CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-692

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

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

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 #_43,097_ YES /_X__/ NO /___/ Explain: _____

_____

Investigation #2

IND #_43,097_ YES /__x_/ NO /___/ Explain: _____

_____

Investigation #3

IND #_43,097_ 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: _____

_____

_____

_____

Parenda Jani
Signature
Title: Project Manager

9-18-97.
Date

Signature of Division Director

9/22/97
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 (— , and 43,097) under which the investigations essential to approval were conducted.

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.

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

29 Mar 96
Date

2 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 20 ...

Kathryn V. Blake, Pharm. D.
Nemours Children's Clinic
807 Nira Street
Jacksonville, Florida 32207

Dear Dr.Blake:

On October 15 and 21-23, 1996, Mr. H. Randy Bringger, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study (protocol #SLD-312 and appendix SLD-PO2) of the investigational drug Serevent(salmeterol xinafoate), performed for Glaxo, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From an evaluation of the inspection report and of the documents collected during the inspection, we conclude that you adhered to all Federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. However, the consent form used in this study did not specifically provide an explanation of whom to contact in the event of a research-related injury to the subject. This statement is required by part 50.25 of our regulations (copy enclosed). Please note item (a)(7).

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Mr. H. Randy Bringger during the inspection.

Sincerely yours,

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations, HFD-344
Office of Compliance
Center for Drug Evaluation

CFN:1062052
Field classification:N
Headquarters classification:
_____1)NAI
_x___2)VAI-no response required
_____3)VAI-response requested

If Headquarters classification is different classification, explain why:

Deficiencies noted:
_x___ inadequate consent form
_____ inadequate drug accountability
_____ failure to adhere to protocol
_____ inadequate records
_____ failure to report ADRS _____
_____ other (specify)

cc:
HFA-224
HFD-344
HFD-340 r/f
HFD-342
HFD-340
HFR-SE200
HFR-SE250
HFD-570 Review Division Div. Dir./Doc. Rm.: NDA#20692
CSO:P.Jani; MO: S. Johnson
HFC-230 IND#35239
HFC-132

r/d:HWJu:12/12/96
d/t:slk:12/12/96

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 20 [illegible]

James Grady, M.D.
Boulder Medical Clinic
Internal Medicine
2750 Broadway
Boulder, Colorado 80320

Dear Dr. Grady:

On October 22-23, 1996, Mr. David K. Glasgow, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as Investigator of record, of a clinical study (Protocol SMD-200) of the investigational drug Serevent (salmeterol xinafoate), performed for Glaxo Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From an evaluation of the inspection report and of the documents submitted with that report, we find some departures from FDA regulations and/or good clinical investigational practices. These findings were itemized on Form FDA-483 and were discussed with you at the close of the inspection. The discussion included: 1) failure to report an adverse event and the treatment of it and 2) lack of documentation to show that the change in time interval between the screening visit and treatment visit, of less than 7-14 day interval was authorized by the sponsor prior to implementation; The time interval of 7-14 day was required by the protocol.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate your cooperation shown to Mr. Glasgow during the inspection.

Sincerely yours,

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations, HFD-344
Officer of Compliance
Center for Drug Evaluation
and Research

cc:
HFA-224
HFD-344
HFD-340 r/f
HFD-342
HFR-SW200
HFR-SW250
HFD-570 Review Division Div. Dir./Doc. Rm.:NDA#20692
CSO:P.Jani; MO:S.Johnson
HFC-230 IND#43097
HFC-132

CFN:1723560

Field Classification: N
Headquarters classification:
___1)NAI
_X_2)VAI-no response required
___3)VAI-response requested

If Headquarters classification is different classification, explain why:

Deficiencies noted:
___inadequate consent form
___inadequate drug accountability
_X_failure to adhere to protocol
___inadequate records
_X_failure to report ADR(1)
___other (specify)

r/d:HWJu:12/13/96
finaled:slk:12/18/96

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR - 6 1997

Anthony R. Rooklin, M.D.
Director of Allergy
Asthma and Allergy Associates
President's House
Crozer Upland, Pennsylvania 19015

Dear Dr. Rooklin:

On January 22 and 23, 1997, Mr. Mike M. Rashti and Dr. Susan Johnson, representing the Food ad Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study (Protocol No. SLGA2004) of the investigational drug Serevent (salmeterol xinafoate) multi-dose powder inhaler(MDPI), performed for Glaxo Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

From an evaluation of the inspection report and of the documents submitted with that report, we find some departures from FDA regulations and/or clinical investigational practices. These findings were itemized on Form FDA-483 and were discussed with you at the close of the inspection. The discussion included: 1) one extra dose was administered to fourteen patients 2) failure to document the fate of unused test material and 3) the missing diary card for one patient.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above, are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Mr. Rashti and Dr. Johnson during the inspection.

Sincerely yours,

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations
Office of Compliance
Center for Drug Evaluation
and Research

CFN:2529691

Field classification: VAI
Headquarters classification:
___1) NAI
_X_2) VAI-no response required
___3) VAI-response requested

If Headquarters classification is different classification, explain why:

Deficiencies noted:

___ inadequate consent form
_x_ inadequate drug.accountability
_X_ failure to adhere to protocol
_x_ inadequate records
___ failure to report ADRS___
___ other: missing screening card

cc:
HFA-224
HFD-344
HFD-340 r/f
HFR-MA100
HFR-MA150
HFD-570 Review Division Div. Dir./Doc. Rm. : NDA#20,692
CSO:P.Jani; MO:S.Johnson IND#43,097
HFC-132
HFC-230
r/d: HWJu:2/28/97
Review date:AEH:2/28/97
Final date:slk:3/3/97

INTEROFFICE MEMO

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

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

N:\nda\20692\pharm\96-6-18.RE3

GlaxoWellcome

September 16, 1997

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

Re: NDA 20-692; Serevent® (salmeterol xinafoate) Diskus® Inhalation Powder
Response to FDA Request/Comment: Phase IV Commitment for Patient Use Expiry

Dear Ms. Jani:

In order to support the eight-week patient use expiry for Serevent Diskus (NDA 20-692, submitted June 18, 1996) and to extend it based on real-time data, Glaxo Wellcome will provide several reports documenting the stability of the drug product following storage at — . Stability data will be generated from the first three post-approval commercial batches and testing will follow the protocol submitted September 15, 1997. In addition, testing of emitted dose and particle size by cascade impaction will be conducted following — storage. The first interim report will be submitted by January 30, 1998 in order to verify the eight-week patient use expiry. Data will continue to be generated on these same three stability batches to support the extension of the patient use expiry for — , if appropriate.

Glaxo Wellcome fully intends to provide data to verify the eight-week patient use expiry in accordance with the above timing; however, due to the possibility of changes in the manufacturing schedule to support launch of Serevent Diskus, delays in the generation and reporting of stability data may occur. If this occurs, Glaxo Wellcome commits to notify the Agency of the delay.

Glaxo Wellcome also agrees to re-evaluate the patient use expiry as the data are generated and commits to revise the labeling in the event that the eight-week patient use expiry is not supported. Likewise, product labeling will be revised if the stability data supports extending the patient use expiry.

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 248 2100

This information is submitted in triplicate, with a desk copy for Dr. Lostritto provided under separate cover. Please contact me at (919) 483-6771 if there are any questions regarding this submission.

Sincerely,

for Darlene Rosario

Darlene Rosario
Assistant Director
CMC Regulatory Affairs and Compliance

cc: Dr. Rick Lostritto

3 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

E L E C T R O N I C M A I L M E S S A G E

Date: 20-Jun-1997 07:18am EDT
From: Cathie Schumaker
SCHUMAKER
Dept: HFD-570 PKLN 10B45
Tel No: 301-827-1050 FAX 301-827-1271

TO: 5 addressees

CC: 4 addressees

Subject: NDA 20-692

Mimi Egas called this morning to say that the field is going out to inspect next month for the dry powder dosage form. She will remove the overall recommendation of approval in the EES. Please adjust your records accordingly. Thanks, CS

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Parinda Jani

FAX Number: 827-1271

Date: 9/11/97

Company: FDA

Address:

No. pages (excluding cover): (1)

Message: Consult as requested

From: Dan Boring

Telephone: (301) 827-2391

FAX Number: (301) 827-2510

Mail:
Division of Antiviral Drug Products
5600 Fishers Lane (HFD-530)
Rockville, Maryland 20857

Courier:
Division of Antiviral Drug Products
HFD-530
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

Consult #866 (HFD-570)

SEREVENT —
SEREVENT — salmeterol for inhalation

The Committee evaluated the proposed use of the terms —
— as distinguishing modifiers for new SEREVENT products that are dry powders for inhalation.

The Committee felt that — was fanciful and had some potential for promotional misuse if adopted. The Committee preferred the term — as being more descriptive and pharmaceutically oriented.

D L Boring 9/11/97, Chair
CDER Labeling and Nomenclature Committee

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Boring, HFD -530			FROM: Parinda Jani, HFD-570	
DATE: July 29, 1997	IND NO.	NDA NO. 20-692	TYPE OF DOCUMENT LNC consult	DATE OF DOCUMENT July 24, 1997
NAME OF DRUG Serevent Diskus (salmeterol xinafoate inhalation dry powder)	PRIORITY CONSIDERATION P		CLASSIFICATION OF DRUG 3S	DESIRED COMPLETION DATE August 24, 1997

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
- ☐ 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 (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER 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 RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
Please see the comments on the attached Trademark Review form.

CC:/ORIG NDA 20-692/HFD-570 DIV FILES/HFD-570 SCHUMAKER, POOCHIKIAN, JANI

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

REQUEST FOR TRADEMARK REVIEW

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

From: Division of Pulmonary Drug Products	**HFD-570**
Attention: Dan Boring, HFD-530	**Phone:** (301) 827-2391
Date: July 29, 1997	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: 1) Serevent — 2) Serevent	**NDA/ANDA#** 20-692
Established name, including dosage form: salmeterol inhalation powder	
Other trademarks by the same firm for companion products: Serevent Inhalation Aerosol	
Indications for Use (may be a summary if proposed statement is lengthy): Serevent Diskus Inhalation Powder is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in 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 regular treatment with inhaled, short-acting beta2-agonists. It should not be used in patients whose asthma can be managed by occasional use of short-acting, inhaled beta2-agonists.	
Initial Comments from the submitter (concerns, observations, etc.): The sponsor had proposed Serevent Diskus as tradename when the NDA was originally submitted, June 18, 1996. Recently, the sponsor has decided to change the tradename. The Division does not like either name. Before we contact the sponsor, we would like input from LNC. The due date for this NDA is September 18, 1997.	

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

cc: Original ; HFD-570/division file; HFD-570/J.Parinda; HFD-570/Poochikian

Rev. December 95

July 24, 1997

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

Re: NDA 20-692; Serevent® (salmeterol xinafoate) Diskus® Inhalation Powder
General Memorandum: Request for Review of Proprietary Name
VIA FACSIMILE: 301-827-1271
Dear Ms. Jani:

As per our conversation, Glaxo Wellcome will be amending NDA 20-692 to provide for new proprietary name(s).

The proprietary name for which we are requesting Agency review is:

Serevent — (salmeterol xinafoate) Inhalation Powder

An alternate proprietary name, which Glaxo Wellcome proposes to be used only in the unlikely event that the Serevent — rademark cannot be used for business reasons, is:

Serevent — salmeterol xinafoate) Inhalation Powder

Glaxo Wellcome has a clear preference for use of Serevent — , nowever, in consideration of the limited remaining NDA review time, this alternate name is being submitted.

Therefore, Glaxo Wellcome respectfully requests that both names be reviewed by the Division and CDER's Labeling and Nomenclature Committee. We appreciate your efforts to expedite these reviews.

If there are any questions regarding this information please contact me at (919) 483-7389.

Sincerely,

Ramona

Ramona Krailler, Ph.D.
Product Director
Regulatory Affairs

77 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

Memorandum of Telephone Facsimile Correspondence

Date: June 20, 1997

To: Ramona Krailler
Regulatory Affairs

From: Parinda Jani
Project Manager

Through: Robert Meyer, M.D.
Team Leader, Medical Officer

Subject: Clinical comments for NDA 20-692

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. Please provide an analysis of the PEFR and diary data which were collected during the study period post-Week 12 in Trials SLD-311 and SLD-312.

2. We request that you submit the final study report for Trial SLGA3009 to this NDA as soon as it becomes available.

3. Submit any evidence of failure of the Diskus or Diskhaler/Rotadisk devices in clinical trials or general clinical use.

4. Please provide any available information regarding use of the Diskus with a spacer device.

5. Please submit draft statement which describes the clinical comparability of the MDPI and MDI salmeterol formulations.

4 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

Memorandum of Telephone Facsimile Correspondence

Date: April 3, 1997

To: Ramona Krailler
Regulatory Affairs

From: Parinda Jani
Project Manager

Through: Robert J. Meyer, M.D. 4/3/97
Clinical Team Leader

Subject: Clinical comments for NDA 20-692/Serevent 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.

The following comments are provided regarding NDA 20-692. We request that your response be submitted no later than April 25, 1997.

1. For Trials SLD-311, SLD-312 and SLGA-2004

   a. Please provide the number of patients who were screened but were not enrolled in each trial and provide an accounting of the reasons that these patients were not enrolled.

   b. Describe the strategy used to categorize patients' use of concurrent corticosteroids as "asthma medication" versus "non-asthma medication."

2. For Trials SLD-311 and SLD-312:

   a. Provide a description of any protocol amendments which were made after initiation of the trial.

   b. Regarding FEV_1 outcomes for Day 1 and Week 4, please provide the following reanalyses for the efficacy population. These reanalyses are intended as supplementary information and will not be used as replacements for the primary analyses.

      i. Mean percent change from daily baseline (not study baseline), including a statistical comparison at each timepoint. Daily baseline can be considered the mean of the -0.5 and 0 Hour timepoints.

      ii. Graphical plots of the percent change from daily baseline.

      iii. Provide the mean time to peak percent change from daily baseline for albuterol (for the first peak of the 12 hour assessment interval) and salmeterol.

   c. Please provide a sample diary reporting form. In addition, indicate whether patients were instructed to record their PEFR and symptom scores in a particular sequence.

3. Please specify the product name and/or indication for the use of sodium chloride for five patients enrolled in Trial SLD-311 (Table 17).

4. For Trial SLD-312:

   a. Please verify the median time to onset for the entire efficacy population (not the responder subset) at Week 4. It appears to be longer than expected based on the mean percent change from baseline profile and data from Trial SLD-311.

b. Identify the number of patients in each treatment group who were less than 80 percent compliant with their assigned treatment regimen.

5. For Trial SLGA-2004:

a. Please clarify the method used to determine patient compliance. The protocol states that counts of blister packages and device counters would be used, but the reported compliance figures appear to be based on diary data.

b. Provide a reanalysis of efficacy population FEV_1 data for Days 1 and 29 using percent change from daily baseline (mean of Hours -0.5 and 0), including a statistical comparison at each timepoint, and plots of percent change from daily baseline for each day.

c. Tables 52, 53, 56, 57, 60 and 61 should be revised to include vital sign data for the entire 12 hour spirometric assessment period on Days 1 and 29.

E L E C T R O N I C M A I L M E S S A G E

Date: 08-May-1997 10:26am EDT
From: Richard Lostritto
LOSTRITTOR
Dept: HFD-350 WOC2 3070
Tel No: 301-594-5630 FAX 301-827-2772

TO: Guiragos Poochikian (POOCHIKIAN)

CC: Dale Koble (KOBLED)

Subject: Serevent Diskus

RE: Serevent Diskus (MDPI) NDA 20-692.

Guirag,

Dar Roasario called me from Glaxo UK this morning to discuss a few administrative and technical issues regarding their pending response to the remaining comments and questions in the IR letter we sent them in February for this NDA. These are enumerated below.

The rest of their response is taking longer than expected to complete. They will have a complete response to all remaining questions by the "end of may" [FYI, 30th is Friday and 31st is Saturday]. This begs the questions as to what we do regarding the June 19 due date? (extension vs action...The second response will be to the more controversial issues and will take at least until the 19th of June for review; I will be out of town the 2nd week of June too).

2. RE: Dispensing/use life after the over wrapped drug product is opened. They have — data which supports a — use life, which is what they plan on proposing in their response. They want to know if they will be able to extend that on the basis of — condisions (or other) in the future. I was non-committal based on our conversations where we were not sure yet just what to ask for. But, I think Glaxo would like to use their — for this purpose. [This might strecth the use life to — I explained that we were interested in the realistic conditions that the patient is likely to encounter which is more like —

3. Their particle size distrubution specs have changed and they have not as well. Let me explain that one. The existing spec proposal is for —

GLAXO WOULD LIKE TO HAVE A TELECON WITH US; IF POSSIBLE THIS WEEK WHILE ROSARIO IS THERE. CONSIDERING THE 5 HOUR TIME DIFFERENCE, WE WOULD HAVE TO DO THAT FRIDAY BEFORE NOON... AND...AFTER WE HAD A CHANCE TO DISCUSS THESE ISSUES. IT'S UP TO YOU. THE ADVANTAGE TO TALKING TO THE COMBINED UK/US TEAM IS THAT THE UK FOLKS (WHO ARE DOING ALL THE WORK ON THIS PRODUCT) HEAR IT FROM THE AGENCY DIRECTLY AND ACT MORE ACCORDINGLY THAN IF THEY HEAR IT FROM THE U.S. SIDE OF THE TEAM. CALL IT HUMAN NATURE, BUT I HAD ESSENTIALLY THE SAME EXPERIENCE WITH BI.

I will call later today, THANKS,

Rik

Minutes of Industry Meeting

IND: 43,097 **Date: September 18, 1995**

Sponsor: Glaxo Wellcome Inc.

Product: Serevent Multi-Dose Powder Inhaler

GW Attendees: Teresa Arledge, DVM
Assistant Director, Clinical Research
John Schaumberg, Ph.D.
Associate Director, Clinical Research
Roger Liddle, Ph.D.
Assistant Director, Biostatistics
Steven Cole, Ph.D.
Research Investigator, Analytical Sciences
Barry Sumby, Bsc
Project Team Leader
Respiratory Product Development U.K.
Robert Woodhouse, Ph.D.
Director
International Inhalations Product Development
Andrew Grant
Device Development Manager
Steven Dammont
Director, Toxicology Science
Michael Golden, Ph.D.
Research Investigator
Inhalations Product Development
John Morgan, Ph.D.
Associate Director, Regulatory Affairs
Deborah van den Honert
Associate Director, Regulatory Affairs
Michael O'Flynn
Assistant Director, Regulatory Affairs

FDA Attendees: Dr. Meyer, Dr. Jenkins, Dr. Gebert, Dr. Sancilio, Dr. Sun, Dr. Koble, Dr. Poochikian, Dr. Sista, Dr. Mehta, Ms. Jani

---

Background: GW submitted a package, requesting a pre-NDA meeting for Serevent MDPI on May 9, 1995. Although, pivotal studies are conducted comparing Serevent Rotadisk to Serevent MDPI, GW will not be filing an NDA for Serevent Rotadisk. Additional data of comparability between Serevent MDPI and Diskhaler devices and stability data on Serevent MDPI drug

product were submitted on August 16, 1995. An internal meeting was held, August 31, 1995 and it was decided that the package, as submitted, would be appropriate for filing. Clinical data will support filing, but the CMC issues need to be discussed. GW submitted an update to the original package on September 12, 1995.

Meeting Minutes: Dr. O'Flynn started the meeting by stating that the objective of the meeting was to confirm that as proposed in the package, the NDA is fileable. Dr. Jenkins clarified that as proposed in the pre-NDA package, the NDA appears to be acceptable for filing and reviewing, although that does not guarantee it will be filed. The program as proposed is acceptable. Filing will still depend on the content of the NDA when it is actually submitted.

Clinical: The overall clinical program is acceptable. The division cannot make a judgement, at this stage, that the clinical comparability is established between Serevent MDPI and Rotadisk. Comparability will be determined upon review of the data that will be submitted in the NDA. The division would like to have full reports of key non U.S. studies in the NDA. Pediatric safety data must be included in the Integrated Summary of Safety. SAS data files should be submitted with the NDA. Dr. Jenkins stated that the division was very disappointed that GW will not submit a CANDA. Dr. Jenkins stated that the division has general concerns regarding breath actuated devices and whether patients with more severe bronchospasm can generate sufficient flow rate through the device. Dr Jenkins suggested that GW generate data to address this issue with this device.

Dr. Jenkins brought to GW's attention that there are going to be 2 Serevent products in the market, MDI and MDPI, which have not been compared to each other. Labeling should state that clinical comparison studies between Serevent MDI and MDPI have not been conducted.

Pharmacokinetics: Since the full PK profile is not available, Dr. Sista asked GW to provide data for peak plasma levels, through inhalation route, with the finally defined device for Serevent MDPI. Also, data for comparison of plasma levels from the Serevent reduced fill Rotadisk (U.S. formulation) and MDPI should be provided. After the meeting, Dr. Sista also told GW that comparison to MDI in these variables would be useful (MDI to MDPI to DPI). This will not be a filing issue. Submission of these data during the review period will be acceptable to the division.

Pre-clinical: — impurity in Serevent MDPI formulation is — The degradation pathway for the drug product should be defined and addressed in the NDA. Impurities studies should be conducted in 2 species for 12 weeks. GW has conducted a 12 week inhalation study of degraded salmeterol in rats. GW needs to justify that one toxicity study is sufficient and the rat is most appropriate species. Furthermore, additional information from a 3 month inhalation toxicity study in rats on the salmeterol MDI has been requested. This will determine whether additional toxicity studies are warranted on the impurity. The sponsor has been conveyed of this requirement.

Chemistry: Ms. van den Honert presented the data for comparability of Serevent Diskus and Diskhaler. The Diskus device has been modified during development but G-W believes the changes will not have any impact on drug delivery and pharmacologic performance of the device. Clinical studies were conducted with the first — device (list attached). Dr. Cole stated that the formulations were identical for both the devices. In-vitro data showing comparability of all the devices were presented. In response to GW questions regarding CMC section of the pre-NDA package, please see attached response by Dr. Koble.

GW is planning to submit the NDA in first quarter of 1996. Long Term Safety data for standard fill formulation (U.K. formulation) will be submitted with the NDA, and data for reduced fill formulation (U.S. formulation) will be submitted by the 120 days safety update.

Parinda Jani

CC:
ORIG IND 43,097
DIV FILE/HFD-570
HFD-570/MEYER/9-26-95
HFD-570/JENKINS
HFD-570/KOBLE/11-15-95
HFD-570/POOCHIKIAN/11-17-95
HFD-570/SANCILIO/10-2-95
HFD-570/SUN/10-2-95
HFD-426/SISTA/9-29-95
HFD-426/MEHTA/9-29-95
HFD-570/JANI/9-21-95
HFD-570/SCHUMAKER/9-27-95

PRE-NDA MEETING MINUTES

Division of Pulmonary Drug Products

ADMINISTRATIVE REVIEW OF NDA

Application Number: NDA 20-692

Name of Drug: Serevent (salmeterol xinafoate) Diskus Inhalation Powder

Sponsor: Glaxo Wellcome Inc.

Indication: 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 regular treatment with inhaled, short-acting beta$_2$-agonists.

Material Reviewed

Submission Date(s): June 18, 1996

Receipt Date: June 19, 1996

Review

Following complete documents are submitted by the sponsor.

1. FDA form 356h.

2. FDA form 3397 (User Fee Cover Sheet).

3. Index to the archival copy of the application

   VII. Human Pharmacokinetic and Bioavailability Summary
   A. Description of Bioavailability/Pharmacokinetic Studies in Humans
   (Above starts on page 215 and not 225 as listed in index.)

4. Letter of Authorization - [redacted]
   reference to DMF # [redacted]

5. Letter of Authorization - [redacted]
   for cross reference to DMF [redacted]

6. No letter of Authorization - [redacted] for cross reference. The letter under "Letters of Authorization" describes the procedure [redacted]

[redacted] They have included acceptance specifications but not a DMF (Volume 2, pages 50, 68 and 84)

7. Letter of Authorization - [redacted] for cross reference to DMF # [redacted]

8. Letter of Authorization - [redacted] for cross reference to DMF # [redacted]

9. Letter of Authorization - [redacted] for cross reference to DMF # [redacted]

10. Letter of Authorization - [redacted] for cross reference to DMF # [redacted]

11. No Letter of Authorization - [redacted] for cross reference to

[redacted]

A letter of compliance is included but not a DMF. (Volume 2, pages 82 and 83)

12. Patent Information

U.S. Patent # 4,992,474 Expiration Date February 12, 2008
U.S. Patent # 5,225,445 Expiration Date February 19, 2012
U.S. Patent # 5,380,922 Expiration Date May 14, 2013

13. Marketing Exclusivity

14. Debarment Certification

15. Application summary

a. Labels and Labeling Summary
   Draft labeling Disk provided
b. Pharmacologic Class, Scientific Rationale, Intended Use and Potential Clinical Benefits Summary
c. Foreign Marketing History
d. Chemistry, Manufacturing and Controls Summary
e. Nonclinical Pharmacology and Toxicology Summary
f. Human Pharmacokinetic and Bioavailability Summary

g. Clinical Data Summary and Results of Statistical Analysis
h. Benefit/Risk Relationship and Proposed Postmarketing Studies

16. Case Report Tabulations are missing.

_____
Denise Toyer
Project Manager

_____(Concur)
Parinda Jani
Project Manager

cc:
Original NDA
HFD-570/Division File