CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20692

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JAN 1 4 1997

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,692 **Submission Date:** June 18, 1996
October 8, 1996

Drug Name, Dose and Formulation: Serevent MDPI Diskus (Salmeterol xinafoate) inhalation powder, 50 μg salmeterol (as xinafoate) per dose

Sponsor: Glaxo Wellcome Inc., 5 Moore Drive, Research Triangle Park, NC-27709

Reviewer: Venkata Ramana S. Uppoor, Ph.D.

Type of Submission: New Drug Application, 3S

BACKGROUND:

Serevent Diskus contains salmeterol xinafoate which is a long-acting β-agonist used in the treatment of upper respiratory tract diseases mainly in mild to moderate asthma. Salmeterol is approved in U.S. as an oral inhalation aerosol (Serevent Inhalation Aerosol which is a CFC MDI). The sponsor has been developing 2 dry powder formulations for this drug, one is Serevent Rotadisk (Diskhaler) under IND and the other being Serevent Multidose Powder Inhaler Diskus (MDPI) under IND . The sponsor for business reasons (upon merger with Burroughs Wellcome) decided not to continue development of the Diskhaler and wants to use the clinical data generated from the Diskhaler along with few other studies to support the approval of the NDA for the Diskus (MDPI). The agency agreed that this is acceptable provided the sponsor conducts a pharmacokinetic study to compare the plasma concentrations of salmeterol following Diskhaler and Diskus.

Serevent Diskus inhalation powder is a specially designed plastic device containing a double-foil blister strip of a powder presentation (60 blisters/strip) of salmeterol xinafoate intended for oral inhalation only. Each blister contains 50 μg of salmeterol as the xinafoate made up to 12.5 mg with lactose.

II. OBJECTIVES

This submission is an NDA to request approval for Serevent Diskus inhalation powder (50 μg bid) for the maintenance treatment of asthma and the prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma, who require treatment with inhaled, short-acting β_2-agonists.

III. PHARMACOKINETIC / BIOAVAILABILITY STUDIES

The pharmacokinetics of salmeterol have been studied following administration via Serevent MDI and Serevent Rotadisk. Studies conducted using Serevent MDI were previously submitted in the NDA for the MDI. Two PK studies conducted using Serevent Rotadisk (using the 25 mg lactose fill formulation) are submitted in this application. These will not be reviewed here since the formulations used are not relevant. A pivotal PK study comparing Serevent MDI, Serevent Rotadisk

(12.5 mg lactose fill formulation) and Serevent Diskus has been submitted as an amendment in October 1996. This review includes the study summary of the pivotal study SLGB1004 (given below) and sponsor's proposed labeling for this product (Attachment I).

STUDY SUMMARY:

STUDY SLGB1004, report GCP/96/035: SINGLE DOSE PHARMACOKINETICS STUDY

A STUDY TO COMPARE PEAK PLASMA CONCENTRATIONS OF SALMETEROL FOLLOWING SINGLE INHALED DOSES OF SALMETEROL XINAFOATE ADMINISTERED TO HEALTHY SUBJECTS BY METERED DOSE INHALER, DISKHALER AND DISKUS INHALER.

Reference: Volume 1 - 1 of submission date, October 8, 1996
Investigator:
Study Location:

Objective:
1. To compare the peak and time to peak plasma concentrations of salmeterol after administration of salmeterol xinafoate by the MDI, reduced-fill Diskhaler and final device Diskus inhaler.
2. A preliminary study (Part I) was performed to identify the appropriate sampling time schedule for the main study.

Drug supply:
Salmeterol inhaler 25 µg 200 dose MDI (batch # W0194MC)
Salmeterol reduced-fill Diskhaler 50 µg Rotadisks (batch # 002)
Salmeterol Diskus inhaler 50 µg 60 dose (batch # U95/328A).

Study design:
This study consisted of 2 parts. Part I was a single dose, open-label, one-period study with two subjects receiving 400 µg salmeterol administered by means of the MDI. Part II consisted of a single dose, open-label, randomized, 3-period crossover design with 12 subjects each receiving 200 µg salmeterol administered by means of MDI, reduced-fill Diskhaler and final device Diskus inhaler. The washout between the drug administrations was at least 6 days. 14 healthy volunteers (2 males in part I and 6 males and 6 females in part II) of age 18 - 50 years participated in the study.

The treatment administration was as follows: Both subjects in part I of the study received one single dose of 400 µg salmeterol xinafoate as 16 inhalations from a 25 µg per inhalation MDI. Subjects in part II received 3 single doses of 200 µg salmeterol xinafoate as:
A. 8 inhalations from a 25 µg per inhalation MDI.
B. 4 inhalations from a 50 µg per inhalation reduced-fill Diskhaler.
C. 4 inhalations from a 50 µg per inhalation final device Diskus inhaler.

The MDI treatment was given at 30 second intervals during part II, while the dry powder treatments were given at 60 second intervals. Dosing was completed within 3.5 minutes in part II.

Blood was collected in part I at 0, 10, 15, 20, 30, 40 and 50 minutes and at 1, 1.5, 2, 3, 4, and 6 hours post-dose. Based on the results of this study, sampling times for part II were selected and blood was collected in part II at 0, 5, 8, 12, 15, 20, 30, 40 and 50 minutes and at 1, 2, and 3 hours post-dose. Plasma sample analysis was conducted using a validated LC/MS method to determine salmeterol concentrations.

Pharmacokinetic parameters, AUC_{last}, C_{max} and t_{max} were derived using standard non-compartmental analysis. Log transformed AUC_{last} and C_{max} were analyzed using ANOVA allowing for the effects due to subject, period and treatment. The analysis of t_{max} was carried out using Wilcoxon signed rank test. 90% confidence intervals were also computed.

Results:

ANALYTICAL METHOD AND ASSAY PERFORMANCE: Assay conducted by Dept. of Bioanalysis, Glaxo Wellcome, Beckenham, UK.

The analytical method used is acceptable.

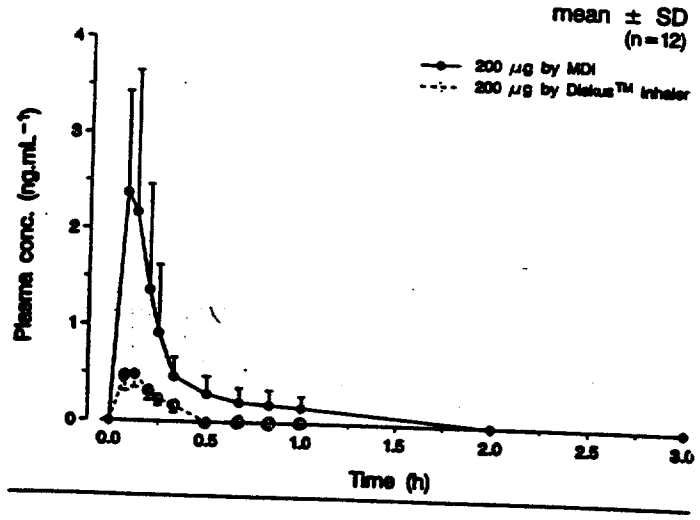
Results of part I showed that peak concentrations were achieved at the first sampling time of 10 minutes. Based on this, appropriate sampling time points for part II were selected.

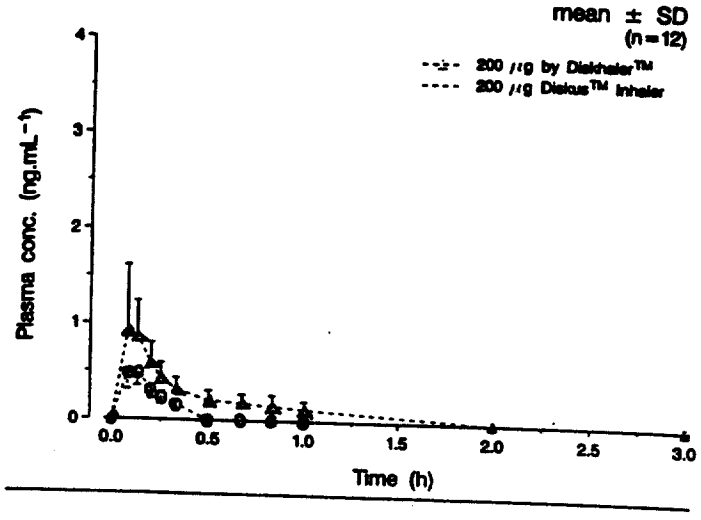
Results of part II:

Mean PK parameters (and %CV), and 90% confidence intervals following single dose administration of salmeterol xinafoate via MDI, Diskhaler and Diskus are shown in the following table.

Parameters	Treatment	Arithmetic mean (%CV)	Ratio	Point estimate	90% C.I.
C_{max} (ng/ml)	A: MDI	2.44 (55.7)	B/A	0.44	0.32 - 0.60
	B: Diskhaler	1.02 (67.2)	*C/A*	***0.26***	***0.19 - 0.36***
	C: Diskus inhaler	0.55 (28.1)	C/B	0.59	0.43 - 0.82
AUC_{last} (ng.hr/ml)	A: MDI	0.752 (71.4)	B/A	0.58	0.38 - 0.89
	B: Diskhaler	0.394 (69.1)	*C/A*	***0.31***	***0.20 - 0.47***
	C: Diskus inhaler	0.225 (79.8)	C/B	0.53	0.35 - 0.81
		Median (range) for T_{max}	Diff.		
T_{max} (hr)	A: MDI	0.08 (0.08 - 0.20)	B-A	0.00	
	B: Diskhaler	0.13 (0.08 - 0.13)	*C-A*	***0.00***	
	C: Diskus inhaler	0.11 (0.08 - 0.13)	C-B	0.00	

Mean plasma concentration-time curves of salmeterol following MDI, Diskhaler and Diskus are shown in the following figures:





• MDI
o DISKUS
△ DISKHALER

CONCLUSION: Both C_{max} and AUC_{last} were significantly lower when salmeterol was given via dry powder formulations as compared to MDI. C_{max} and AUC was also significantly lower after administration of salmeterol from Diskus than the Diskhaler. T_{max}, however is comparable across all the three dosage forms. Terminal rate constant could not be calculated because of secondary peaks and absence of clear terminal phase in certain cases.

IV. COMMENTS TO THE MEDICAL OFFICER

Pharmacokinetics of salmeterol could not be determined due to low concentrations achieved following administration of salmeterol by inhalation. Although the assay methodology is quite sensitive with a limit of quantitation of _ _ , the entire plasma concentration-time profile could not be characterized. However, it is still important from a safety perspective, to determine the peak plasma concentrations and compare to that of the currently marketed Serevent inhalation aerosol (MDI). The pivotal study SLGB1004 was carried out to compare the concentrations achieved with Diskus (final formulation), MDI and the Diskhaler. Results indicate that the peak concentrations and AUC of salmeterol achieved via Diskus are lower than those of MDI and Diskhaler. This indicates lower systemic absorption. Whether this is due to less deposition in lungs (which might lead to lower efficacy) or less deposition in the oropharyngeal region cannot be discerned from this study.

V. LABELING COMMENTS

Plasma concentrations mentioned in the label under a) the pharmacokinetics section and b) use in nursing mothers' section is not based on the pivotal study SLGB1004. This information is obtained from Diskhaler, not the Diskus. The labeling should be modified to include data obtained from study SLGB1004. This will reflect plasma concentrations achieved using the Diskus (product of this NDA).

VI. RECOMMENDATION

This submission has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and is found to be acceptable. The systemic availability of salmeterol following administration via Serevent Diskus is lower than that of MDI and Diskhaler. Please forward the above labeling comment to the sponsor.

Uppoor 01/09/97

Venkata Ramana S. Uppoor, Ph.D.
Division of Pharmaceutical Evaluation-I

FT Initialed by Dale Conner, Pharm.D. DC 1/14/97

CC list:
HFD-570: NDA 20,692; HFD-570: Division file; HFD-570: CSO\Parinda Jani;
HFD-570: Medical Reviewer\Susan Johnson; HFD-570: Chemist; HFD-570: Pharmacologist;
HFD-870: Dale Conner; HFD-870: John Hunt; HFD-870: ChenMe; HFD-860: Marroum;
HFD-850: Biopharm\Lesko; HFD-870: Chron; HFD-870: Drug; HFD-870: Reviewer;
HFD-860: Venkata Ramana S. Uppoor; HFD-340: Viswanathan.

CM

14 pages

PURGED

(Draft Labeling)

JUL 10 1996

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,692 **Submission Date:** June 18, 1996

Drug Name, Dose and Formulation: Serevent MDPI Diskus (Salmeterol xinafoate) inhalation powder, 50 μg salmeterol (as xinafoate) per dose

Sponsor: Glaxo Wellcome Inc., 5 Moore Drive, Research Triangle Park, NC-27709

Reviewer: Venkata Ramana S. Uppoor, Ph.D.

Type of Submission: New Drug Application, 3S

ISSUE: 21-day Filing

BACKGROUND:

Serevent Diskus contains salmeterol xinafoate which is a long-acting β-agonist used in the treatment of upper respiratory tract diseases mainly in mild to moderate asthma. Salmeterol is approved in U.S. as an oral inhalation aerosol (Serevent Inhalation Aerosol which is a CFC MDI). The sponsor has been developing 2 dry powder formulations for this drug, one is Serevent Rotadisk under INL and the other being Serevent Multidose Powder Inhaler Diskus (MDPI) under IND . The sponsor for business reasons (upon merger with Burroughs Wellcome) decided not to continue development of the Rotadisk and wants to use the clinical data generated from the Rotadisk along with few other studies to support the approval of the NDA for the multidose powder inhaler product (MDPI).

Serevent Diskus inhalation powder is a specially designed plastic device containing a double-foil blister strip of a powder presentation (60 blisters/strip) of salmeterol xinafoate intended for oral inhalation only. Each blister contains 50 μg of salmeterol as the xinafoate made up to 12.5 mg with lactose.

II. OBJECTIVES

This submission is an NDA to request approval for Serevent Diskus inhalation powder (50 μg bid) for the maintenance treatment of asthma and the prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma, who require treatment with inhaled, short-acting β_2-agonists.

III. PHARMACOKINETIC / BIOAVAILABILITY STUDIES

The pharmacokinetics of salmeterol have been studied following administration via Serevent MDI and Serevent Rotadisk. Studies conducted using Serevent MDI were previously submitted in the NDA for the MDI. Two PK studies conducted using Serevent Rotadisk (using the 25 mg lactose fill formulation) are submitted in this application. A PK study comparing Serevent MDI, Serevent Rotadisk (12.5 mg lactose fill formulation) and Serevent Diskus is being conducted. The study report will be provided by the 4-month safety update. The summary table of studies submitted is provided in attachment I. The sponsor has also submitted the analytical method validation report.

IV. COMMENTS

1. Studies to investigate the pharmacokinetics of salmeterol following administration via Serevent powder formulations have been conducted. Despite development of a sensitive analytical method (LC-MS assay with a LOQ of 100 pg/ml) for the assay of salmeterol, determination of the pharmacokinetic profile was not possible due to low salmeterol plasma concentrations. At the pre-NDA meeting, the agency requested the sponsor to carry out a PK study to compare the pharmacokinetics (at least the peak plasma concentrations) of salmeterol following administration via Serevent MDI, reduced fill Rotadisk (12.5 mg lactose) and to-be marketed Diskus. It was also stated at that time that the report could be submitted by the 4-month safety update. Hence, delayed submission of this study report is acceptable.

2. Information regarding metabolism of salmeterol is submitted in the Pharm/Tox section of this NDA. A copy of this study (Report WBP/93/062) investigating the specific enzymes responsible for the metabolism of salmeterol in human liver microsomes is needed for review.

3. It has been noted that device modifications, in the polymer of the device, have been made after the final PK study (on the Diskus). It may be a minor change, however, it may not be possible to assess the impact of these changes pharmacokinetically due to assay limitations. The chemist involved should look at this more closely to find out the impact of this change.

V. RECOMMENDATION

This submission has been reviewed for fileability by the Office of Clinical Pharmacology and Biopharmaceutics. This section of the NDA is organized, indexed, and paginated in a manner to initiate a substantial review. Hence, the submission is fileable.

Uppoor 07/10/96

Venkata Ramana S. Uppoor, Ph.D.
Division of Pharmaceutical Evaluation II

FT Initialed by Dale Conner, Pharm.D. DC 7/10/96

CC list:
HFD-570: NDA 20,692; HFD-570: Division file; HFD-570: CSO\Parinda Jani;
HFD-570: Medical Reviewer\Robert Meyer; HFD-570: Chemist; HFD-570: Pharmacologist;
HFD-870: Dale Conner; HFD-870: John Hunt; HFD-870: ChenMe; HFD-860: Malinowski;
HFD-880: FleischerN; HFD-850: Biopharm\Lesko; HFD-870: Chron; HFD-870: Drug;
HFD-870: Venkata Ramana S. Uppoor; HFD-340: Viswanathan; HFD-205: FOI.

ATTACHMENT (1)

Table 1: Biopharmaceutics Study Summary

Report Number Protocol Number Investigators Publications	Location Vol./Page	Route	Dosage Form(s)[1] Study Design	Dose	Batch Number (s)/ Plant/ Date Manufld.	Number Treated Each Treatment/ Sex	Applicant (Sponsor) Conclusion
WBP/90/028 SLGT06 [See Footnote] N/A	11/57	Inhaled	L, Randomized, Double-Blind, Double-Dummy, Parallel Group	50mcg RD bid	U88/311A/ GOps, Ware/ June, 1988	7 3M, 4F	Peak salmeterol plasma levels are detected in plasma 5 to 45 minutes after dosing. Steady state plasma concentrations are similar for the aerosol and powder formulations of salmeterol.
WBP/91/079 SLPT02 [See Footnote] N/A	12/1	Inhaled	O,L Randomized, Double-Blind, Parallel Group	25mcg RD bid 50mcg RD bid	U90/315A/ GOps, Ware/ March, 1990 U90/316A/ GOps, Ware/ March, 1990	20 20 26M, 14F	Plasma concentrations of salmeterol and HNA were similar to the results seen with adults; however, direct comparisons are difficult because samples were taken at different times post-dose in the pediatric and adult studies.
N/A SLGB1004 Wemer N/A	12/168	Inhaled	Part I - B Part II- B, H, P, Part I- Open Part II - Open, Randomized, Crossover	I - 400mcg MDI II - 200mcg MDI - 200mcg RD - 200mcg MDPI	W0194MC/ GOps, Ware/ September, 1994 AX1670-002/ Laboratoires Glaxo, Evreux/ April, 1994 U95/328A/ GOps, Ware/ September, 1995	NA	Data not available

[1] Product Code = See key at end of table. RD = Rotadisk

WBP/90/028
(SLGT06) (**Pharmacokinetic analysis conducted at Glaxo Group Research Limited (Greenford, UK). Refer to the SLGT06 listing in the controlled clinical studies section for a list of study sites.)

WBP/91/079
(SLPT02) (*Pharmokinetic analysis conducted at Glaxo Group Research Limited (Ware, UK). Refer to the SLPT02 listing in the controlled clinical studies section for the list of study sites.)

PRODUCT CODES

A	Metered-dose inhaler 12.5mcg salmeterol/actuation
B	Metered-dose inhaler 25mcg salmeterol/actuation
C	Metered-dose inhaler 50mcg salmeterol/actuation
D	Metered-dose inhaler 100mcg salmeterol/actuation
E	Rotadisk 25mcg salmeterol in 25mg lactose/blister, 4-place Diskhaler
F	Rotadisk 50mcg salmeterol in 25mg lactose/blister, 4-place Diskhaler
G	Rotadisk 25mcg salmeterol in 12.5mg lactose/blister, 4-place Diskhaler
H	Rotadisk 50mcg salmeterol in 12.5mg lactose/blister, 4-place Diskhaler
I	Rotadisk 50mcg salmeterol in 12.5mg lactose/blister, 8-place Diskhaler
J	Rotadisk 12.5mcg salmeterol in 25mg lactose/blister, 8-place Diskhaler
K	Rotadisk 25mcg salmeterol in 25mg lactose/blister, 8-place Diskhaler
L	Rotadisk 50mcg salmeterol in 25mg lactose/blister, 8-place Diskhaler
M	Rotadisk 100mcg salmeterol in 25mg lactose/blister, 8-place Diskhaler
O	Rotadisk 25 mcg salmeterol in 12.5 lactose/blister,8-place Diskhaler
P	Multi-dose powder inhaler 50mcg salmeterol in 12.5mg lactose/blister
Q	Multi-dose powder inhaler 25mcg salmeterol in 12.5mg lactose/blister

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20692

ADMINISTRATIVE DOCUMENTS

II. Patent Information

Patent Information for Serevent® Diskus® Inhalation Powder

Active Ingredient:	Salmeterol Xinafoate
Strength of Drug Product	50 micrograms of salmeterol (as xinafoate) per blister
Dosage Form:	Inhalation Powder
Route of Administration:	Oral Inhalation
Applicant Firm Name:	Glaxo Wellcome Inc.
Patent Number:	4,992,474 (covers Salmeterol per se, composition and method of use)
Issue Date:	February 12, 1991
Expiration Date:	February 12, 2008
Patent Number:	5,225,445 (covers the use of Salmeterol inpatients with reversible airways obstruction)
Issue Date:	July 6, 1993
Original Expiration Date:	July 6, 2010
Expiration Date:	February 19, 2012 (Extended by action of the Uruguay Round Agreements Act, Public Law 103-465, signed by the President on December 8, 1994)
Patent Number:	5,380,922 (covers micronisable Salmeterol and a process for its production)
Issue Date:	January 10, 1995

Original Expiration Date: January 10, 2012

Expiration Date: May 14, 2013
(Extended by action of the Uruguay Round Agreements Act, Public Law 103-465, signed by the President on December 8, 1994)

The Undersigned certifies that Patent Nos. 4,992,474, 5,225,445 and 5,380,922 are valid patents (to the best of his knowledge and belief), claiming salmeterol xinafoate, the subject of a New Drug Application.

03/22/96
Date

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

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 20-692 SUPPL # _____

Trade Name Serevent Diskus
Generic Name salmeterol xinafoate inhalation powder

Applicant Name Glaxo Wellcome Inc HFD- 570

Approval Date September 19, 1997

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 questions 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

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?

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 /_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 # _____ _____

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 /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be

bioavailability studies.

(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 /___/

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: _____

_____

© 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:

Investigation #1, Study # SLD-311

Investigation #2, Study # SLD-312

Investigation #3, Study # SLGA2004

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

Investigation #3 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:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

Investigation #3 YES /___/ NO /_X__/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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"):

Investigation #_1_, Study # SLD-311

Investigation #_2_, Study # SLD-312

Investigation #_3_, Study # SLGA2004

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 _____

_____ _____

_____ _____

© 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: _____

_____

_____

_____

Parende Jani 9-18-97.

Signature Date

Title: Project Manager

9/22/97

Signature of Division Director Date

cc: Original NDA 20-692
Division File 570
HFD-85 Mary Ann Holovac

III. Marketing Exclusivity

Serevent® (salmeterol xinafoate) Diskus® Inhalation Powder
NDA 20-692

Request for Marketing Exclusivity

Under Sections 505(c)(3)(D)(iii) of the Federal Food, Drug, and Cosmetic Act, Glaxo Wellcome requests three years of exclusivity from the date of approval of Serevent® (salmeterol xinafoate) Diskus® Inhalation Powder for long-term twice daily (morning and evening) administration in the maintenance treatment of asthma in patients 12 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma.

Glaxo Wellcome 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. These investigations are "essential to the approval of the application" in that the application could not be approved by FDA without the following investigations:

SLGA2001	A randomized, double-blind, double-dummy, five-way crossover comparative clinical trial of single doses of salmeterol xinafoate via multidose powder inhaler versus salmeterol xinafoate via Rotadisk™/Diskhaler® versus placebo in adolescent and adult patients with chronic moderate asthma
SLGA2006	A randomized, double-blind, double-dummy, five-way crossover comparative clinical trial of single doses of salmeterol xinafoate via multidose powder inhaler versus salmeterol xinafoate via Rotadisk™/Diskhaler® versus placebo in adolescent and adult subject with mild asthma.
C94-041	A cumulative dose comparison of salmeterol xinafoate inhaled via a multidose powder inhaler and the Diskhaler® on systemic pharmacodynamic effects .
SLD-311	A randomized, double-blind, comparative clinical trial of twelve week courses of salmeterol xinafoate Rotadisk™ versus albuterol versus placebo in adolescent and adult patients with chronic reversible obstructive airways disease.
SLD-312	A randomized, double-blind, comparative clinical trial of twelve week courses of salmeterol xinafoate Rotadisk™ versus albuterol versus placebo in adolescent and adult patients with chronic reversible obstructive airways disease.
SLGA2004	A randomised double-blind, double dummy, placebo controlled comparative clinical trial of salmeterol xinafoate via multidose powder inhaler versus salmeterol xinafoate via the Diskhaler for four weeks in adolescent and adult subjects with mild-to-moderate asthma.

SLGT06 Inhaled GR33343G in reversible airways obstruction - efficacy and safety over three months: A double-blind, parallel group study comparing dry powder formulation of inhaled GR33343G (50 mcg) administered twice a day and inhaled salbutamol (400 mcg) administered four times a day.

The clinical investigations are defined as "new" as they have not been relied on by the FDA to demonstrate substancial 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.

These investigations were "conducted or sponsored by Glaxo Wellcome" in that Glaxo was the sponsor of the investigational new drug application (IND ") under which the investigations essential to approval were conducted.

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DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-692 Trade (generic) names Serevent Diskus (salmeterol xinafoate inhalation powder)

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support the claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126© for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or # 4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product as some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1). Studies are ongoing.
____ (2). Protocols have been submitted and approved.
____ (3). Protocols have been submitted and

are under review.

____ (4). If no protocol has been submitted, explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written respond to that request.

____ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

_X_ 5. If none of the apply, explain.

Explain, as necessary, the foregoing items: The pediatric studies are completed. The supplemental NDA will be submitted as soon as the sponsor gets the approval letter for this NDA.

Parveda Jani

Signature of Preparer

9-18-97

Date

CC: Orig NDA 20-693
HFD-570/Div file
NDA Action Package

IV. Debarment Certification

Serevent® Diskus® Inhalation Powder
NDA 20-692

DEBARMENT CERTIFICATION

In accordance with the certification provision of the Generic Drug Enforcement Act of 1992 as outlined in correspondence dated July 29, 1992, from Daniel L. Michels, Office of Compliance, Glaxo Wellcome Inc. hereby certifies that to the best of its knowledge and belief, it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

29 Mar 96

David R. Savello, Ph.D
Vice-President, North American Regulatory Affairs

Date

INTEROFFICE MEMO

TO: NDA 20692
FROM: C. Joseph Sun, Ph. D.
SUBJECT: Team Leader NDA Review Memo
Date: September 18, 1997

C Joseph Sun Sept 18, 1997

I concur with the Pharmacologist's conclusion that the pharmacology and toxicology of Salmeterol xinafoate have been adequately studied and that the drug is approval from a preclinical standpoint.

Salmeterol is a beta 2 adrenergic agonist. It possesses potent and long acting bronchodilating properties. They were demonstrated in vitro using the guinea pig trachea and human bronchial smooth muscle. It has been shown that it blocked platelet activating factor-induced eosinophil accumulation and inhibited histatmine-induced plasma protein extravasation in the lungs of guinea pigs. Furthermore, it protected guinea pigs and cats from the bronchoconstrion induced by histamine or serotonin.

Chronic toxicity studies were performed in rats (oral and inhalation up to 26 weeks and inhalation up to 78 weeks) and dogs (oral and inhalation up to 12 months). 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. Toxicity of tapetum in dogs was not considered clinical relevant as humans do not have a tapetum.

Salmeterol did not impair the 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 bones at oral doses of [redacted] mg/kg and above. However, at a higher oral dose of 10 mg/kg, it caused only delayed ossification of the frontal cranial bones in New Zealand White rabbits.

CJSun

CJSun

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 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 at oral doses of 1.4 mg/kg/day and above. The incidence of leiomyosarcoma was not statistically significant . No carcinogenic effects occurred at the lower dose of 0.2 mg/kg/day. In rats, similar findings of mesovariun leiomyomas and ovarian cysts were reported at oral doses of 0.68 mg/kg/day and above. No such effects

were seen at a dose of 0.21 mg/kg/day. These findings in rodents are typical for beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

With regard to labeling, carcinogenesis, mutagenesis and impairment of fertility and pregnancy category C sections on the package insert have been revised 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

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Clinical Team Leader Summary Review Memorandum

Memorandum to:	NDA 20-692 file
Product:	Serevent Diskus Inhalation Powder
Memo date:	9-15-97
Memo from:	Robert J. Meyer, MD Medical Team Leader, DPDP

This memorandum is to document the secondary review conclusions on the Serevent Diskus Inhalation Powder NDA, application number 20-692. The secondary review was carried out concurrently with Dr. Johnson's primary clinical review. As such, much of the secondary review opinion was incorporated, as appropriate, into the Medical Officer's Review. However, this memorandum will highlight some of the crucial efficacy and safety review issues that form the basis of the finding of clinical approvabililty.

Overview:

Salmeterol xinafoate as a molecular entity was approved in 1994 under the proprietary name Serevent Inhalation Aerosol. This approval was for the long-term, maintenance treatment of asthma and the prevention of bronchospasm (including exercise-induced bronchospasm) in patients ages 12 and above with reversible airways obstruction. This current NDA is for a multidose, dry powder formulation of salmeterol xinafoate 50 mcg with lactose (to a total weight of 12.5 mg) as the only excipient. The development program for the dry powder formulation(s) began as a 'stand-alone' program utilizing the Rotadisk administered by the Diskhaler, with the Diskus product being a "switch" program from the Rotadisk, not from the MDI. Following the merger of Glaxo and Burroughs Wellcome, Glaxo Wellcome determined that they did not wish to market the Rotadisk formulation. It was agreed to by the sponsor and the division that if the Rotadisk formulation program was fully clinically approvable and a "switch" program for the Diskus from the Rotadisk was fulfilled in keeping with the division's "Points to Consider" document of Sept. 1994, this application for the Serevent Diskus could be filed. This particular "switch" is largely based on the 'same formulation, different device' portion of this guidance, since the drug substance and lactose formulation are identical, although the devices clearly differ. There was no requirement for the sponsor to demonstrate comparability of this product to the MDI product, since the clinical development of the dry powder formulation was designed by the sponsor to be a stand-alone program. Notable from the clinical standpoint is that, as submitted, there is no current proposed claim for EIB for the Serevent Diskus, although this is an approved indication for the MDI formulation. Also, the under 12 pediatric population is not addressed in this application. The pediatric indication for the MDI has not been approved. It should also be noted that a preclinical issue unique to the dry powder formulation of salmeterol arose, with a new drug substance-related degradant being identified for which the division requested pre-clinical qualification. This issue is addressed in the pharm/tox. review.

EFFICACY:

THE TWO MAIN TRIALS UPON WHICH JUDGMENT OF EFFICACY (COMPARED TO PLACEBO AND REGULARLY ADMINISTERED ALBUTEROL) IS BASED WERE STUDIES SLD-311 AND 312, BOTH DONE WITH THE ROTADISK FORMULATION. [*THESE TRIALS FOLLOWED A SERIES OF DOSE IDENTIFICATION TRIALS WHICH ESTABLISHED THAT 50 MCG FROM A DRY POWDER FORMULATION WAS A REASONABLE DOSE AND THAT THIS DOSE PERFORMED SIMILARLY IN TERMS OF BRONCHODILATION TO A 50 MCG (EX-VALVE) DOSE FROM THE MDI.*] THESE STUDIES WERE SIMILAR IN DESIGN TO THE PIVOTAL STUDIES DONE IN SUPPORT OF THE SEREVENT MDI APPLICATION. THEY FOLLOW BOTH FEV_1'S (PRIMARY VARIABLE SERIALLY PERFORMED 12-HOUR FEV_1) DONE AT MULTIPLE TIME POINTS IN THE 12 WEEK TRIALS, AS WELL AS OTHER PHYSIOLOGIC AND CLINICAL MEASURES OF ASTHMA CONTROL. THESE STUDIES SUPPORT THE EFFICACY AND SAFETY OF THE SALMETEROL DRY POWDER FORMULATION IN PROVIDING > 12 HOURS OF BRONCHODILATION (MEDIAN RESPONSE) WITHOUT DEFINABLE TOLERANCE TO THE BRONCHODILATION OCCURRING OVER A 12 WEEK TREATMENT PERIOD. OTHER MEASURES OF ASTHMA CONTROL (PEFR'S, RESCUE BETA-AGONIST USE, SYMPTOMS, NIGHTTIME AWAKENINGS) ALSO SUPPORT EFFICACY OF THIS FORMULATION RELATIVE TO PLACEBO, AND IN SOME CASES, TO REGULARLY ADMINISTERED ALBUTEROL, WITH ACCEPTABLE ADVERSE EVENT PROFILE RELATIVE TO PLACEBO AND ALBUTEROL. THESE STUDIES, THEREFORE, FORM THE BASIS OF A FINDING OF EFFECTIVENESS OF A SALMETEROL DRY POWDER FORMULATION IN THE TREATMENT OF ASTHMATICS (ALBEIT WITH THE DISKHALER DEVICE).

TRIAL SLGA2004 WAS A STUDY COMPARING THE EFFICACY OF THE 50 MCG BID FROM THE DISKUS DEVICE COMPARED TO THE SAME FORMULATION DELIVERED FROM THE ROTADISK PRODUCT/DISKHALER DEVICE VS. PLACEBO. THIS WAS A 'LIFE-OF-DEVICE' STUDY LOOKING AT COMPARATIVE SAFETY AND EFFICACY OVER A FOUR WEEK PERIOD, WHICH WAS SUPPLEMENTED IN TERMS OF THE SWITCH BY TWO SINGLE-DOSE CROSS-OVER STUDIES FOR PD COMPARISONS OVER A DOSE RANGE OF THESE TWO PRODUCTS (SLGA2001 AND 2006). THE CONCLUSION DRAWN FROM THESE DATA IS THAT THESE TWO DEVICES/PRODUCTS, WHEN DELIVERING THIS FORMULATION, PERFORMED COMPARABLY IN THE CLINICAL SETTING BOTH IN TERMS OF PD (WITH THE DISKUS ≥ ROTADISK FOR SPIROMETRIC MEASURES) AND IN TERMS OF CLINICAL USE, INCLUDING SAFETY MEASURES. THERE WERE NO SPECIAL ISSUES WITH THE DISKUS DEVICE EVIDENT IN THE REPORTED DATA FOR THE USE STUDY, WITH NO DEVICE FAILURES OR USAGE PROBLEMS, PARTICULARLY RELATIVE TO THE DISKHALER/ROTADISK DEVICE. TWO COMMENTS WORTH NOTING - PATIENT PREFERENCE FOR USE APPEARED TO FAVOR THE DISKUS IN SOME PATIENT-SCORED RATINGS, COMPARED TO ROTADISK ADMINISTERED VIA DISKHALER. ALSO, THE CROSS-OVER STUDIES (SLGA2001 AND 2006) REVEALED THAT THE DISKUS DEVICE PROVIDED SIMILAR BRONCHODILATORY EFFECTS TO THE ROTADISK/DISKHALER (IN THESE STUDIES, DISKUS ≤ ROTADISK). HOWEVER, THESE STUDIES DID NOT RELIABLY DETECT THE DIFFERENCE BETWEEN 50 AND 100 MCG AND THEREFORE THE SENSITIVITY OF THESE STUDIES IS QUESTIONABLE. HOWEVER, TAKEN ALL TOGETHER, THESE DATA SUPPORT THAT THE SAME NOMINAL DOSE DELIVERED FROM THESE TWO DEVICES PRODUCE COMPARABLE CLINICAL RESULTS BOTH IN SINGLE DOSE AND MULTIDOSE COMPARISONS.

SAFETY:

THE SAFETY DATA IN THIS NDA WERE EXTENSIVE, INCLUDING NOT ONLY NUMEROUS EFFICACY TRIALS OF VARIOUS DRY POWDER FORMULATIONS (E.G., LACTOSE TO 25 MG VS. LACTOSE TO 12.5 MG), BUT ALSO LONG-TERM SAFETY STUDIES (OUT TO 12 MONTH) WITH THE PROPOSED FOR MARKETING FORMULATION. THERE ARE, ADDITIONALLY, POST-MARKETING DATA FROM THE MORE THAN 20 COUNTRIES WHERE THE FORMULATION HAS BEEN APPROVED. AS THESE DATA ARE

SUMMARIZED BY THE MEDICAL REVIEWER, MY ONLY COMMENT ON THESE IS THE ADVERSE EVENT PROFILE IS ACCEPTABLE CONSIDERING THE POPULATION AND INDICATION PROPOSED AND NOT SURPRISING GIVEN WHAT IS KNOWN ABOUT THIS MOLECULE AND THE MODERATE TO SEVERE ASTHMATIC POPULATION. IT IS WORTH STATING THAT ALTHOUGH DEATHS WERE NOTED IN THIS DATABASE, AS WITH THE SEREVENT MDI, THESE APPEAR MORE RELATED TO UNDERLYING DISEASE THAN TO SALMETEROL EXPOSURE. NO CASES CAN BE CONVINCINGLY LINKED TO SALMETEROL AS THE CAUSE OF THE DEATH.

OTHER EFFICACY/SAFETY INFORMATION:

FINALLY, THERE WERE THREE TRIALS DIRECTLY COMPARING THE MDI AND DISKUS PRODUCTS WHICH WERE SUBMITTED LATE IN THE ORIGINAL 12 MONTH REVIEW CYCLE. THESE INCLUDED A SINGLE DOSE, DOSE-RANGING, CROSSOVER STUDY [2015] IN WHICH THE 100 µG DISKUS DOSE APPEARED MOST SIMILAR IN EFFICACY TO THE 50 µG MDI DOSE (THOUGH THE DISKUS GROUP SUFFERED SOMEWHAT MORE ADVERSE EFFECTS). IN TWO PARALLEL GROUP 12-WEEK EFFICACY TRIALS [STUDIES 3010 AND 3011] OF STANDARD 50 µG DOSES FROM THE TWO DEVICES (42 µG EX-ACTUATOR FOR THE MDI), THESE TWO PRODUCTS WERE STATISTICALLY INDISTINGUISHABLE, THOUGH IT APPEARS THAT THE MDI HAD A NUMERICAL ADVANTAGE ON SEVERAL EFFICACY PARAMETERS. HOWEVER, THE DISKUS GROUP STILL HAD CLEAR EFFICACY IN REFERENCE TO PLACEBO.

OVERALL CONCLUSIONS:

I AM IN AGREEMENT WITH DR. JOHNSON'S ASSESSMENT THAT THIS APPLICATION IS APPROVABLE FROM THE CLINICAL STANDPOINT FOR THE PROPOSED AGE RANGE AT THE PROPOSED DOSES. SINCE THE ADEQUATE AND WELL-CONTROLLED DATA WE RECEIVED RELATING THE MDI TO THE DISKUS FORMULATIONS OF SALMETEROL SHOW SOME APPARENT DIFFERENCES IN THE DELIVERY AND EFFICACY OF THE TWO PRODUCTS, THERE NEEDS TO BE SOME SPECIFIC MENTION OF THESE DATA IN THE LABELING SO THAT PATIENTS AND PHYSICIANS KNOW THAT THE CLINICAL RESULTS OF THE TWO PRODUCTS MAY VARY (ALTHOUGH IT IS CLEAR THAT AS A STAND ALONE CONSIDERATION, THE MDPI IS SAFE AND EFFECTIVE AND, OVERALL, IS REASONABLY COMPARABLE TO THE MDI IN SAFETY AND EFFICACY).

RECOMMENDATION:

I RECOMMEND APPROVAL OF THIS PRODUCT, ONCE ALL CMC ISSUES AND LABELING ISSUES ARE RESOLVED TO A SUFFICIENT DEGREE. IT IS STILL AN OPEN ISSUE WITH THE CFC PHASE-OUT IN THE UNITED STATES WHETHER DPIS IN GENERAL WOULD BE CONSIDERED AS VIABLE ALTERNATIVES TO CFC-BASED MDIS FOR PURPOSES OF ESSENTIAL. THE FDA WOULD NEED CONSIDERABLY MORE DATA ON THIS PRODUCT SPECIFICALLY DUE TO SOME OF THE DIFFERENCES APPARENT IN THE MDPI-MDI HEAD-TO-HEAD TRIALS. IF THE SEREVENT DISKUS PRODUCT WERE TO BE CONSIDERED AS A TECHNICALLY FEASIBLE ALTERNATIVE (TEFA) TO THE SEREVENT CFC-BASED MDI, IT WOULD BE VERY USEFUL TO HAVE SOME POST-MARKETING USE TRIAL, PARTICULARLY EXAMINING ISSUES OF TOLERABILITY WHEN CLINICALLY SWITCHING BETWEEN THE MDI AND DPI. SINCE THE RULE MAKING PROCESS ON THE ESSENTIAL USES AND PHASE-OUT OF CFCS IS NOT TO A SUFFICIENT STAGE NOW TO DETERMINE WHETHER AN MDPI WILL BE CONSIDERED AS A TEFA TO AN MDI, WE CERTAINLY CANNOT REQUIRE ANY SUCH STUDY.

Robert J. Meyer, MD 9/15/97
Medical Team Leader
Division of Pulmonary Drug Products

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CC: Johnson/Medical Officer/HFD-570
Meyer/Medical Team Leader/HFD-570
Jani/project manager/HFD-570
Division File/HFD-570
NDA #20-692

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