CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-077

CORRESPONDENCE

GlaxoWellcome

February 25, 2000

Robert J. Meyer, M.D., Director
Division of Pulmonary and Allergy Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Food and Drug Administration
HFD-570, Room 10B-3
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-077; ADVAIR™ DISKUS® (salmeterol/fluticasone propionate inhalation powder)

Amendment to Pending Application
Response to Approvable Letter of January 27, 2000

Dear Dr. Meyer:

Reference is made to the Agency's letter of January 27, 2000, in which it was stated that NDA 21-077 was found to be approvable, and to our letter of February 3, 2000, in which we stated our intent to file an amendment to fully respond to the remaining issues for the approval of ADVAIR DISKUS. Reference is also made to our submissions of February 10.(2) and teleconferences of February 7, 8, 18 and 24, 2000.

This amendment to NDA 21-077 provides complete responses to the comments presented in the Agency's letter of January 27. To facilitate review this submission is organized into 3 parts:

Volume 1
Part I: Responses to CMC Questions # 1-10.

Volume 2
Part I: Responses to CMC Questions #11-16, and 19.c.

Volume 3
Part II: Responses to Labeling Questions # 17-30
Part III: Labeling: Revised package insert (clean and revision-marked versions),
Revised patient information leaflet (PIL) (clean and revision-marked versions),
Revised device, overwrap, and carton Labels,
Electronic copies of package insert and PIL.

A more detailed table of contents follows.

Glaxo Wellcome Research and Development
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709
Telephone
919 483 2100
A Division of
Glaxo Wellcome Inc

WITHHOLD 45 PAGE (S)

Draft
Labeling

GlaxoWellcome

BL

DUPLICATE

January 13, 2000

Robert J. Meyer, M.D., Director
Division of Pulmonary Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Food and Drug Administration
HFD-570, Room 10B-3
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-077; ADVAIR™ DISKUS® (salmeterol/fluticasone propionate inhalation powder)

Response to FDA Request/Comment: Revised Draft Labeling
Patent Information (Updated Item 13)

Dear Dr. Meyer:

In the Agency's fax dated October 21, 1999 to NDA 20-236 (**SEREVENT®** Inhalation Aerosol) and NDA 20-692 (**SEREVENT® DISKUS®**), revisions were requested to standardize the presentation of information in the CLINICAL PHARMACOLOGY: Pharmacokinetics section of the labeling. In the same fax, it was requested that the draft labeling currently under review by the Agency for the three strengths of **ADVAIR DISKUS** be similarly revised to standardize the CLINICAL PHARMACOLOGY Pharmacokinetics and Pharmacodynamics subsections.

In accordance with the Agency's request, please find enclosed (Attachment 1) both paper copies and electronic files (using Microsoft® WORD 97) for the following:

Draft Package Insert: revised clean version
Draft Package Insert: revision-marked version
Patient's Instructions for Use: clean version identical to that submitted in the submission of August 30, 1999 (resubmitted here for completeness only).

APPEARS THIS WAY
ON ORIGINAL

Glaxo Wellcome Research and Development

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

Telephone
919 483 2100

A Division of
Glaxo Wellcome Inc.

Advair Diskus Labeling History

Date of Submission	Labeling Component Modified
March 24, 1999	Original NDA draft labeling
August 30, 1999	All labeling: Generic name modified across all labeling. Draft Package Insert: • DESCRIPTION • HOW SUPPLIED • Patent Number and Copyright Patient's Instructions for Use Overwrap labels Carton labels Device labels
October 13, 1999	Draft Package Insert: • INDICATION AND USAGE • CLINICAL TRIALS • ADVERSE REACTIONS • DOSAGE AND ADMINISTRATION
January 13, 2000	Draft Package Insert: • CLINICAL PHARMACOLOGY

Revised Patent Information

At this time we are also amending Item 13 of NDA 21-077 pursuant to 21 CFR 314.53 to reflect those patents applicable to Advair Diskus which should be listed in the U.S. Department of Health and Human Services "Orange Book" of Approved Drug Products, pending approval of the NDA. Revised patent information is provided in Attachment 2 to this letter.

This submission is submitted in duplicate. If you have any questions, I may be reached by calling (919) 483-5211.

Sincerely,

Joy E. Ferrell

Joy E. Ferrell
Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

cc: Ms. Parinda Jani., HFD-570

WITHHOLD 44 PAGE (S)

Draft labeling

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 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 APPLICATIONS 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 SAF
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

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: FOI

Phone Number: _____

Fax Number: _____

FROM: Parinda Jani

AP letter NDA 21-077

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

CDER Pulmonary Group (HFD-570), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1050 FAX: (301) 827-1271

Total number of pages, including cover sheet: _____ Date: 8-24-00

COMMENTS:

OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA # 21077 Drug ADVAIR DISKUS (salmeterol xinafoate/fluticasone propionate inhalation powder
DATE January 27, 2000
Applicant_ Glaxo Wellcome Inc. CSO Parinda Jani /Phone (301) 827-1064

User Fee Goal Date: January 25, 2000

Arrange package in the following order:	Check or Comment
1. ACTION LETTER with supervisory signatures Are there any Phase 4 commitments?	AP___ AE_✓_ NA___ Yes_____ No_____
2. Have all disciplines completed their reviews? If no, what review(s) is/are still pending?	Yes_✓_ No_____
3. Completed copy of this CHECKLIST in package	Chem/Ther Types__3S__
4. LABELING (package insert and carton and container labels). (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)	Draft_✓_ Revised Draft_____ Final_____
5. PATENT INFORMATION	✓
6. EXCLUSIVITY CHECKLIST	✓
7. PEDIATRIC PAGE	✓
8. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992).	✓
9. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status. If no audits were requested, include a memo explaining why.	✓
10. REVIEWS:	
DIVISION DIRECTOR'S MEMO (If more than 1 review for any discipline, separate reviews with a sheet of colored paper. Any conflicts between reviews must have resolution documented)	✓
GROUP LEADER'S MEMO	✓
MEDICAL REVIEW	✓
SAFETY UPDATE REVIEW	✓
STATISTICAL REVIEW	✓
BIOPHARMACEUTICS REVIEW	✓
PHARMACOLOGY REVIEW (Include pertinent IND reviews)	✓
Statistical Review of Carcinogenicity Study(ies)	NA
CAC Report/Minutes	NA
CHEMISTRY REVIEW	✓
Labeling and Nomenclature Committee Review Memorandum	✓
Date EER completed 1/24/00_____ (attach signed form or CIRTS printout) FUR needed _____ FUR requested _____	OK_✓_ No_____
Have the methods been validated?	Yes (attach)_____ No_✓_
Environmental Assessment Review / FONSI (EXEMPTION)	Review _____ FONSI_____
MICROBIOLOGY REVIEW What is the status of the monograph?	_____
11. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes	✓
12. MINUTES OF MEETINGS Date of End-of-Phase 2 Meeting _____ Date of pre-NDA Meeting _____	_____
13. ADVISORY COMMITTEE MEETING MINUTES or, if not available, 48-Hour Info Alert or pertinent section of transcript.	Minutes_____ Info Alert_____ Transcript_✓_ No mtg____
14. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS	NA
15. If approval letter, has ADVERTISING MATERIAL been reviewed? If no and this is an AP with draft labeling letter, has advertising material already been requested?	Yes_____ No_____ Yes, documentation attached_____ No, included in AP ltr _____
16. INTEGRATED SUMMARY OF EFFECTIVENESS	_____
17. INTEGRATED SUMMARY OF SAFETY	_____

Jani

NDA 21-077

MAR - 2 2000

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

Attention: Joy E. Farrell
Director, Regulatory Affairs

Dear Ms. Farrell:

We acknowledge receipt on February 25, 2000, of your February 25, 2000, resubmission to your new drug application (NDA) for ADVAIR DISKUS ——— (salmeterol 50 mcg/ fluticasone propionate 100 mcg inhalation powder), ADVAIR DISKUS ——— (salmeterol 50 mcg/fluticasone propionate 250 mcg inhalation powder) and ADVAIR DISKUS ——— (salmeterol 50 mcg/fluticasone propionate 500 mcg inhalation powder).

This resubmission contains additional chemistry, manufacturing, and controls (CMC) information submitted in response to our January 27, 2000, action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is August 25, 2000.

If you have any questions, contact me at (301) 827-1064.

Sincerely yours,

/S/

Parinda Jani
Project Manager
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-077
HFD-570/Div. Files
HFD-570/P.Jani
HFD-570/Johnson
HFD-570/Meyer
HFD-570/Sancilio
HFD-570/Koble
HFD-570/Sun
HFD-570/Elashoff
HFD-570/Wilson
HFD-570/Uppoor
HFD-570/Chen
HFD-570/Poochikian
DISTRICT OFFICE

Drafted by: pj/February 29, 2000
Initialed by: gtrout/3-1-00
final: jani/3-1-00
filename: n21077ak.rs

CLASS 2 RESUBMISSION ACKNOWLEDGEMENT (AC)
(DDR: Update the user fee goal date based on the class of resubmission.)

APPEARS THIS WAY
ON ORIGINAL

Jani

APR 8 1999

NDA 21-077

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

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

Dear Dr. Jones:

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

Name of Drug Products: ADVAIR DISKUS ——— (salmeterol xinafoate 50 mcg/fluticasone propionate 100 mcg inhalation powder)
ADVAIR DISKUS ——— (salmeterol xinafoate 50 mcg/fluticasone propionate 250 mcg inhalation powder) and
ADVAIR DISKUS ——— (salmeterol xinafoate 50 mcg/fluticasone propionate 500 mcg inhalation powder)

Therapeutic Classification: Standard (S)

Date of Application: March 24, 1999

Date of Receipt: March 25, 1999

Our Reference Number: 21-077

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 24, 1999, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be January 25, 2000, and the secondary user fee goal date will be March 25, 2000.

APPEARS THIS WAY
ON ORIGINAL

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). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study 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 10 days from the date of this letter. We will notify you within 120 days of receipt of your response 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" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary Drug Products, HFD-570
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21077
HFD-570/Div. Files
HFD-570/P.Jani
HFD-570/Schumaker/4-6-99
DISTRICT OFFICE

Drafted by: pj/March 29, 1999
Initialed by:
final:
filename: c:\my documents\n21077.akn

/S/

4-7-99

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Tom Gerdy

Phone Number: (919) - 483- 9884

Fax Number: (919) 315 - 8940

FROM: Parinda Jani

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

CDER Pulmonary Group (HFD-570), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1050 FAX: (301) 827-1271

Total number of pages, including cover sheet:_____ Date: 8/24/00

COMMENTS:

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TRANSMISSION OK

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RESULT	OK

Memorandum of Telephone Facsimile Correspondence

Date: August 9, 2000

To: Tom Gerding
Regulatory Affairs

From: Parinda Jani
Project Manager

Through: Guirag Poochikian, Ph.D.
Chemistry Team Leader

/S/

Subject: Comments for NDA 21-077

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

Memorandum of Telephone Facsimile Correspondence

Date: August 9, 2000

To: Tom Gerding
Regulatory Affairs

From: Parinda Jani
Project Manager

Through: Guirag Poochikian, Ph.D.
Chemistry Team Leader

/S/

Subject: Comments for NDA 21-077

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

NDA 21-077/ADVAIR DISKUS
Draft CMC comments

Memorandum of Telephone Facsimile Correspondence

Date: August 2, 2000

To: Joy Ferrell
Regulatory Affairs

From: Parinda Jani
Project Manager

Subject: Labeling comments/NDA 21-077

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

1. Replace the slash in the established name with "and" consistently throughout the labeling, packaging and promotional materials.

2. Compress the ADVAIR portion of the Pharmacodynamics subsection of the CLINICAL PHARMACOLOGY section to

[ ]

3. For Studies 1, 2, and 3 in the Clinical Trials subsection of the CLINICAL PHARMACOLOGY section, include baseline FEV_1 and PEFR, where appropriate, data for each treatment group.

4. In the Clinical Trials subsection of the CLINICAL PHARMACOLOGY section, include Ns at week 0, 6, 12, and endpoint for Figure 1. For Figure 2, change ——— to " Week" and add Ns at the same timepoints. Add Ns for Figures 3 and 4.

5. Additional comments regarding the Clinical Trials subsection of the CLINICAL PHARMACOLOGY section are pending.

6. Revise the WARNINGS section (black box and other text) to retain information regarding the potential hazards associated with titrating patients off of oral corticosteroids, while reflecting that ADVAIR DISKUS should not be used during this process.

7. Revise Table 3 in the ADVERSE REACTIONS section based on Studies 1 and 2 only. Use an incidence of ≥ 3 percent to identify the relevant events.

8. Modify Tables 4 and 5 to reflect the correct tradename (i.e., ——— vs 100/50).

P.01

TRANSACTION REPORT

JUL-18-2000 TUE 02:27 PM

DATE START	RECEIVER	TX TIME	PAGES	TYPE	NOTE	M#	DP
JUL-18 02:26 PM	919193158940	49"	2	SEND	OK	119	

TOTAL : 49S PAGES: 2

BEST POSSIBLE COPY

Memorandum of Telephone Facsimile Correspondence

Date: July 18, 2000

To: Tom Gerding
Regulatory Affairs

From: Parinda Jani
Project Manager

Through: Craig Bertha Ph.D. for Guirag Poochikian, Ph.D.
Chemistry Team Leader

Subject: Comments for NDA 21-077

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW

Orig NDA -21-077
Div file - 570
570 - Jani, Koble, Poochikian

Memorandum of Telephone Facsimile Correspondence

Date: July 18, 2000

To: Tom Gerding
Regulatory Affairs

From: Parinda Jani
Project Manager

Through: Craig Bertha Ph.D. for Guirag Poochikian, Ph.D. 7/18/00
Chemistry Team Leader

Subject: Comments for NDA 21-077

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

NDA 21-077/ADVAIR DISKUS
Draft CMC comments

APPEARS THIS WAY
ON ORIGINAL

N21-077 JANI

Memorandum of Telephone Facsimile Correspondence

Date: May 15, 2000

To: Tom Gerding
Regulatory Affairs

/S/ 5/15/00

From: Parinda Jani
Project Manager

Subject: Comments for the QOL studies

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

cc: Div File
CSO

APPEARS THIS WAY
ON ORIGINAL

NDA 21-077

All information requests described below pertain to the datasets "PECONNEW.SD2" for Studies 3002 and 3003.

1. Clarify whether the overall quality of life score was the average of all 32 questions, or the average of the domain averages.

2. For Studies 3002 and 3003, define the variable PHETY and the values "D24" and "D16". In Study 3003, some of the PHETY values are missing. Describe what this means.

3. In Study 3003, out of 29,932 responses for the variable QUESRLT, 4,244 (14%) answers were letters (i.e. "A", "AM", "CL", "C", "CI", "D", "DM", "E", "F", "H", "K", etc.). Define these codes.

4. Study 3002, Patient #120 had a result for Question #3 = "C". Clarify.

5. The AQLQ has values 1-32, and the questions following the AQLQ at Visit 10/11 has values 33-40. In Study 3003, the variable QUESNO has values 1-43, 2A-2F, 3A-3H, and 8A-8J. To what questions are the values in the dataset for QUESNO 41-43, 2A-2F, 3A-3H and 8A-8J referring?

6. Study 3002, Patient #45 has answers for Questions #33, 34 and 35 at Visit 2 (SESS=2). The answers are all numeric:

   33. 2
   34. 1
   35. 2

   Since there are only 32 questions at Visit 2, please explain. (Note: I checked to make sure the Visit 10/11 answers were not coded incorrectly as Visit 2 answers.)

7. When a patient had >25% missing data within a domain, the patient was given a missing value for that domain. When were patients assigned missing values for the overall quality of life score? Describe the patients who were assigned missing values for the overall quality of life score.

MESSAGE CONFIRMATION

03/30/00 12:58
ID=PULMONARY DIV FDA

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
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APPEARS THIS WAY
ON ORIGINAL

03/30/00 12:57 PULMONARY DIV FDA → 919193150033 NO.131 P01

Memorandum of Telephone Facsimile Correspondence

Date: March 30, 2000

To: Joy Farrell
Regulatory Affairs

From: Parinda Jani
Project Manager

Subject: Comments for the Trade name

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Memorandum of Telephone Facsimile Correspondence

Date: March 30, 2000

To: Joy Farrell
Regulatory Affairs

From: Parinda Jani
Project Manager

Subject: Comments for the Trade name

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

APPEARS THIS WAY
ON ORIGINAL.

NDA 21-077

The trade name for ADVAIR should be revised as follows for all the product labelings.

ADVAIR DISKUS 100/50
(fluticasone propionate 100 mcg and salmeterol* 50mcg inhalation powder)
*As salmeterol xinafoate salt 72.5mcg, equivalent to salmeterol base 50 mcg

Jani

MESSAGE CONFIRMATION

11/02/99 15:48
ID=PULMONARY DIV FDA

NO.	MODE	BOX	GROUP
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DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
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Orig NDA 21.077
Div file - 570
570 / Jani

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Joy Farrell

Phone Number: 919-483-5211

Fax Number: 919-315-0033

FROM: Pamela Jani

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

CDER Pulmonary Group (HFD-570), 5600 Fishers Lane
Rockville, Maryland 20857

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Joy Farrell

Phone Number: 919-483-5211

Fax Number: 919-315-0033

FROM: Pamela Tam

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

CDER Pulmonary Group (HFD-570), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1050 FAX: (301) 827-1271

Total number of pages, including cover sheet: 3 **Date:** 11-2-98

COMMENTS:

Discussion Background for the Committee –

For a fixed-combination drug to meet regulatory requirements, the following must be demonstrated (21 CFR 300.50):

> *Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effect and the dosage of each component (amount, frequency) is such that the combination is safe and effective for a significant patient population requiring concurrent therapy as defined in the labeling.*

The sponsor's proposed indication states [redacted]

A few key discussion points

- Given the variability of asthma and clinical circumstances which arise in the treatment of asthmatics, what are the advantages and limitations of a fixed-dose combination in the practice setting?

- Is the inability to titrate with a single strength of Advair (i.e., to increase the number of puffs temporarily for increased symptoms) an important limitation that will be acceptable in actual use and understood by patients and caregivers?

- How will caregivers and patients best assess the optimal corticosteroid dose in the face of an effective long-acting bronchodilator to assure that the fluticasone component is neither overdosed nor underdosed?

Questions for the PADAC regarding ADVAIR (salmeterol xinafoate/fluticasone propionate inhalation powder) NDA 21-077:

1. Given the efficacy data presented for the combination compared to its components alone and the hypothesized benefit of increased convenience and compliance, do the benefits of ADVAIR as a fixed-dose combination outweigh its risks?

IF YES (Questions 2 – 4):

2. For what population of asthmatics should this product be indicated?

   - Patients inadequately controlled on short-acting beta agonists alone?
   - Patients inadequately controlled on inhaled corticosteroids alone?
   - Patients inadequately controlled on short and long-acting beta agonists?
   - Patients already well-controlled on ICS and salmeterol?

3. Do you recommend any additions or changes to the sponsor's proposed labeling on how this product might best be used in practice?

4. What, if any, Phase 4 studies should be <u>required</u> to address the safe and effective use of this product in the general population?

IF NO:

5. What additional studies or data would the sponsor need to provide to gain approval for ADVAIR?

<u>Pediatrics</u>:

6. Fluticasone propionate inhalation powder is approved down to age 4 (Flovent Rotadisk) at either 50 mcg or 100 mcg twice daily, salmeterol xinaphoate inhalation powder (Serevent Diskus) is also approved down to age 4 at a dose of 50 mcg twice daily.

   Given the prior approval of both Flovent and Serevent in the pediatric population down to age 4 and given the data discussed for Advair, what studies would you recommend the sponsor conduct to provide adequate data for ADVAIR use in the pediatric population (e.g., what dosage strength for the combination, what control groups, what age ranges)?

Jani

MESSAGE CONFIRMATION

Orig NDA - 21-077.
DIV file 1520
5w/Jani

10/29/99 14:08
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10/29/99 14:06 PULMONARY DIV FDA → 919193150033 NO.594 D01

Memorandum of Telephone Facsimile Correspondence

Date: October 29, 1999

To: Joy Farrell
Regulatory Affairs

From: Parinda Jani
Project Manager

Subject: Draft questions for the PADAC meeting

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Memorandum of Telephone Facsimile Correspondence

Date: October 29, 1999

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Regulatory Affairs

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Thank you.

APPEARS THIS WAY
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Jani

MESSAGE CONFIRMATION

Orig NDA 21077
Div file 570
570 / Jani

10/15/99 15:21
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10/15/99 15:19 PULMONARY DIV FDA → 919193158319 NO.522 P01

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Joy Farrell

Phone Number: 919-483-5211

Fax Number: 919 ~~483~~ 315 -8319

FROM: Pamela Jani

DIVISION OF PULMONARY

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Joy Farrell

Phone Number: 919-483-5211

Fax Number: 919-~~483~~ 315-8319

FROM: Pamela Tawi

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

CDER Pulmonary Group (HFD-570), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1050 FAX: (301) 827-1271

Total number of pages, including cover sheet: 3 **Date:** 10-15-99

COMMENTS:

Memorandum of Telephone Facsimile Correspondence

Date: October 15, 1999

To: Joy Ferrell
Director, Regulatory Affairs

From: Parinda Jani
Project Manager

/S/

Through: Steve Wilson, Ph.D.
Biostatistics, Team Leader

Subject: Comments for NDA 21-077/ADVAIR DISKUS

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

APPEARS THIS WAY
ON ORIGINAL

Memorandum of Telephone Facsimile Correspondence

Date: September 8, 1999

To: Joy Ferrell
Director, Regulatory Affairs

From: Parinda Jani
Project Manager /S/

Through: Steve Wilson, Ph.D.
Biostatistics, Team Leader 9/8/99

Subject: Comments for NDA 21-077/ADVAIR DISKUS

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

Jani

Orig NDA 21-077.
DIV file 520 - Jani

MESSAGE CONFIRMATION

09/17/99 13:07
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09/17	00'42"	919 315 0033	CALLING	02	OK	0000

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09/17/99 13:06 PULMONARY DIV FDA → 919193150033 NO.370 D01

Memorandum of Telephone Facsimile Correspondence

Date: September 17, 1999

To: Joy Ferrell
Director, Regulatory Affairs

From: Parinda Jani
Project Manager

Through: Steve Wilson, Ph.D. /S/ for SW 9/17/99
Biostatistics, Team Leader

Subject: Comments for NDA 21-077/ADVAIR DISKUS

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS

Memorandum of Telephone Facsimile Correspondence

Date: September 17, 1999

To: Joy Ferrell
Director, Regulatory Affairs

From: Parinda Jani
Project Manager

/S/ per AW 9/17/99

Through: Steve Wilson, Ph.D.
Biostatistics, Team Leader

Subject: Comments for NDA 21-077/ADVAIR DISKUS

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

APPEARS THIS WAY
ON ORIGINAL

NDA 21-077

1. As per our conversation, I checked for a date variable in INVYN. There is no date variable in the dataset INVYN. Is there another dataset with a date variable for each visit? If not, please submit a dataset with the following variables: SUBJECT, VISIT, DATE.

2. Also, as per our conversation, I went back and checked the two datasets INCLEXCL and INVYN to determine if the value of LSTVISIT in INCLEXCL was much greater than that of the last visit in INVYN. (Glaxo had stated that for 16 patients, it probably was 1 visit off.) In Study 3002, the value for LSTVISIT in the dataset INCLEXCL is more than 2 visits greater than the last visit in the dataset INVYN for 58 patients. (For 30 of these 58 patients, the difference is ≥ 7 visits.) I've listed the data from the dataset INVYN for one of the 58 patients in the table below. (Note, I did not count the instances when the value for LSTVISIT was *less than* the value of the last visit in INVYN because Glaxo stated in the telecon that LSTVISIT referred to the last visit that the patient had met all the protocol rules, not just the continuation criteria. Please confirm my understanding of this situation.)

Subject #2 has a value of 10 for LSTVISIT in dataset INCLEXCL. In the table below, it appears that this patient should have had a value of 3 for LSTVISIT.

Table 1: Study 3002 Subject #2 in the dataset INVYN

SUBJECT	OCC1	ELIG	SESS
2	1	Y	2
2	2	Y	2
2	3	Y	2
2	4	Y	2
2	5	Y	2
2	6	Y	2
2	7	Y	2
2	1	Y	3
2	2	Y	3
2	3	N	3
2	4	Y	3

As far as I can tell, there is no more data after SESS 3 for this patient in this dataset.

Please check my work and address this inconsistency.

/s/

Meeting Date: July 21, 1999 **Time:** 12:30-1.30 PM
Location: Conference Room "C" **IMTS #:** 4296
Sponsor: Glaxo Wellcome, Inc.
NDA: 21-077
Product: ADVAIR DISKUS

FDA Attendees:

Barbara Elashoff	Biostatistics Reviewer
Lydia Gilbert-McClain, M.D.	Medical officer
Parinda Jani	Project Manager
John K. Jenkins, M.D.	Office Director, ODE II
Susan Johnson, Pharm.D., Ph.D.	Medical Officer
Dale Koble, Ph.D.	Chemistry Reviewer
Guirag Poochikian, Ph.D.	Chemistry Team Leader
Robert Meyer, M.D.	Acting Division Director
Steve Wilson, Ph.D.	Statistician, Team Leader

Glaxo Attendees:

Elaine Jones, Ph.D.	Product Director, Regulatory Affairs
Rick Kent, M.D.	VP, US Medical Operations and Chief Medical Officer
John Morgan, Ph.D.	Director, Regulatory Affairs
Kathleen Prodan	Director, Regulatory Affairs
Tushar Shah, M.D.	Director, Respiratory Clinical research
Richard Wolgemuth, Ph.D.	VP, Regulatory Affairs

Background: NDA 21-077 was submitted on March 24, 1999. The applicant requested a "Priority Review", and upon preliminary review it was decided that the NDA did not qualify for a "Priority Review." GW was informed of this decision on May 18, 1999. As a follow-up, GW requested this meeting to better understand why ADVAIR did not meet the criteria for a priority review, and explore the options for achieving an interactive review to gain approval of ADVAIR in the first review cycle (i.e., 10 or 12 months).

The determination of Priority (P) vs. Standard (S) review for a particular application is made by the Medical Team leader by the 45 day filing meeting.

Definition of Priority Review per MAPP 6020.3: The drug product, if approved, would be a significant improvement compared to marketed products [approved (if such is required), including non-"drug" products/therapies] in the treatment, diagnosis, or prevention of a disease. Improvement can be demonstrated by, for example: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment limiting drug reaction; (3) documented (emphasis added) enhancement of patient compliance; or (4) evidence of safety and effectiveness of a new subpopulation.

The Agency stated that the rationale submitted for Priority Review is based on first and third component of the above definition for Priority Review.

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of disease: Salmeterol and fluticasone are both approved and marketed in multiple inhalation formulations, including DPIs. Even if a combination product is not available, concomitant use of these products is possible. Therefore, the combination therapy is available, just not as a single product.

- Documented (emphasis added) enhancement of patient compliance: There is no documentation of increased compliance. The application does contain some data that relates to this issue, however, all the non-US studies for this product used concomitant therapy of salmeterol/fluticasone separately administered as a control for the ADVAIR product. In the summary data from these studies, there is no evidence to show a clear clinical superiority of the combination over the concomitantly administered components, except minor numerical advantages. Therefore, the application will be reviewed as a "Standard" NDA.

GW believes there would considerable benefit of this product when approved, and questioned how it can interact with the Agency, especially with the CMC reviewer, to get ADVAIR approved in the first review cycle.

The Agency responded that most of the crucial CMC issues related to ADVAIR, were raised with other DISKUS products. GW should go through all the applications for consistency, and make sure that all the comments are addressed adequately. If there have been any changes, their relationship to previous applications should be explained in details. The Agency acknowledges that the CMC issues are the most complex of the review process. It is the Agency's policy to share the comments with the applicant, once a review is completed.

GW stated that currently, the Agency has ——— Flovent Diskus NDAs, under review, and — are due before ADVAIR Diskus NDA, whether ——— would help the Division to prioritize its workload in terms of GW applications.

The Agency declined to comment on ——— The Agency stated that the goals and priorities are set based on the User Fee due date and all pending review work, ———

In addition, the Agency stated that even though ADVAIR may have better efficacy (a review issue), there are following general safety concerns with the combination product.

- **The dose titration of the steroid component**. The issue is not only whether a patient should be on fluticasone component or not, but whether the patient is prescribed enough fluticasone. A patient would require a new prescription for another strength of ADVAIR for the titration of the corticosteroid component.

- **Overdosing of the salmeterol component**. There are concerns with patients double-dosing and hence getting high dose of salmeterol component. There are cardiac safety concerns with high dose of salmeterol.

There will be specific questions for the Pulmonary and Allergy Advisory Committee for the safety concerns with the combination product.

GW stated that the general prescribing practice is to use a combination product instead of prescribing the individual components. GW believes that the population that will benefit from this product outweighs the risk. GW believes that the safety issues that the Agency has raised could be addressed through labeling and educational efforts, and an Advisory Committee meeting to get answers for these issues may not be necessary.

Conclusion:

- The decision regarding the PADAC meeting will be made by end of August. GW will be informed of the date.

- GW will submit an updated CMC package during the first week of September. The package will include responses to the CMC issues raised with other DISKUS products that should be addressed for ADVAIR.

- Additional stability data will be submitted by the end of September.

/S/

Parinda Jani
Project Manager

APPEARS THIS WAY
ON ORIGINAL

CC:
ORIG NDA 21-077
DIV FILE/HFD-570
HFD-570/KOBLE/8-24-99
HFD-570/POOCHIKIAN
HFD-570/JOHNSON/8-30-99
HFD-570/MEYER/9-7-99
HFD-570/ELASHOFF/8-24-99
HFD-570/WILSON/9-1-99
HFD-102/JENKINS/8-31-99
HFD-570/JANI/8-24-99

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Joni

MESSAGE CONFIRMATION

09/08/99 11:10
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09/08	03'05"	919 315 0033	CALLING	07	OK	0000

Orig NDA 21-077
Div file / 570
570 / Joni

09/08/99 11:06 PULMONARY DIV FDA → 919193150033 NO.305 P01

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Joy Ferrell

Phone Number: 919-483-5211

Fax Number: 919-315-0033

FROM: Pamela Joni

NDA 21-077

The following questions pertain to both Studies 3002 and 3003.

1. The study report states that there were patients who did not meet the "continuation criteria" at a visit but continued in the study. (Volume 55, page 60 and Volume 64, page 52). Does the study report state how many times this happened and at which centers?

2. The dataset INVYN (identified as the "continuation criteria dataset") includes a variable called OCC1 that has four values per visit (1-4). I assume this variable is referring to the 4 continuation criteria the patients had to meet at each visit in order to continue. Is the value of the variable "ELIG" a "Y" if the patients met the criterion and an "N" if they didn't? There are no values for any patient after an "N" was recorded at a visit. Since the study reports state that there were patients who continued in the study after not meeting all of the criteria, I assume the values after an "N" was recorded were deleted. Is this right?

3. In the INCLEXCL dataset (identified as "Status in efficacy population") there is a variable called "LASTVST" – which is labeled "Last evaluable visit" in the Proc Contents. I assumed this variable would tell me the visit number that the patient last met the evaluation criteria. However, this number did not correspond to the visit before the visit labeled "N" in the INVYN dataset.

4. I couldn't find dates for any of the visits except first and last visits. Can you tell me where this information is in the datasets?

WITHHOLD 40 PAGE (S)

draft labeling

Jan1

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM TO THE FILE

DATE: April 29TH 1999

FROM: Robert J. Meyer, MD, Medical Team Leader DPDP /S/

TO: NDA 21-077 FILE

SUBJECT: REQUEST FOR PRIORITY REVIEW FOR THE SALMETEROL / FLUTICASONE COMBINATION PRODUCT

According to MAPP 6020.3, the determination of Priority (P) vs. Standard (S) review for a particular application is to be made by the Medical Team Leader by the 45 day filing meeting. This determination is to be done in consultation with other disciplines involved in the review, along with the Division Director. To document the Medical Team Leader's opinion, this memo is being constructed to place in the file..

MAPP Definition:

P – Priority review
The drug product, if approved, would be a significant improvement compared to marketed products [approved (if such is required), including non-"drug" products/therapies] in the treatment, diagnosis, or prevention of a disease. Improvement can be demonstrated by, for example: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment limiting drug reaction; (3) documented [emphasis added] enhancement of patient compliance; or (4) evidence of safety and effectiveness of [sic] a new subpopulation.

The sponsor's rationale, contained in their cover letter, stems on the 1st and 3rd components of this definition. The problem with invoking the first item is that both drug substances are approved and marketed in multiple inhalation formulations, including DPIs. Therefore, concomitant use is possible, even if a combination product is not currently available. So despite what superficially looks to be very impressive efficacy results of Advair over its separate (i.e., non-concomitant) components, combination therapy is available, just not in a single product.

The third item related to compliance is also invoked by the sponsor, but always with conditional terms - such as "may" enhance patient acceptance and compliance. They have no documentation of increased compliance, for which the MAPP explicitly calls. The NDA does contain some data that relate to this issue, however. All the non-US studies for this product used concomitant therapy of salmeterol/fluticasone separately administered as a control for the Advair product. In the summary data from these studies, there is no evidence to show a clear clinical superiority of

the combination over the concomitantly-administered components (though there are minor numerical advantages seen for the combination product over the concomitantly administered components).

Finally, although not invoked by the sponsor, neither of the other MAPP criteria for P designation – i.e., enhanced safety or a new subpopulation treated – apply.

In summary, it is my recommendation that the sponsor's request for a "P" designation be denied on the grounds that the NDA fails to meet the criteria in MAPP 6020.3.

cc:
Orig NDA 21-077
Div file/570
570/ Jones, Meyer Johnson, Elashoff, Wilson, Sheridan
Sancho, Sun, Kobb, Poochikian, Chen, Uppoor, Jenkins

APR 28 1999

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
DIVISION OF PHARMACEUTICAL EVALUATION II

Date: April 22, 1999

To: Project Manager, Ms. Parinda Jani (HFD-570)

Through: Director, Mei-Ling Chen, Ph.D. (HFD-870)
Deputy Director, Mr. John Hunt (HFD-870)
Team Leader, Ramana Uppoor Ph.D. (HFD-870) /S/ 04/28/99

From: Tien-Mien Chen, Ph.D. (HFD-870) /S/ 04/26/99

RE: Filing Meeting for NDA 21-077 (ADVAIR Diskus; Salmeterol/Fluticasone Propionate Combination DPI Product) Code: 4S

SYNOPSIS:

On 03/24/99, GlaxoWellcome (GW) submitted an original NDA 21-077 (ADVAIR Diskus) for review. This is a combination DPI (dry powder inhalation) product of salmeterol (Sal)/fluticasone propionate (FP). The sponsor is seeking approval for three strengths, 50/100, 50/250, and 50/500 μg. ADVAIR Diskus contains Sal and FP in lactose. The only differences among the three strengths are the amounts of FP ——

Sal is reported as a long-acting β-adrenergic agonist and its products have been reviewed and approved under NDA 20-236 (Serevent Inhalation Aerosol) on 02/04/94 and under NDA 20-692 (Serevent Diskus Inhaler) on 09/19/97. Sal is indicated for the maintenance treatment of asthma and in prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease.

FP is a synthetic, trifluorinated corticosteroid reportedly to possess potent anti-inflammatory activity and its products have also been reviewed and approved under NDA 20-548 (Flovent Inhalation Aerosol) on 03/27/96 and NDA 20-549 (Flovent Rotadisk Dry Powder Inhaler) on 11/07/97. FP is indicated for prophylactic therapy of asthma in patients 12 years of age and older. NDA 20-770 (Flovent Rotadisk Dry Powder Inhaler) was later approved for children 4 to 12 years old. NDA 20-833 (Flovent Diskus Dry Powder Inhaler) was concluded to be approvable for patients 4 years of age and older in the Agency's 03/31/99 letter.

ADVAIR Diskus is a combination product of Sal/FP designed to benefit the patients to produce a greater improvement in pulmonary function and symptom control than Sal or FP used alone at their recommended dosages. The combination product is indicated for the maintenance treatment of asthma _____ in patients 12 years of age and older by orally inhaled route only. It is NOT indicated for the relief of acute bronchospasm. The recommended dosing regimen is one inhalation BID. For starting dose and the highest recommended dose of ADVAIR Diskus based on prior antiasthma therapy, please see the proposed package insert (PI) in Attachment 1 for details.

Under Human Pharmacokinetics/Bioavailability section of this NDA, there were 6 pharmacokinetic (PK) studies submitted. Three had been reviewed previously which included a single-dose study using ADVAIR Diskus 50/100 µg. The 3 new PK studies are considered to be pivotal for the following comparisons, i.e.,

1) A multiple-dose, incomplete block, crossover study for ADVAIR 50/250 µg BID vs. Sal 50 µg BID vs. FP 250 µg BID vs. placebo for 11 days in male and female normal volunteers (Study No. **SFCB1004**),
2) A single-dose, crossover study for ADVAIR Diskus 2x 50/500 µg vs. concurrent administration of Sal 2x 50 µg and FP 2x 500 µg vs. FP 2x 500 µg alone in male and female normal volunteers (Study No. **SFCB1005**), and
3) A multiple-dose, parallel study for ADVAIR 50/500 µg BID vs. concurrent administration of Sal 50 µg and FP 500 µg BID vs. FP 500 µg BID alone for 196 days in male and female asthmatic patients (Study No. **SFCB3019**, a PK section obtained from a pivotal clinical trial).

Three strengths of ADVAIR Diskus were employed in the single-dose and multiple-dose PK studies and also in clinical trials. However, the PK comparison of Sal/FP combination product vs. concurrent administration of Sal + FP via BID dosing was done only for the highest combination strength Sal/FP 50/500 µg (Study No. SFCB 3019). Strictly speaking, there is no PK study conducted to investigate the dose proportionality regarding FP 100, 250, and 500 µg using the combination products. Interstudy comparison for FP 100, 250, and 500 µg doses using combination products was done, although it is less than ideal. Drug-Drug interaction (DDI) of Sal on FP (concurrent administration of Sal/FP vs. FP alone) was assessed in most of the PK studies. However, due to assay limitation for plasma Sal levels, no Sal arm alone was employed in most of the pivotal PK studies. Very limited plasma levels for Sal were obtained (10-30 min postdose) and analyzed for DDI of FP on Sal (C_{max} data mainly) in Study Nos. SFCB1004 and SFCB1005.

Pharmacodynamic (PD) effects of Sal and FP were also monitored in most of the studies. However, no PK/PD relationships were analyzed. Finally, the clinically tested formulations are the same as the to-be-marketed ones and both assay methods for Sal and FP are provided.

RECOMMENDATION:

GW's NDA 21-077 for ADVAIR Diskus (a combination Sal/FP DPI product) that was submitted on 03/24/99 has been briefly reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB is of the opinion that the NDA is acceptable for filing. The following Comment needs to be conveyed to the sponsor ASAP.

COMMENT: (Needs to be sent to the sponsor)

It is recommended that electronic format of package insert and Item 6 Human PK/Bio summary plus summary section of each individual study report be submitted in order to facilitate the review.

APPEARS THIS WAY
ON ORIGINAL

cc: HFD-870 (T.M. Chen, R. Uppoor, J. Hunt, M.L. Chen)

Jani

Division of Pulmonary Drug Products APR 6 1999

ADMINISTRATIVE REVIEW OF NDA

Application Number:	NDA 21-077
Name of Drug Products;	ADVAIR DISKUS —— (salmeterol xinafoate 50 mcg/fluticasone propionate 100 mcg inhalation powder) ADVAIR DISKUS —— (salmeterol xinafoate 50 mcg/fluticasone propionate 250 mcg inhalation powder) and ADVAIR DISKUS —— (salmeterol xinafoate 50 mcg/fluticasone propionate 500 mcg inhalation powder)
Sponsor:	Glaxo Wellcome Inc.
Submission Date:	March 24, 1999
Receipt Date:	March 25, 1999

Background: Glaxo Wellcome has submitted this NDA to support the use of ADVAIR DISKUS for the maintenance treatment of asthma ———— in patients 12 years of age and older.

The following complete documents and information are submitted by the sponsor.

1. FDA form 356h.
2. FDA form 3397 (User Fee Cover Sheet).
3. Letter Of Authorization – ————
4. Letter of Authorization – ————
5. Letter of Authorization - ————
6. Letter of Authorization – ————
7. Letter of Authorization - ————
8. Letter of Authorization – ————
9. Letter of Authorization – ————
10. Index to the archival copy of the application.
11. Debarment Certification
12. Financial Disclosure
13. Marketing Exclusivity Request (3 Years)

14. Field Copy Certification

15. Patent Information

U.S.Patent #	Expiration Date	Form of Patent Claims
4,992,474	February 12, 2008	Drug Product/Methods of Use
5,225,445	February 12, 2008	Methods of Use
5,380,922	January 10, 2012	Drug Product/Process of Production
5,126,375	February 12, 2008	Drug Product and Compositions Thereof
D342,994	January 4, 2008	Product Administration System
4,335,121	November 14, 2003	Drug product
5,270,305	September 7, 2010	Drug Product
5,860,419	March 1, 2011	Product Administration System
5,590,645	March 1, 2011	Product Administration System
5,873,360	February 23, 2016	Product Administration System

16. Establishment Information in Tabular Form

17. Application summary

a. Rationale for Combination Product/Justification for Priority Review
b. Proposed labeling (draft and annotated)
c. Pharmacological Class, Scientific Rationale, Intended Use and Potential Clinical Benefits summary
d. Foreign marketing history
e. Chemistry, Manufacturing and Controls summary
f. Non-clinical Pharmacology and Toxicology summary
g. Human Pharmacokinetics and bioavailability summary
h. Clinical Data summary and Results of Statistical Analysis
j. Risk/benefit summary

18. List of Supportive INDs and NDAs (INDs: [redacted] NDAs: 20-121; 20-548; 20-549; 20-770; 20-833; 20-236; and 20-692).

19. CRFs and CRTs

/S/

Parinda Jani
Project Manager

CC:
ORIG NDA 21-077
DIV FILE/HFD-570
HFD-570/JANI/3-30-99

/S/
1/6/99

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications
Evidence Review Branch IV

Consult Response

TO: Parinda Jani, Project Manager
HFD: 570

Re: **NDA :** 21-077
SPONSOR: Glaxo Wellcome
PROPRIETARY NAME: Advair
USAN/Established Name: Salmeterol/fluticasone propionate Diskus inhaler
CATEGORY OF DRUG: Asthma
ROUTE: Oral inhaler

SUBMISSION:
Document date:
CDER stamp date:
Branch IV receipt date:
Submission type: HRQL protocol

REVIEWER: Iris P. Masucci, PharmD
REVIEW DATE: December 29, 1999

This consult provides comments on the use of the Asthma Quality of Life Questionnaire (AQLQ) used in Protocols SFCA 3002 and 3002 evaluating salmeterol/fluticasone propionate Diskus inhalation powder for the maintenance treatment of asthma.

Overview of submission

Results of the AQLQ from these two studies would not be available for use in promotion because their evaluation was not part of an integrated data analysis plan. The measurement of health-related quality of life endpoints in clinical studies should follow the same standards for scientific rigor as measurement of any other clinical outcome if the trial is to support labeling or advertising claims. Adequate and well-controlled clinical trials should have an *a priori* data analysis plan that includes all study endpoints. AQLQ data cannot be evaluated separately from other endpoints in the study.

In addition, the analysis plan should include any necessary adjustments for multiple comparisons. The analysis of multiple endpoints may increase the probability of a type I error (i.e., incorrectly concluding that a difference between treatments exists). All sources of alpha-level inflation due to multiple endpoints and other multiplicities should be prospectively identified and strategies for dealing with these multiple comparisons should be prospectively identified in the protocol.

Recommended regulatory action

These comments should be relayed to the sponsor

SIGNED: Branch IV Reviewer: _____ **Date:** 1/11/00

Concur: _____ **Date:** 1-12-00

CC: HFD-42 Masucci/Branch IV Chron File/Hankin/Doc Room NDA 21-077
HFD-570 Johnson/Jani

APPEARS THIS WAY
ON ORIGINAL

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

REQUEST FOR CONSULTATION

TO: *(Division/Office)* Biometrics (HFD-570)			FROM: Dale L. Koble	
;-99	IND NO.	NDA NO. 21-077	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 29-SEP-99
NAME OF DRUG Advair Diskus		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG 3s	DESIRED COMPLETION DATE 03-JAN-00
NAME OF FIRM Glaxo Wellcome Inc.				

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER	✗ CHEMISTRY ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABLITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ *IN-VIVO* MAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

The NDA holder has submitted statistical analysis of the drug product stability data.. Please review the submitted information and provide a recommendation concerning the appropriateness of the statistical analysis:

Expiry estimation: (1) Summary provided in the introduction to the amendment in Vol. 8.1 (2) Vol. 8.1, Section G6 (pages 120 – 128) (3) Vol. 8.3, Appendix G2 (pages 21-193). Please note that the applicant has proposed two statistical methods.

Comparison of primary batches to commercial batches: Vol. 8.1, Section G1.6 (pages 5-9).

cc:
NDA # 21-077
'0/Div. File
atlN21077.con

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)* ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Memorandum to the File

NDA: 21-077

Product: Advair Diskus 100/50, 250/50, and 500/50

Sponsor: Glaxo Wellcome, Inc.

The sponsor has requested categorical exclusion under 21 CFR 25.31(b), which is acceptable.

/S/

Parinda Jani
Project Manager

APPEARS THIS WAY
ON ORIGINAL

/S/

for LSM 3/4/2000

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
(Division/Office) PharmTox/HFD-570			FROM: Dale L. Koble	
DATE March 3, 00	IND NO.	NDA NO. 21-077	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 25-FEB-00
NAME OF DRUG Advair		PRIORITY CONSIDERATION 3	CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE
NAME OF FIRM Glaxo Wellcome, Inc.				

/S/ 3/3/00

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE-NDA MEETING	X 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	☐ OTHER *(Specify below)*
☐ MEETING PLANNED BY _____		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABLITY 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 SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*:

Please provide a recommendation concerning the adequacy of the safety information concerning the colorant in the mouthpiece of the device submitted in response to Question 12a of the approvable letter dated 27-JAN-00. A copy of the information provided in the submission dated 25-FEB-00 is attached.

CC: ☒ Orig. NDA ☒ HFD-570 Div. File ☒ CSO/Pijani	☒ Chemist/ Dkoble X TL/GPoochikian
SIGNATURE OF REQUESTER /S/ 2/3/00	METHOD OF DELIVERY *(Check one)* ☐ MAIL x HAND
SIGNATURE OF REQUESTER	SIGNATURE OF DELIVERER

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

REQUEST FOR CONSULTATION

TO: *(Division/Office)* DPADP/pharmacolgy/toxicology

FROM: Dale Koble

12/15/99	IND NO.	NDA NO. 21-077	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 8/30/99
NAME OF DRUG Advair Diskus		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG 4S	DESIRED COMPLETION DATE 1/3/00

NAME OF FIRM: Glaxo Wellcome

REASON FOR REQUEST

/S/ for GP 12/15/99

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ NTROLLED STUDIES TOCOL REVIEW .IER	☐ CHEMISTRY ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABLITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ *IN-VIVO* MAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
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- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

Safety qualification of the colorants used in the Diskus device components, including the mouthpiece is provided on pages 186-189 of Vol. 6.1 of the amendment dated 30-AUG-99. Please review the information provided and provide a recommendation concerning the adequacy of the safety qualification of the colorants.

cc:
Orig. NDA # 21-077
HFD-570/Div. File
570/DKoble/GPoochikian/LSancilio/Lcobbs
onN21077co.doc

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SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION

TO: *(Division/Office)* HFD-570 Pharmacology/Toxicology			FROM: Dale L. Koble, Ph.D.	
DATE 8/20/99	IND NO.	NDA NO. 21-077	TYPE OF DOCUMENT Origin. NDA	DATE OF DOCUMENT 24-MAR-99
NAME OF DRUG ADVAIR		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG ASTHMA	DESIRED COMPLETION DATE 10/20/99

NAME OF FIRM GLAXO/WELLCOME

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ *IN-VIVO* MAIVER REQUEST

IV. DRUG EXPERIENCE

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- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

DRUG SUBSTANCE IMPURITIES: The drug substance specifications for impurities are referenced by the application to NDA 20-236 (Serevent MDI) for salmeterc xinafoate and NDA 20-121 (Flonase Nasal Spray). A comparison of the proposed specifications with NDA 20-236 and NDA 20-549 (Flovent Rotadisk, approvec following approval of Flonase Nasal Spray) indicates nearly identical specifications for individual impurities. The fluticasone impurities specifications were found acceptable by pharmacology/toxicology (review dated 9/5/97 and addendum dated 9/24/97 by Larry Sancilio). However, impurity [redacted] in salmeterol xianafote although included in the specifications for NDA 20-236, was not included in the consult request to pharmacology/toxicology dated 8/17/92 or in the pharmacolog toxicology review dated 11/8/92 (see attached information for the structure of this impurity). **Please provide a safety recommendation on the specification fo impurity** [redacted]

DRUG PRODUCT IMPURITIES: The only individual degradation impurity specification proposed for the drug product [redacted] Thi impurity was qualified at this level for Serevent Diskus (NDA 20-692; review dated 12/21/91 by Larry Sancilio; see attached information);

cc:
Orig. NDA # 21-07
HFD-570/DivFile
HFD-570/DKoble
HFD-570/GPoochikian
HFD-570/PJani

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DRAFT LABELING