., Suite 203
North Dartmouth, MA 02747

OCT 29 1999

Dear Dr. Chervinsky:

The purpose of this letter is to inform you of our conclusions concerning your conduct of the clinical study (protocols # SFCA 3002 and SFCA 3003) of salmeterol/fluticasone propionate inhalation powder [Advair™ Diskus®] that you conducted for Glaxo Wellcome Inc.

From August 31 to September 9, 1999, Ms. Constance DeSimone, representing the Food and Drug Administration (Agency), inspected the study identified above. We reviewed (a) the inspection report prepared by Ms. DeSimone, and (b) copies of study records obtained during the inspection. Based on our review, we conclude that you conducted your studies in compliance with the Federal regulations and good clinical practices that apply to clinical studies of investigational new drugs.

This inspection is part of the Agency's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

We appreciate the cooperation shown Ms. DeSimone during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

Bette L. Barton, Ph.D., M.D.
Chief
Good Clinical Practices Branch I (HFD-46)
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

Jani

INTEROFFICE MEMO

TO: NDA 21077
FROM: C. Joseph Sun, Ph. D. /S/ Jan, 24, 2000
SUBJECT: Team Leader NDA Review Memo
Date: January 24, 2000

The pharmacology and toxicology of salmeterol xinafoate and fluticasone proprianate and the combination drug have been adequately studied and that the drug is approval from a preclinical standpoint.

Salmeterol is a beta 2 adrenergic agonist. Chronic toxicity studies were performed in rats and dogs. Hypoglycemia, ovarian cysts, leiomyoma, and hyperplasia and metaplasia of the larynx were observed in rats. Typical beta 2 adrenergic agonism effects of hypoglycemia, tarchycardia, vasodilatation and papillary fibrosis were seen in dogs. Fibrosis in the heart was also reported in mice administered orally for 18 months.

Salmeterol did not have any effects on fertility nor caused any teratogenic effects in rats. In Dutch rabbits, it produced teratogenic and developmental effects resulting form its beta-adrenergic activity; these included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw fixtures and delayed ossification of the frontal cranial. However, at a higher oral dose, it caused only delayed ossification of the frontal cranial bones in New Zealand White rabbits. It crossed the placenta in mice.

Salmeterol was not genotoxic in four mutagenicity assays (Ames test, mammalian gene mutation assay in Chinese hamster ovary cells, chromosome aberration in human lymphocytes and in vivo rat micronucleus test).

Carcinogenicity studies of salmetereol were conducted in mice (18 months by oral) and rats (24 month by oral and inhalation). In mice, it caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia and leiomyomas of the uterus and ovarian cysts. The incidence of leiomyosarcoma was not statistically significant In rats, similar findings of mesovariun leiomyomas and ovarian cysts were reported. These findings in rodents are typical for beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Fluticasone is a synthetic corticoid with anti-inflammatory activity. Chronic toxicity studies were performed in rats and dogs. Toxicity revealed in both species is typical glucocorticoid activity as evidenced by changes in thymus and adrenal and lymphoid depletion. In rats, keratitis was reported in rats in the 78-week study and 2-year carcinogencity study.

Fluticasone did not impair the fertility in rats. It was teratogenic in mice, rats and rabbits. It excreted in the milk in rats and crossed the placenta in mice, rats and rabbits.

Fluticasone was not genotoxic in four mutagenicity studies (Ames test, forward mutation assay of hamster fibroblast cells, chromosome aberration test of human lymphocytes and in vivo mouse micronucleus test).

Fluticasone demonstrated no carcinogenic potential in a 78-week mouse oral carcinogenicity study and in a 2-year rat inhalation carcinogenicity study.

No unexpected findings other than typical glucocorticoid and beta 2 adrenergic agonism activities were reported in the combination (fluticasone and salmeterol) inhalation studies in dogs and rats. Typical teratogenic effects of salmeterol and fluticasone were reported in the combination teratology studies in mice and rats.

With regarding to labeling, carcinogenesis, mutagenesis and impairment of fertility and pregnancy category C sections on the package insert should be revised as recommended in the review to incorporate the above-mentioned preclinical findings.

There is no outstanding preclinical issues.

CC: Orig. NDA
HFD-570/Division file
HFD-570/Sun
HFD-570/Jani
HFD-570/Sancilio

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21077/000
Stamp: 25-MAR-1999
Regulatory Due: 25-AUG-2000
Applicant: GLAXO WELLCOME
5 MOORE DR
RESEARCH TRIANGLE PARK, NC
Priority: 27709
Org Code: 4S

Action Goal:
District Goal: 26-JUN-2000
Brand Name: ADVAIR
DISKUS (SALMETEROL/FLUTICASONE
PRO
Estab. Name:
Generic Name: SALMETEROL/FLUTICASONE
PROPIONATE INHALA

Dosage Form: (AEROSOL)
Strength: 50 UG/100, 250, 500 UG

FDA Contacts: P. JANI (HFD-570) 301-827-1050 , Project Manager
D. KOBLE (HFD-570) 301-827-1066 , Review Chemist
G. POOCHIKIAN (HFD-570) 301-827-1050 , Team Leader

Overall Recommendation: ACCEPTABLE on 24-JAN-2000 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 05-MAY-2000 by M. EGAS (HFD-322) 301-594-0095

Establishment: 9610411
GLAXO OPERATIONS UK LTD
WARE, HERTFORDSHIRE, UK
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE [redacted]
FINISHED DOSAGE MANUFACTURER
Profile: ADM OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	07-JUN-1999				EGASM
SUBMITTED TO DO	07-JUN-1999	10D			EGASM
ASSIGNED INSPECTION '	25-JUN-1999	GMP			EGASM
ASSIGNED INSPECTION '	01-JUL-1999	GMP			RKIMMEL
INSPECTION SCHEDULED	10-NOV-1999		18-NOV-1999		IRIVERA
INSPECTION PERFORMED	17-NOV-1999		17-NOV-1999		IRIVERA
DO RECOMMENDATION	24-JAN-2000			ACCEPTABLE INSPECTION	EGASM
OC RECOMMENDATION	24-JAN-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM
SUBMITTED TO OC	04-MAY-2000				KOBLED
SUBMITTED TO DO	04-MAY-2000	10D			EGASM
DO RECOMMENDATION	05-MAY-2000			ACCEPTABLE BASED ON FILE REVIEW	EGASM
BASED ON EI OF 11/17/99					
OC RECOMMENDATION	05-MAY-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Profile: CRU OAI Status: NONE
Estab. Comment: [redacted] OF SALMETEROL XIANFOATE AND FLUTICASONE PROPIONATE (BUILDING A). MANUFACTURE, PACKAGING, AND QUALITY CONTROL OF DRUG PRODUCT (BUILDINGS U,S, P, AND A). MICROBIOLOGICAL TESING (BUILDING N10).

STABILITY TESTING IS PERFORMED IN BUILDINGS P AND N10 AT THE PRIORY STREET ADDRESS AND BUILDING 5 AT THE PARK ROAD ADDRESS. (on 28-MAY-1999 by D. KOBLE (HFD-570) 301-827-1066)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-JUN-1999				KOBLED
OC RECOMMENDATION	07-JUN-1999			ACCEPTABLE	EGASM

26-JUN-2000

25-AUG-2000
GLAXO WELLCOME
4S
570

Priority:
Org Code:
Application Comment: FUR (on 03-MAY-2000 by D. KOBLE (HFD-570) 301-827-1066)

		BASED ON PROFILE	
SUBMITTED TO OC	04-MAY-2000		KOBLED
SUBMITTED TO DO	04-MAY-2000 10D		EGASM
DO RECOMMENDATION	05-MAY-2000	ACCEPTABLE	EGASM
		BASED ON FILE REVIEW	
BASED ON EI OF 11/17/99			
OC RECOMMENDATION	05-MAY-2000	ACCEPTABLE	EGASM
		DISTRICT RECOMMENDATION	

Establishment: 9611205
GLAXO WELLCOME
2262
JURONG, , SN

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment: SYNTHESIS OF SALMETEROL XIANAFOATE (BUILDING 2). (on 28-MAY-1999 by D. KOBLE (HFD-570) 301-827-1066)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-JUN-1999				KOBLED
SUBMITTED TO DO	07-JUN-1999	GMP			EGASM
ASSIGNED INSPECTION	25-JUN-1999	GMP			EGASM
INSPECTION PERFORMED	29-JUN-1999		29-JUN-1999		EGASM
DO RECOMMENDATION	24-JAN-2000			ACCEPTABLE INSPECTION	EGASM
OC RECOMMENDATION	24-JAN-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM
SUBMITTED TO OC	04-MAY-2000				KOBLED
OC RECOMMENDATION	04-MAY-2000			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: 9610421
GLAXO WELLCOME LTD
DL128DT
BARNARD CASTLE, , UK

DMF No: AADA:
Responsibilities: FINISHED DOSAGE STABILITY TESTER
Profile: CTL OAI Status: NONE -
Estab. Comment: STABILITY TESTING IS PERFORMED IN BUILDING L BLOCK (on 28-MAY-1999 by D. KOBLE (HFD-570) 301-827-1066)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator

SUBMITTED TO OC	06-JUN-1999		KOBLED
OC RECOMMENDATION	07-JUN-1999	ACCEPTABLE BASED ON PROFILE	EGASM
SUBMITTED TO OC	04-MAY-2000		KOBLED
OC RECOMMENDATION	04-MAY-2000	ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: 9610414
GLAXO WELLCOME OPERATIONS UK
DA1 5AH
DARTFORD, KENT, UK
DMF No: AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CTL OAI Status: NONE
Estab. Comment: MICROBIOLOGICAL TESITING IN BUILDING 320. (on 28-MAY-1999 by D. KOBLE (HFD-570) 301-827-1066)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-JUN-1999				KOBLED
SUBMITTED TO DO	07-JUN-1999	GMP			EGASM
ASSIGNED INSPECTION	25-JUN-1999	GMP			EGASM
INSPECTION SCHEDULED	29-JUN-1999		11-JUN-1999		EGASM
INSPECTION PERFORMED	29-JUN-1999		11-JUN-1999		EGASM
DO RECOMMENDATION	12-JUL-1999			ACCEPTABLE INSPECTION	EGASM
BASED ON EI OF 6/1-11/99 COVERING NDA 19-489/S-019					
OC RECOMMENDATION	12-JUL-1999			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM
SUBMITTED TO OC	04-MAY-2000				KOBLED
OC RECOMMENDATION	04-MAY-2000			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: 9617236
GLAXO WELLCOME SPAIN SA
28760
TRES CANTOS, MADRID, SP
DMF No: AADA:
Responsibilities: FINISHED DOSAGE STABILITY TESTER
Profile: CTL OAI Status: NONE
Estab. Comment: STABILITY TESTING IS PERFORMED IN BUILDING A (on 28-MAY-1999 by D. KOBLE (HFD-570) 301-827-1066)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-JUN-1999				KOBLED
OC RECOMMENDATION	07-JUN-1999			ACCEPTABLE BASED ON PROFILE	EGASM
SUBMITTED TO OC	04-MAY-2000				KOBLED
OC RECOMMENDATION	04-MAY-2000			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: 9610419
GLAXOCHEM LTD
DD10 8EA
MONTROSE ANGUS, SCOTLAND, UK

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment: SYNTHESIS OF SALMETEROL XIANAFOATE (BUILDINGS 77 SOUTH, 101, 117, AND 129) AND FLUTICASONE PROPIONATE (BUILDINGS 78, 85, AND 88). (on 28-MAY-1999 by D. KOBLE (HFD-570) 301-827-1066)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-JUN-1999				KOBLED
SUBMITTED TO DO	07-JUN-1999	GMP			EGASM
ASSIGNED INSPECTION '	25-JUN-1999	GMP			EGASM
INSPECTION SCHEDULED	10-NOV-1999		03-DEC-1999		IRIVERA
INSPECTION PERFORMED	24-JAN-2000		03-DEC-1999		EGASM
DO RECOMMENDATION	24-JAN-2000			ACCEPTABLE INSPECTION	EGASM
OC RECOMMENDATION	24-JAN-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM
SUBMITTED TO OC	04-MAY-2000				KOBLED
OC RECOMMENDATION	04-MAY-2000			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: [redacted]

DMF No: AADA:
Responsibilities: [redacted]
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-JUN-1999				KOBLED
OC RECOMMENDATION	07-JUN-1999			ACCEPTABLE BASED ON PROFILE	EGASM
SUBMITTED TO OC	04-MAY-2000				KOBLED
OC RECOMMENDATION	04-MAY-2000			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: [redacted]

DMF No: AADA:
Responsibilities: [redacted]
Profile: CTL OAI Status: NONE
Estab. Comment: [redacted] (on 28-MAY-1999 by D. KOBLE (HFD-570) 301-827-1066)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-JUN-1999				KOBLED
SUBMITTED TO DO	07-JUN-1999	GMP			EGASM
ASSIGNED INSPECTION '	25-JUN-1999	GMP			EGASM
INSPECTION SCHEDULED	22-JUL-1999		05-AUG-1999		IRIVERA
INSPECTION PERFORMED	09-AUG-1999		05-AUG-1999		IRIVERA
DO RECOMMENDATION	29-OCT-1999			ACCEPTABLE INSPECTION	ADAMSS
OC RECOMMENDATION	29-OCT-1999			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

SUBMITTED TO OC	04-MAY-2000			KOBLED
OC RECOMMENDATION	04-MAY-2000		ACCEPTABLE	EGASM
			BASED ON FILE REVIEW	
FUR				

Establishment: 9611905
LABORATOIRES GLAXO
27000
EVREUX, CEDEX, FR

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE [redacted]

Profile: CRU OAI Status: NONE

Estab. Comment: [redacted] OF SALMETEROL XINAFOATE AND FLUTICSONE PROPIONATE (BUILDING D). (on 28-MAY-1999 by D. KOBLE (HFD-570) 301-827-1066)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-JUN-1999				KOBLED
SUBMITTED TO DO	07-JUN-1999	GMP			EGASM
DO RECOMMENDATION	10-AUG-1999			ACCEPTABLE	EGASM
				BASED ON FILE REVIEW	
BASED ON EI OF 3/1-4/99 COVERING CRU					
OC RECOMMENDATION	10-AUG-1999			ACCEPTABLE	FERGUSONS
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	04-MAY-2000				KOBLED
OC RECOMMENDATION	04-MAY-2000			ACCEPTABLE	EGASM
				BASED ON PROFILE	

Establishment: [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile: CTL OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-JUN-1999				KOBLED
OC RECOMMENDATION	07-JUN-1999			ACCEPTABLE	EGASM
				BASED ON PROFILE	
SUBMITTED TO OC	04-MAY-2000				KOBLED
OC RECOMMENDATION	04-MAY-2000			ACCEPTABLE	EGASM
				BASED ON FILE REVIEW	
FUR					

APPEARS THIS WAY
ON ORIGINAL