

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-692

CHEMISTRY REVIEW(S)

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-692 **CHEM. REVIEW #** 4 **REVIEW DATE:** 9/18/97

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	6/18/96	6/19/96	7/01/96
AMENDMENT [BC]	4/17/97	4/17/97	4/17/97
AMENDMENT [AC]	5/30/97	6/92/97	6/02/97
AMENDMENT [BC]	6/18/97	6/19/97	6/25/97
AMENDMENT [BC]	7/22/97		
AMENDMENT [BZ]*	8/22/97	8/25/97	8/25/97
AMENDMENT [BC]*	8/24/97		8/25/97
AMENDMENT [BC]*	9/12/97		
AMENDMENT [BC]*	9/15/97		
AMENDMENT [BC]*	9/15/97		

* subject of this review

NAME & ADDRESS OF APPLICANT: Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park, North Carolina 27709

DRUG PRODUCT NAME

<u>Proprietary:</u>	Serevent (salmeterol xinafoate) Diskus Inhalation Powder
<u>Nonproprietary/USAN:</u>	salmeterol xinafoate inhalation powder
<u>Code Name/#:</u>	none
<u>Chem. Type/Ther. Class:</u>	bronchodilator

PHARMACOL. CATEGORY/INDICATION: long acting bronchodilator (beta₂-adrenoceptor agonist) for relief of bronchospasm.

DOSAGE FORM: Metered Dose Powder for Inhalation (MDPI)
STRENGTHS: 72.5 mcg salmeterol xinafoate *equivalent to*
50.0 mcg salmeterol base per metered dose

ROUTE OF ADMINISTRATION: 28 and 60 metered dose drug products.
Oral Inhalation
DISPENSED: X Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

See USP Dictionary of USAN and International Drug Names, 1996, page 624.

SUPPORTING DOCUMENTS:

NDA 20236 Serevent (salmeterol xinafoate) Inhalation Aerosol (metered dose inhaler).
IND 43097 Serevent (salmeterol xinafoate) Inhalation Powder

DMFs and Other Supporting Documents

Document No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1
DMF —			adequate	CR#5 9/16/97 R. Lostritto	B7
DMF —			adequate	01/16/97 D. Koble	B7
DMF —			adequate for this NDA only	CR #2 8/13/97	DMF —
DMF —			adequate for — only	01/18/96 L. Ng	see NDAs —
DMF —			adequate	01/31/97	B7
DMF —			adequate	1/10/97 D. Koble	NDA —
DMF —			adequate	1/31/97	B7
NDA 20236			approved	not applicable	not applicable

NDA 20-692 Chem Review #4
page 3

RELATED DOCUMENTS (if applicable):

IND 43097
NDA 20236 for Serevent Inhalation Aerosol. This is the currently marketed metered dose inhaler dosage form of salmeterol xinafoate.
NDA 20692 Chemistry Review # 3 dated 8/14/97

CONSULTS:

Statistics: For stability data analysis: Initiated 8/22/97. Status: Pending. NOTE: [BZ] amendment dated 8/22/97 has been forwarded to the Statistician (Gebert) as part of this consult. This consult has been completed and is discussed herein. [The stability results analysis by the statistician does not support ε — shelf life.]

Nomenclature: (not needed)

Environmental Assessment (EA): EA review forwarded to the Center EA Officer and it has been signed off by that Officer.

Methods Validation: Will be initiated when all methods and specifications are found satisfactory. NOTE: Volume 2 of the 8/24/97 [BC] amendment contains an updated and now outdated methods validation package. THE APPLICANT WILL BE ASKED TO PROVIDE AN UPDATED METHODS VALIDATION PACKAGE.

Establishment Evaluation Request (EER): Initiated 09/23/96,
Amended 4/15/97. Status: Pending

REMARKS/COMMENTS:

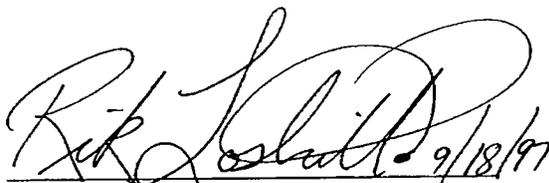
See Review Notes.

CONCLUSIONS & RECOMMENDATIONS:

There are several CMC issues remaining regarding the control of the quality of the drug product. Most notable of these, the applicant agrees to evaluate in greater detail, their proposed 8 week patient-use-life for the unwrapped drug product. The applicant agrees to an interim report date of 12/31/97 (or 90 days from start of stability studies) to substantiate the patient-use-life.

The **Project Manager** will follow up on the pending EER results and will forward the updated Methods Validation Package. The updated Methods Validation package is expected prior to product launch and will reflect all changes noted in the attached draft letter.

Based on this and the other commitments noted in the attached draft letter, this application may be approved from a CMC view point. It is recommended that this NDA (20-692) be approved.


Richard Lostritto, Ph.D. Review Chemist


Guirag Poochikian, Ph.D. Chemistry Team Leader

R/D Init by: QV 9/18/97

filename: N:\nda\20692\chem\97-09-19.rev

NDA 20-692 Chem Review #4
page 5

cc:

Org. NDA 20-692
HFD-570/Division File
HFD-570/PJani (CSO)
HFD-570/R.Lostritto
HFD-570/GPoochikian

71 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry 1

AUG 14 1997

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-692 **CHEM. REVIEW #** 3 **REVIEW DATE:** 8/14/97

SUBMISSION TYPE **DOCUMENT DATE** **CDER DATE** **ASSIGNED DATE**

ORIGINAL	6/18/96	6/19/96	7/01/96
AMENDMENT [BC]	4/17/97	4/17/97	4/17/97
AMENDMENT [AC]*	5/30/97	6/92/97	6/02/97
AMENDMENT [BC]*	6/18/97	6/19/97	6/25/97
AMENDMENT [BC]*	7/22/97		

* subject of this review

NAME & ADDRESS OF APPLICANT:

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

DRUG PRODUCT NAME

<u>Proprietary:</u>	Serevent (salmeterol xinafoate)Diskus Inhalation Powder
<u>Nonproprietary/USAN:</u>	salmeterol xinafoate inhalation powder
<u>Code Name/#:</u>	none
<u>Chem.Type/Ther.Class:</u>	bronchodilator

PHARMACOL. CATEGORY/INDICATION: long acting bronchodilator (beta₂-adrenoceptor agonist) for relief of bronchospasm.

DOSAGE FORM:

Metered Dose Powder for Inhalation (MDPI)

STRENGTHS:

72.5 mcg salmeterol xinafoate **equivalent to**
50.0 mcg salmeterol base per metered dose

ROUTE OF ADMINISTRATION:

28 and 60 metered dose drug products.

Oral Inhalation

DISPENSED:

Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

See USP Dictionary of USAN and International Drug Names, 1996, page 624.

SUPPORTING DOCUMENTS:

NDA 20236 Serevent (salmeterol xinafoate) Inhalation Aerosol (metered dose inhaler).
IND 43097 Serevent (salmeterol xinafoate) Inhalation Powder

DMFs and Other Supporting Documents

Document No.	Holder Name	Subject	Status	Date Reviewed 1*	Reference in CR#1
DMF		/	remains deficient	CR#4 8/13/97 R. Lostritto	B7
DMF			adequate	01/16/97 D. Koble	B7
DMF			adequate for this NDA only	CR #2 8/13/97	DMF
DMF			adequate for only	01/18/96 L. Ng	see NDAs
DMF			adequate	01/31/97	B7
DMF			adequate	1/10/97 D. Koble	NDA
DMF			adequate	1/31/97	B7
NDA 20236				approved	not applicable

*1 Letter date if deficient.

NDA 20-692 Chem Review #3
page 3

RELATED DOCUMENTS (if applicable):

IND 43097

NDA 20236 for Serevent Inhalation Aerosol. This is the currently marketed metered dose inhaler dosage form of salmeterol xinafoate.

NDA 20692 Chemistry Amendment dated 4/17/97 (see CR #2).

CONSULTS:

Statistics: For stability data analysis Status: Will be initiated using Agency "e.g." values for PSD specifications.

Nomenclature: (not needed)

Environmental Assessment (EA): EA review forwarded to the Center EA Officer and it has been signed off by that Officer.

Methods Validation: Will be initiated when all methods and specifications are found satisfactory.

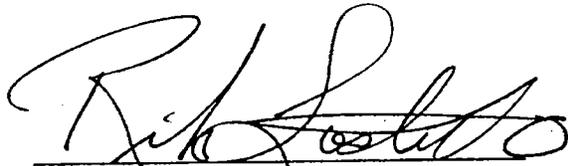
Establishment Evaluation Request (EER): Initiated 09/23/96, Status: Pending
Updated 4/17/97, Status: Pending

REMARKS/COMMENTS:

See Review Notes.

CONCLUSIONS & RECOMMENDATIONS:

There are deficiencies in the excipient, drug product, container closure, specifications and controls and stability sections of this NDA. The applicant should be informed of these deficiencies in a letter.


Richard Lostritto, Ph.D. Review Chemist 8/14/97


Guirag Poochikian, Ph.D. Chemistry Team Leader 8/14/97

R/D Init by: _____

filename: N:\nda\20692\chem\97-05-30.rev

NDA 20-692 Chem Review #3
page 5

cc:
Org. NDA 20-692
HFD-570/Division File
HFD-570/PJani (CSO)
HFD-570/R.Lostritto
HFD-570/GPoochikian

60 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry 2

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-692 **CHEM. REVIEW #** 2 **REVIEW DATE:** 06/11/97

SUBMISSION TYPE **DOCUMENT DATE** **CDER DATE** **ASSIGNED DATE**

ORIGINAL 6/18/96 6/19/96 7/01/96
AMENDMENT [BC]* 4/17/97 4/19/87 4/23/97

* subject of this review

NAME & ADDRESS OF APPLICANT: Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park, North Carolina 27709

DRUG PRODUCT NAME

Proprietary: Serevent (salmeterol xinafoate) Diskus Inhalation Powder
Nonproprietary/USAN: salmeterol xinafoate inhalation powder
Code Name/#: none
Chem. Type/Ther. Class: bronchodilator

PHARMACOL. CATEGORY/INDICATION: long acting bronchodilator (beta₂-adrenoceptor agonist) for relief of bronchospasm.

DOSAGE FORM: Metered Dose Powder for Inhalation (MDPI)
STRENGTHS: 72.5 mcg salmeterol xinafoate *equivalent to*
50.0 mcg salmeterol base per metered dose

ROUTE OF ADMINISTRATION: 28 and 60 metered dose drug products.
Oral Inhalation
DISPENSED: X Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

See USP Dictionary of USAN and International Drug Names, 1996, page 624.

SUPPORTING DOCUMENTS:

NDA 20236 Serevent (salmeterol xinafoate) Inhalation Aerosol (metered dose inhaler).
IND 43097 Serevent (salmeterol xinafoate) Inhalation Powder

DMFs and Other Supporting Documents

Document No.	Holder Name	Subject	Status	Date Reviewed 1*	Reference in CR#1
DMF		/	remains deficient	in progress	B7
DMF			adequate	01/16/97 D. Koble	B7
DMF			deficient do <i>not</i> reference in NDA IR letters	in progress	DMF
DMF			adequate for only	01/18/96 L. Ng	see NDAs
DMF			adequate	01/31/97	B7
DMF			adequate	1/10/97 D. Koble	NDA
DMF			adequate	1/31/97	B7
NDA 20236			approved	not applicable	not applicable

*1 Letter date if deficient.

RELATED DOCUMENTS (if applicable):

IND 43097
NDA 20236 for Serevent Inhalation Aerosol. This is the currently marketed metered dose inhaler dosage form of salmeterol xinafoate.

CONSULTS:

Statistics: For stability data analysis Status: To be initiated after the specifications have been set for the critical attributes.

Microbiology: May be initiated based on the applicant's response to comments from this review regarding microbial controls of drug product (see comment 7 of attached Draft Letter)

Nomenclature: (not needed)

Environmental Assessment (EA): EA review forwarded to the Center EA Officer and it has been signed off by that Officer.

Methods Validation: Will be initiated when all methods and specifications are found satisfactory.

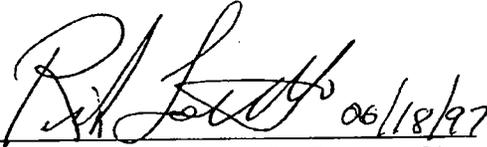
Establishment Evaluation Request (EER): Initiated 09/23/96, Status: Pending

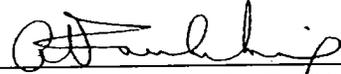
REMARKS/COMMENTS:

See Review Notes.

CONCLUSIONS & RECOMMENDATIONS:

There are deficiencies in the micronized drug substance, excipient, drug product, container closure, specifications and controls and stability sections of this NDA. The applicant should be informed of these deficiencies in a letter.


Richard Lostritto, Ph.D. Review Chemist


Guirag Poochikian, Ph.D. Chemistry Team Leader

R/D Init by: 6/19/97

filename: N:\nda\20692\chem\97-06-19.rev

NDA 20-692 Chem Review #2
page 5

cc:

Org. NDA 20-503
HFD-570/Division File
HFD-570/PJani (CSO)
HFD-570/R.Lostritto
HFD-570/GPoochikian

43 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry 3

FEB 5 1997

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-692 **CHEM. REVIEW #** 1 **REVIEW DATE:** 02/04/97

SUBMISSION TYPE **DOCUMENT DATE** **CDER DATE** **ASSIGNED DATE**

ORIGINAL* 6/18/96 6/19/94 7/01/96

* subject of this review

NAME & ADDRESS OF APPLICANT: Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park, North Carolina 27709

DRUG PRODUCT NAME

Proprietary: Serevent (salmeterol xinafoate) Diskus Inhalation Powder
Nonproprietary/USAN: salmeterol xinafoate inhalation powder
Code Name/#: none
Chem.Type/Ther.Class: bronchodilator

PHARMACOL. CATEGORY/INDICATION: long acting bronchodilator (beta₂-adrenoceptor agonist) for relief of bronchospasm.

DOSAGE FORM: Metered Dose Powder for Inhalation (MDPI)
STRENGTHS: 72.5 mcg salmeterol xinafoate *equivalent to*
50.0 mcg salmeterol base per metered dose

ROUTE OF ADMINISTRATION: 28 and 60 metered dose drug products.
Oral Inhalation
DISPENSED: X Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

See USP Dictionary of USAN and International Drug Names, 1996, page 624.

SUPPORTING DOCUMENTS:

NDA 20236 Serevent (salmeterol xinafoate) Inhalation Aerosol (metered dose inhaler).
IND 43097 Serevent (salmeterol xinafoate) Inhalation Powder

DMFs and Other Supporting Documents

Document No.	Holder Name	Subject	Status	Date Reviewed 1*	Reference in CR#1
DMF			deficient	01/28/97	B7
DMF			adequate	01/16/97 D. Koble	B7
DMF			deficient do <i>not</i> reference in NDA IR letters	01/28/97	DMF
DMF			adequate for only	01/18/96 L. Ng	see NDAs
DMF			adequate	01/31/97	B7
DMF			adequate	1/10/97 D. Koble	NDA
DMF			adequate	1/31/97	B7
NDA			approved	not applicable	not applicable

*1 Letter date if deficient.

RELATED DOCUMENTS (if applicable):

IND 43097

NDA 20236 for Serevent Inhalation Aerosol. This is the currently marketed metered dose inhaler dosage form of salmeterol xinafoate.

CONSULTS:

Statistics: For stability data analysis Status: To be initiated after the applicant responds to comments from this review regarding stability.

Microbiology: May be initiated based on the applicant's response to comments from this review regarding microbial controls of drug substance, excipients and drug product.

Nomenclature: (not needed)

Environmental Assessment (EA): To be initiated

Establishment Evaluation Request (EER): Initiated 09/23/96, Status: Pending

REMARKS/COMMENTS:

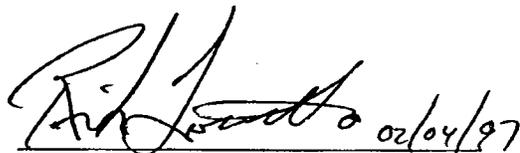
See Review Notes.

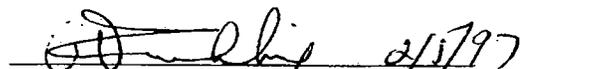
CONCLUSIONS & RECOMMENDATIONS:

There are deficiencies in the drug substance, excipient, drug product, container closure, specifications and controls and stability sections of this NDA. The applicant should be informed of these deficiencies in a letter. **If all deficiencies are not satisfactorily resolved, this NDA should be "not approvable".**

cc:

Org. NDA 20-503
HFD-570/Division File
HFD-570/PJani (CSO)
HFD-570/R.Lostritto
HFD-570/GPoochikian


Richard Lostritto, Ph.D. Review Chemist


Guirag Poochikian, Ph.D. Supervisory Chemist

R/D Init by: _____

filename: N:\nda\20692\chem\97-02-04.rev

71 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry-4

CDER Establishment Evaluation Report
for September 19, 1997

Page 1 of 2

Application: NDA 20692/000 Priority: 3S Org Code: 570
Stamp: 19-JUN-1996 Regulatory Due: 19-SEP-1997 Action Goal: District Goal: 17-FEB-1997
Applicant: GLAXO WELLCOME Brand Name: SEREVENT DISKUS 50MCG INHALAT
5 MOORE DR Established Name:
RESEARCH TRIANGLE PARK, NC 2 Generic Name: SALMETETROL XINAFOATE
Dosage Form: PDR (POWDER)
Strength: 50 MCG/INHALATION
FDA Contacts: H. KHORSHIDI (HFD-570) 301-827-1096 , Review Chemist

Overall Recommendation:

ACCEPTABLE on 19-SEP-1997 by M. EGAS(HFD-322)301-594-0095

Establishment: 9610411
GLAXO OPERATIONS UK LTD
PRIORY ST
WARE, HERTFORDSHIRE, UK

DMF No:

AADA No:

Profile: ADM OAI Status: NONE
Last Milestone: OC RECOMMENDAT 19-SEP-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities:
DRUG SUBSTANCE
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE STABILITY TESTER

Profile: CRU OAI Status: NONE
Last Milestone: OC RECOMMENDAT 14-MAY-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDAT 18-OCT-1996
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

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

DMF No:

AADA No:

Profile: NEC OAI Status: NONE
Last Milestone: OC RECOMMENDAT 18-OCT-1996
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities:
FINISHED DOSAGE STABILITY TESTER

Establishment: 9610419
GLAXOCHEM LTD
COBDEN ST
MONTROSE ANGUS, SCOTLAND, U

DMF No:

AADA No:

CDER Establishment Evaluation Report
for September 19, 1997

Page 2 of 2

Profile: CSN OAI Status: NONE Responsibilities:
Last Milestone: OC RECOMMENDAT 18-OCT-1996 DRUG SUBSTANCE MANUFACTURER
Decision: ACCEPTABLE DRUG SUBSTANCE STABILITY TESTER
Reason: BASED ON PROFILE

Establishment: / DMF No:
AADA No:

Profile: NEC OAI Status: NONE Responsibilities:
Last Milestone: OC RECOMMENDAT 30-JAN-1997 /
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: / DMF No:
DA No:

Profile: NEC OAI Status: NONE Responsibilities:
Last Milestone: OC RECOMMENDAT 18-OCT-1996 /
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: 9611905 DMF No:
LABORATOIRES GLAXO
ZONE INDUSTRIELLE 2 27000 AADA No:
EVREUX, CEDEX, FR

Profile: CSN OAI Status: NONE Responsibilities:
Last Milestone: OC RECOMMENDAT 10-JAN-1997 DRUG SUBSTANCE
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: 9610414 DMF No:
WELLCOME FDN LTD AADA No:
DARTFORD, KENT DA1 5AH, , UK

Profile: NEC OAI Status: NONE Responsibilities:
Last Milestone: OC RECOMMENDAT 11-JUN-1997 FINISHED DOSAGE OTHER TESTER
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

3 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling