CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-077

CHEMISTRY REVIEW(S)

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

NDA #: 21-077 **CHEM. REVIEW #: 4** **REVIEW DATE: 24-AUG-00**

RECOMMEND ACTION: Approval

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
Original	24-MAR-99	25-MAR-99
Amendment	30-JUN-99	02-JUL-99
Amendment	30-AUG-99	31-AUG-99
Amendment	29-SEP-99	30-SEP-99
Amendment	25-FEB-00	25-FEB-00
Amendment	18-APR-00	19-APR-00
Amendment	15-MAR-00	16-MAR-00
Amendment	25-JUL-00	26-JUL-00
Amendment	26-JUL-00	27-JUL-00
Amendment*	14-AUG-00	
Amendment*	18-AUG-00	
Amendment*	23-AUG-00	

*Subject of this review

NAME & ADDRESS OF APPLICANT:

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

DRUG PRODUCT NAME:
Proprietary: Advair Diskus
Nonproprietary/USAN: salmeterol xinafoate and fluticasone propionate inhalation powder
Chem. Type/Ther. Class: 4S
PHARMACOL. CATEGORY/INDICATION: asthma
DOSAGE FORM: powder
STRENGTHS: 50/100, 50/250, 50/500 mcg (salmeterol and fluticasone propionate respectively). The salmeterol is present as salmeterol xinafoate (72.5 mcg).

The trade pack contains 60 doses/device. The institutional and sample packs contain 28 doses/device.

ROUTE OF ADMINISTRATION: oral inhalation
DISPENSED: X Rx _ OTC
SPECIAL PRODUCTS: _ YES x NO
(If yes, fill out the form for special products and deliver to the TIA through the team leader for data entry)

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

See USAN

SUPPORTING DOCUMENTS:

DMFs and Other Referenced Information

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in Reviews
[redacted]			Adequate		[redacted]
			Adequate		"
			Adequate		"
			Adequate		"
			Adequate		"
			Adegaute		"
N20-236,N 20692	Glaxo Wellcome	Salmeterol xinafoate drug substance	Adequate		See this review, Question 1.
N 20-121	Glaxo Wellcome	fluticasone propionate drug substance	Adequate		See CR#1, page 9
			Adequate	24-JAN-00	See CR#1, page 42

RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject	Status	Date
NDA	20-692	Glaxo	Serevent Diskus	Approved	19-SEP-97
NDA	20-833	Glaxo	Flovent Diskus	Approvable	28-NOV-99

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	05-MAY-00	AC	
Microbiology, HFD-160	Not applicable		
Biometrics, HFD-710	08-DEC-99	Stability consult review dated 24-JAN-00	the biometrics comments concerning statistical analysis of the aerodynamic fine particle size data on stability were forwarded to the applicant, see comments from CR#1. For review of the firms responses, see review of Questions 14c and 14d in CR#2.
Environmental Assessment	N/A		
Pharm/Tox HFD-570	20-AUG-99	Consult review dated 12/17/99	the consult review recommended that levels proposed for [redacted] in salmeterol xinafoate drug substance and for [redacted] in the drug product be considered acceptable. The pharm/tox

			comment that the specification for most abundant other impurity in salmeterol xiaafoate drug substance be tightened to — — was forwarded to the applicant; see comments for CR#1. The final specifications provided by the applicant have incorporated these recommendations (see **attachments I and II** to this review).
Pharm/Tox HFD-570	3/3/00	Consult review dated 3/8/00	the pharm/tox review found the potential exposure to the colorant in the mouthpiece to be acceptable.
Labeling & Nomenclature Committee	24-MAY-99	Accept-able*	

CONCLUSIONS AND RECOMMENDATIONS:

From a chemistry, manufacturing, and controls perspective, it is recommended that the NDA be approved. The approval letter should include the **COMMENTS** at the end of this review.

cc:
Orig. NDA 21-077
HFD-570/Division File
HFD-570/DKoble
HFD-570/PJani
HFD-570/GPoochikian
HFD-570/SJohnson
HFD-570/BElashoff
R/D Init. by: /S/ 8/24/00
filename: NDA21-077.cr4

/S/

8/24/00

Dale L. Koble, Ph.D., Review Chemist

REMARKS

1. Methods Validation Package: The applicant provided an updated methods validation package in the submission dated 23-AUG-00. This submission was not reviewed in detail, but will be reviewed for completeness before it is sent to the FDA laboratories.

2. Master Batch Records: The applicant provided updated master batch records in the submission dated 23-AUG-00. This submission was not reviewed in detail. The firm provided a list of updates in the introduction to the section on the master batch records and a spot check of the master batch records indicates that they were appropriately updated.

   The applicant had previously indicated that a series of master batch records would be established that describe the products by specific strength, pack size, and filling overage. The — — will not be specified in the MBR. An internal production scheduling system will take into account specific — — for product strengths and pack size based upon validation data. The applicant indicated in the

15-MAR-00 submission that appropriate master batch records will be provided once the expiration dating periods are agreed upon (see evaluation of Question 2 in CR#2).

The applicant had previously provided a commitment (response to Question 5 below) to provide an updated master batch record once agreement has been reached with the agency on a number of issues [ ] See responses to Questions 2, 3, 4, 5, and 6 below).

3. The information concerning the _____ _____ is provided in the NDA rather than referenced to a DMF.

4. The following agreements should be included in the final approval letter.

5. The project manager should incorporate the standard methods validation paragraph in the approval letter.

COMMENTS:

See at end of review.

APPEARS THIS WAY
ON ORIGINAL

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

NDA #: 21-077 **CHEM. REVIEW #: 3** **REVIEW DATE: 21-AUG-00**

RECOMMEND ACTION:

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
Original	24-MAR-99	25-MAR-99
Amendment	30-JUN-99	02-JUL-99
Amendment	30-AUG-99	31-AUG-99
Amendment	29-SEP-99	30-SEP-99
Amendment	25-FEB-00	25-FEB-00
Amendment	18-APR-00	19-APR-00
Amendment*	15-MAR-00	16-MAR-00
Amendment*	25-JUL-00	26-JUL-00
Amendment*	26-JUL-00	27-JUL-00

*Subject of this review

NAME & ADDRESS OF APPLICANT: Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

DRUG PRODUCT NAME:
Proprietary: Advair Diskus

Nonproprietary/USAN: salmeterol xinafoate and fluticasone propionate inhalation powder

Chem. Type/Ther. Class:4S
PHARMACOL. CATEGORY/INDICATION: asthma
DOSAGE FORM: powder
STRENGTHS: 50/100, 50/250, 50/500 mcg (salmeterol and fluticasone propionate respectively). The salmeterol is present as salmeterol xinafoate (72.5 mcg).
The trade pack contains 60 doses/device. The institutional and sample packs contain 28 doses/device.
ROUTE OF ADMINISTRATION: oral inhalation
DISPENSED: X Rx _ OTC
SPECIAL PRODUCTS: _ YES x NO
(If yes, fill out the form for special products and deliver to the TIA through the team leader for data entry)

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

See USAN

SUPPORTING DOCUMENTS:

DMFs and Other Referenced Information

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in Reviews
			Adequate		
			Adequate		"
			Adequate		"
			Adequate		"
			Adequate		"
			Adequate		"
			Adeqaute		"
N20-236,N 20692	Glaxo Wellcome	Salmeterol xinafoate drug substance	Adequate		See this review, Question 1.
N 20-121	Glaxo Wellcome	fluticasone propionate drug substance	Adequate		See CR#1, page 9
			Adequate	24-JAN-00	See CR#1, page 42

RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject	Status	Date
NDA	20-692	Glaxo	Serevent Diskus	Approved	19-SEP-97
NDA	20-833	Glaxo	Flovent Diskus	Approvable	28-NOV-99

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	05-MAY-00	AC	
Microbiolcgy, HFD-160	Not applicable		
Biometrics, HFD-710	08-DEC-99	Stability consult review dated 24-JAN-00	the biometrics comments concerning statistical analysis of the aerodynamic fine particle size data on stability were forwarded to the applicant, see comments from CR#1.
Environmental Assessment	N/A		
Pharm/Tox HFD-570	20-AUG-99	Consult review dated 12/17/99	the consult review recommended that levels proposed for ——— in salmeterol xinafoate drug substance and for ——— in the drug product be considered acceptable. The pharm/tox comment that the specification for most abundant other impurity in salmeterol xianafoate drug substance be tightened to —

			[redacted] was forwarded to the applicant; see comments for CR#1.
Pharm/Tox HFD-570	3/3/00	Consult review dated 3/8/00	the pharm/tox review found the potential exposure to the colorant in the mouthpiece to be acceptable.
Labeling & Nomenclature Committee	24-MAY-99	Accept-able*	

* Advair Diskus was found acceptable. The LNC commented that the [redacted] is misleading and that the sponsor should re-do expression of potency to include both ingredients. A consult dated 1/11/00 has been sent to OPDRA concerning this and other labeling issues by CSO Parinda Jani.

CONCLUSIONS AND RECOMMENDATIONS:

From a chemistry, manufacturing, and controls perspective, it is recommended that the NDA be considered approvable. See comments under **REMARKS** and **COMMENTS** below.

cc:
Orig. NDA 21-077
HFD-570/Division File
HFD-570/DKoble
HFD-570/PJani
HFD-570/GPoochikian
HFD-570/SJohnson
HFD-570/BElashoff
R/D Init. by: GP 8/23/00
filename: NDA21-077.cr3

/S/

8/21/00

Dale L. Koble, Ph.D., Review Chemist

REMARKS

* Note that This was previously reviewed by Dr. Poochikian.

1. The applicant has provided a commitment to provide an **updated methods validation package** once agreement has been obtained with the agency on tests and specifications.

2. In the 15-MAR-00 submission, the applicant indicates that a series of master batch records will be established that describe the products by specific strength, pack size, and filling overage. The [redacted] will not be specified in the MBR. An internal production scheduling system will take into account specific [redacted] for product strengths and pack size based upon validation data. The applicant indicates in the 15-MAR-00 submission that appropriate **master batch records** will be provided either pre-approval or post-approval as required, once the expiration dating periods are agreed upon (see evaluation of Question 2 in CR#2).

3. The applicant has provided a commitment (response to Question 5 below) to provide **an updated master batch record** once agreement has been reached with the agency on a number of issues [redacted]. See responses to Questions 2, 3, 4, 5, and 6 below).

4. The following agreements should be included in the final approval letter.

[ ]

5. The information concerning the [redacted] is provided in the NDA rather than referenced to a DMF.

COMMENTS:

See at end of review.

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

NDA #: 21-077 **CHEM. REVIEW #: 2** **REVIEW DATE: 18-APR-00**

RECOMMEND ACTION:

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
Amendment	25-FEB-00	
Amendment	18-APR-00	

NAME & ADDRESS OF APPLICANT:

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

DRUG PRODUCT NAME:
Proprietary: Advair Diskus

Nonproprietary/USAN: salmeterol xinafoate and fluticasone propionate inhalation powder

Chem. Type/Ther. Class:4S
PHARMACOL.
CATEGORY/INDICATION: asthma
DOSAGE FORM: powder
STRENGTHS: 50/100, 50/250, 50/500 mcg (salmeterol and fluticasone propionate respectively). The salmeterol is present as salmeterol xinafoate (72.5 mcg).
ROUTE OF ADMINISTRATION: oral inhalation

The trade pack contains 60 doses/device. The institutional and sample packs contain 28 doses/device.

DISPENSED: X Rx _ OTC
SPECIAL PRODUCTS: _ YES x NO
(If yes, fill out the form for special products and deliver to the TIA through the team leader for data entry)

APPEARS THIS WAY
ON ORIGINAL

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

See USAN

SUPPORTING DOCUMENTS:

DMFs and Other Referenced Information

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in Reviews
			Adequate		[ ]
			Adequate		"
			Adequate		"
			Adequate		"
			Adequate		"
			Adequate		"
			Adequate		"
N20-236,N 20692	Glaxo Wellcome	Salmeterol xinafoate drug substance	Inadequate		See this review, Question 1.a.
N 20-121	Glaxo Wellcome	fluticasone propionate drug substance	Adequate		See CR#1, page 9
			Adequate	24-JAN-00	See CR#1, page 42

RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject	Status	Date
NDA	20-692	Glaxo	Serevent Diskus	Approved	19-SEP-97
NDA	20-833	Glaxo	Flovent Diskus	Approvable	28-NOV-99

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	05-MAY-00	AC	
Microbiology, HFD-160	Not applicable		
Biometrics, HFD-710	08-DEC-99	Stability consult review dated 24-JAN-00	to provide statistical analysis of expiration dating period. Aerodynamic fine particle size distribution was analyzed (this is the [redacted]
Environmental Assessment	N/A		
Pharm/Tox HFD-570	20-AUG-99	Consult review dated 12/17/99	to provide a recommendation for the safety of salmeterol drug substance impurity [redacted]
Pharm/Tox HFD-570	15-DEC-99	Consult review dated 1/18/00	safety qualification of colorants used in mouthpiece of Diskus device
Labeling & Nomenclature Committee	24-MAY-99	Acceptable*	

* Advair Diskus was found acceptable. The LNC commented that the [redacted] is misleading and that the sponsor should re-do expression of potency to include both ingredients. A consult dated 1/11/00 has been sent to OPDRA concerning this and other labeling issues by CSO Parinda Jani.

CONCLUSIONS AND RECOMMENDATIONS:

From a chemistry, manufacturing, and controls perspective, it is recommended that the NDA be considered approvable. See comments under **REMARKS** and **COMMENTS** below.

cc:
Orig. NDA 21-077
HFD-570/Division File
HFD-570/DKoble
HFD-570/PJani
HFD-570/GPoochikian
HFD-570/SJohnson
HFD-570/BElashoff
R/D Init. by: 7/24/00
filename: NDA21-077.cr2

/S/ 7/18/00

Dale L. Koble, Ph.D., Review Chemist

REMARKS

1. Labeling comments have been obtained from OPDRA.

2. The applicant has provided a commitment to provide an updated methods validation package and master batch record once agreement has been obtained with the agency on tests and specifications.

3. The information concerning the [redacted] is provided in the NDA rather than referenced to a DMF.

4. A request is included in the draft letter for annotation of a portion of the Description section of the updated package insert. A complete review of this section will not be performed until the annotated labeling is received.

COMMENTS:

See at end of review.

APPEARS THIS WAY
ON ORIGINAL

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

NDA #: 21-077 **CHEM. REVIEW #:** 1 **REVIEW DATE:**

RECOMMEND ACTION: Not approvable 1/25/00

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
ORIGINAL	24-MAR-99	25-MAR-99
AMENDMENT	30-JUN-99	02-JUL-99
AMENDMENT	30-AUG-99	31-AUG-99
AMENDMENT	29-SEP-99	30-SEP-99

NAME & ADDRESS OF APPLICANT:

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

DRUG PRODUCT NAME:
Proprietary: Advair Diskus

Nonproprietary/USAN: salmeterol xinafoate and fluticasone propionate inhalation powder

Chem. Type/Ther. Class:4S
PHARMACOL.
CATEGORY/INDICATION: asthma
DOSAGE FORM: powder
STRENGTHS: 50/100, 50/250, 50/500 mcg (salmeterol and fluticasone propionate respectively). The salmeterol is present as salmeterol xinafoate (72.5 mcg).
ROUTE OF ADMINISTRATION: oral inhalation

The trade pack contains 60 doses/device. The institutional and sample packs contain 28 doses/device.

DISPENSED: X Rx _ OTC
SPECIAL PRODUCTS: _ YES x NO
(If yes, fill out the form for special products and deliver to the TIA through the team leader for data entry)

APPEARS THIS WAY
ON ORIGINAL

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

See USAN

SUPPORTING DOCUMENTS:

DMFs and Other Referenced Information

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in Reviews
[			Adequate		[ ]
			Adequate		"
			Adequate		"
			Adequate		"
			Adequate		"
			Adequate		"
			Adequate		"
N20-236,N 20692	Glaxo Wellcome	Salmeterol xinafoate drug substance	Inadequate		See this review, page 6
N 20-121	Glaxo Wellcome	fluticasone propionate drug substance	Adequate		See this review, page 9
			Adequate	24-JAN-00	See this review, page 42

RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject	Status	Date
NDA	20-692	Glaxo	Serevent Diskus	Approved	19-SEP-97
NDA	20-833	Glaxo	Flovent Diskus	Approvable	28-NOV-99

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	25-MAR-99	Pending	
Microbiology, HFD-160	N/A		
Biometrics, HFD-710	08-DEC-99	Stability consult review dated 24-JAN-00	to provide statistical analysis of expiration dating period. Aerodynamic fine particle size distribution was analyzed (this is the
Environmental Assessment	N/A		
Pharm/Tox HFD-570	20-AUG-99	Consult review dated 12/17/99	to provide a recommendation for the safety of salmeterol drug substance impurity
Pharm/Tox HFD-570	15-DEC-99	Consult review dated 1/18/00	safety qualification of colorants used in mouthpiece of Diskus device
Labeling & Nomenclature Committee	24-MAY-99	Accept-able*	

* Advair Diskus was found acceptable. The LNC commented that the [redacted] is misleading and that the sponsor should re-do expression of potency to include both ingredients. A consult dated 1/11/00 has been sent to OPDRA concerning this and other labeling issues by CSO Parinda Jani.

CONCLUSIONS AND RECOMMENDATIONS:

From a chemistry, manufacturing, and controls perspective, it is recommended that the NDA be considered approvable. See comments under **REMARKS** and **COMMENTS** below.

cc:
Orig. NDA 21-077
HFD-570/Division File
HFD-570/DKoble
HFD-570/PJani
HFD-570/GPoochikian
HFD-570/Sjohnson
HFD-570/Belasheff
R/D Init. by: (S) 1/25/00
filename: NDA21-077.cr1

/S/
1/25/00
Dale L. Koble, Ph.D., Review Chemist

REMARKS

1. Note that labeling comments have been requested from OPDRA and are pending.

2. Note that the applicant has provided a commitment to provided an updated methods validation once agreement has been obtained with the agency on tests and specifications.

3. The project manager should check on the EIR before taking an action.

4. Note that the information concerning the [redacted] is provided in the NDA rather than referenced to a DMF.

5 The acceptability of [redacted] and the [redacted] depends upon the comparison of the stability of the "commercial" stability batches in which these were used and the primary stability batches. A comment on this comparison has been included in the draft comments to the applicant.

COMMENTS:

See at end of review.

APPEARS THIS WAY
ON ORIGINAL

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FROM: Dale Koble
Review Chemist

/S/ 8/23/00

TO: NDA 21-077 Division File

DATE: 23-AUG-00

RE: Diskus mechanical reliability

Glaxo submitted an assessment of the durability of device in actual use (based upon customer complaints from European marketing of the fluticasone/salmeterol drug product) on page 54 of Vol.13.1 of the 25-FEB-00 submission to the NDA.

Complaints were classified as unsubstantiated, inconclusive, and substantiated. Out of ——— manufactured devices there were the following substantiated complaints:

5 cases of device jamming were substantiated. The firm indicates that this was identified as an assembly issue and currently 100% inspection is in place to monitor this problem

6 substantiated complaints of multi-clicking when the device lever was actuated (the device should click only once per actuation). The firm indicates that this has been addressed with the supplier of the device component.

EVALUATION:

The information provided indicates satisfactory mechanical reliability (3.5 substantiated complaints per ——— devices) of the Diskus device for Advair Diskus (NDA 21-077).

The issue of device reliability should be reconsidered for

DEVICE JAMMING

The Diskus device is mechanically identical (varying only in color) for Advair, Serevent, Flovent, [redacted] Diskus pending or approved NDAs. While no specific information was provided in the information under review, the issue of device jamming was reviewed in detail for NDA 20-833 (CR#1, pages 43-47 and CR#2, pages 35-37). Problems with blister strip jamming were addressed by [redacted] (second refinement of the device), change to a [redacted] design (third refinement of the device), and [redacted]

MULTIPLE CLICKING

This problem was not previously addressed in chemistry reviews of Diskus drug products. However, due to the low criticality, the low incidence is acceptable for Advair.

CC:
Original NDA 21-077
HFD-570: Divfile
HFD-570: Dkoble
HFD-570:Gpoochikian
HFD-570: Sjohnson
HFD-570: Pjani

APPEARS THIS WAY
ON ORIGINAL

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