

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20983

CHEMISTRY REVIEW(S)

**ENVIRONMENTAL ASSESSMENT
Statement Of Categorical Exclusion
For
Albuterol/GR106642X Inhalation Aerosol
NDA 20-983**

DATE: June 15, 1998

APPLICANT: Glaxo Wellcome Inc.

ADDRESS: Five Moore Drive
Research Triangle Park, NC 27709

STATEMENT: The proposed action is subject to the categorical exclusion listed in 21 CFR Part 25.31(a). The request for categorical exclusion approval is for a manufacturing site change. Therefore the criteria outlined in 21 CFR Part 25.31(a) that an action on an NDA or abbreviated application where the action does not increase the use of the active moiety is categorically excluded from environmental assessment requirements is met. Glaxo Wellcome does not have knowledge of any extraordinary circumstances that might cause this action to have a significant affect on the quality of the human environment.

Jani

**MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: June 21, 1999

TO: N 20-983 File, Ventolin HFA (albuterol sulfate inhalation aerosol)

THROUGH: Guirag Poochikian, Ph.D.
Chemistry Team Leader
Division of Pulmonary Drug Products (HFD-570)

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
Division of Pulmonary Drug Products (HFD-570)

SUBJECT: Consult to Pharmacologist/Toxicologist acting team leader Mark Vogel, Ph.D. regarding the levels of formaldehyde found in aged placebo for the corresponding drug product.

BACKGROUND: Comment 10e(6) of the 10/26/98 CMC information request letter requested that a study be undertaken to determine the levels of the potential extractable/leachable that may be emanating from the components of the valve used with the drug product. The amendment of 2/26/99 indicated that 2 year aged placebo product exhibited concentrations of about ppm which would correspond to a daily intake (at 12 actuations/day) of about micrograms of
See 6/21/99 electronic mail requesting input on the safety from a toxicological perspective of the and the response of 6/21/99 in attachment.



/S/

Craig M. Bertha, Ph.D.

Chemistry Reviewer

cc:
Orig. NDA 20-983
HFD-570/Div. Files
HFD-570/CBertha
HFD-570/GPoochikian *GP/2/24*
HFD-570/PJani

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

<u>NDA #:</u>	20-983	<u>CHEM. REVIEW #</u>	8	<u>REVIEW DATE:</u>	4/19/01
<u>SUBMISSION TYPE</u>		<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>	
ORIGINAL	6/30/98	7/1/98	7/1/98	7/8/98	
AMENDMENT (BC)	7/10/98	7/13/98	7/13/98	7/15/98	
AMENDMENT (BC)	7/23/98	7/24/98	7/24/98	7/27/98	
AMENDMENT (BC)	7/27/98	7/28/98	7/28/98	8/6/98	
AMENDMENT (BC)	12/18/98	12/21/98	12/21/98	12/23/98	
AMENDMENT (BC)	2/26/99	3/2/99	3/2/99	3/8/99	
AMENDMENT (AC)	3/31/99	4/1/99	4/1/99	4/5/99	
AMENDMENT (BC)	6/2/99	6/3/99	6/3/99	6/14/99	
AMENDMENT (AC)	6/29/00	7/3/00	7/3/00	7/5/00	
AMENDMENT (BC)	7/19/00	7/20/00	7/20/00	7/25/00	
CORRESPONDENCE	8/25/00	8/28/00	8/28/00	8/29/00	
AMENDMENT (BC)	9/29/00	10/2/00	10/2/00	10/10/00	
AMENDMENT (BC)	10/12/00	10/13/00	10/13/00	10/19/00	
AMENDMENT (BC)	12/6/00	12/7/00	12/7/00	12/7/00	
AMENDMENT (BC)	12/22/00	12/27/00	12/27/00	12/29/00	
AMENDMENT (AC)	1/4/01	1/5/01	1/5/01	1/9/01	
AMENDMENT (AC)	2/2/01	2/5/01	2/5/01	2/5/01	
AMENDMENT (BC)	2/20/01	2/22/01	2/22/01	2/28/01	
AMENDMENT (BC)	2/26/01	2/28/01	2/28/01	2/28/01	
AMENDMENT (BC) ¹	3/30/01	4/2/01	4/2/01	4/4/01	
AMENDMENT (BC) ¹	4/12/01	4/16/01	4/16/01	4/16/01	
AMENDMENT (BC) ¹	4/19/01	4/19/01 ²	4/19/01 ²	4/19/01	

¹Subject of the current CR#8; ²As telephone facsimile.

NAME & ADDRESS OF APPLICANT:

GlaxoSmithKline
 Five Moore Drive
 P.O. Box 13398
 Research Triangle Park, NC 27709

DRUG PRODUCT NAME

Proprietary:

Ventolin® HFA Inhalation Aerosol

Nonproprietary/USAN:

albuterol sulfate HFA inhalation aerosol*

Code Name/#:

AH3365F

Chem. Type/Ther. Class:

3S

PHARMACOL. CATEGORY/INDICATION:

For treatment or prevention of bronchospasm in patients 4 yrs. and older with reversible obstructive airway disease and for prevention of exercise-induced bronchospasm

DOSAGE FORM:

inhalation aerosol

STRENGTHS:

108 µg albuterol sulfate (90 µg base)/act from actuator (120 µg of albuterol sulfate/act from valve), 75 mg suspension/act

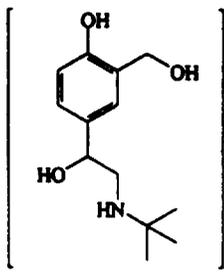
ROUTE OF ADMINISTRATION:

Inhalation

DISPENSED:
SPECIAL PRODUCTS:

Rx OTC
 Yes No

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



Albuterol Sulfate, α^1 -[*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene- α,α' -diol sulfate (2:1) (salt); Molecular Formula: $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$; Molecular Weight: 576.72 (base 239.32)

$\cdot H_2SO_4$

SUPPORTING DOCUMENTS:

See chemist's review notes below, p. 8.

RELATED DOCUMENTS:

NDA:

- N18-473 Ventolin[®] (albuterol) Inhalation Aerosol (AP 5/81)
- N19-112 Ventolin[®] (albuterol) Tablets (AP 7/86)
- N19-269 Ventolin[®] (albuterol sulfate) Inhalation Solution (AP 1/87)
- N19-489 Ventolin[®] (albuterol sulfate) Rotocaps for Inhalation (AP 5/88)
- N19-621 Ventolin[®] (albuterol sulfate) Syrup (AP 6/87)
- N19-773 Ventolin[®] (albuterol sulfate) Inhalation Solution (AP 4/92)

IND:

CONSULTS:

Consult	Date Forwarded	Status	Comments
EES	Forwarded on 8/31/98 Update forwarded 7/5/00 Update forwarded 2/22/01	-Acceptable -Acceptable -Acceptable	OC decision 6/25/99 OC decision 7/13/00 OC decision 2/26/01
Separate request for contract extractables laboratories (3)	Forwarded on 7/20/00	-Acceptable	OC decision 11/13/00
Separate request for additional extractables contract laboratories (3)	Forwarded on 4/4/01	-Pending	
Microbiology	5/25/99	-Acceptable, 5/28/99	Requested comments on results of microorganism survivability studies performed as per comment 11 of the 10/26/98 Agency letter.
	-9/10/98	-Acceptable, 2/4/99	-HFA-134a Impurities Consult
	-10/9/98	-Unacceptable, 7/1/99	Gasket
	-Updated request 6/21/99 ¹	-Unacceptable, 8/23/00	-Comment 37 of 7/1/99 AE
	-7/6/00 (response to comment 37)	-Acceptable, 10/19/00	-See p. 23 of CR#4
	-8/22/99	-Unacceptable, 7/1/99	-Comment 37 of 7/1/99 AE
	-7/6/00 (response to comment 37)	-Unacceptable, 8/23/00	-See p. 23 of CR#4
	10/19/00	-Acceptable, 10/19/00	
	-10/9/98	-Unacceptable, 7/1/99	-Comments 4 & 36 of 7/1/99 AE
		-Acceptable, 8/23/00	
	-11/16/98	-Acceptable, 4/22/99	
	-3/22/99	-Acceptable, 6/17/99	
	-4/16/99	-Acceptable, 6/7/99	
Method Validation	Not forwarded.		-Updated packages from 12/22/00 amendment need to have DP specifications and method for can assay (concentration with limits for individual units) included (see final commitment draft letter).
Labeling and Nomenclature Committee	Not forwarded.		-The trademark Ventolin® is already in use for six other albuterol or albuterol sulfate products from the applicant.
Biometrics	-12/7/00	-See review for details and discussion p. 30 of CR#5	Expiry for Batches 6ZX012, 6ZX013, and 6ZX015
	-12/13/00	-Acceptable	Expiry for Batch 7ZX027 for mean DCU (beg and end of can)
	-10/18/00 ¹	-See p. 14 of CR#6	-Request comments on MDI stress test sampling plan (GSK response to comment 3.d of 8/17/00)
	-2/6/01 ¹	-See p. 3 of CR#7	-Request review of GSK response to comments 3 and 4 of 1/26/01 Agency facsimile.

Team meeting of 4/9/01 found comparative statistical approach to interim the 4/12/01 amendment, to be acceptable (see p. 14 of review below).

testing as in

REMARKS/COMMENTS:

See chemist's review notes below, p. 6.

CONCLUSIONS & RECOMMENDATIONS: In terms of Chemistry, Manufacturing, and Controls information, the application is recommended for approval (AP). The applicant should also be reminded of their prior commitments and agreements when an action is taken on this application (see those attached to this review following review of the 4/19/01 amendment).

cc:

Org. NDA 20-983

HFD-570/Division File

HFD-570/CBertha/4/19/01

HFD-570/PJani

HFD-570/GPoochikian

R/D Init by: _____

filename: 01-04-19.rev.doc

Craig M. Bertha, Ph.D.
Review Chemist

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Craig Bertha
4/19/01 03:58:58 PM
CHEMIST

Guiragos Poochikian
4/19/01 05:19:21 PM
CHEMIST

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Manufacturing And Control

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

<u>NDA #:</u>	20-983	<u>CHEM. REVIEW #</u>	7	<u>REVIEW DATE:</u>	3/1/01
<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>		
ORIGINAL	6/30/98	7/1/98	7/8/98		
AMENDMENT (BC)	7/10/98	7/13/98	7/15/98		
AMENDMENT (BC)	7/23/98	7/24/98	7/27/98		
AMENDMENT (BC)	7/27/98	7/28/98	8/6/98		
AMENDMENT (BC)	12/18/98	12/21/98	12/23/98		
AMENDMENT (BC)	2/26/99	3/2/99	3/8/99		
AMENDMENT (AC)	3/31/99	4/1/99	4/5/99		
AMENDMENT (BC)	6/2/99	6/3/99	6/14/99		
AMENDMENT (AC)	6/29/00	7/3/00	7/5/00		
AMENDMENT (BC)	7/19/00	7/20/00	7/25/00		
CORRESPONDENCE	8/25/00	8/28/00	8/29/00		
AMENDMENT (BC)	9/29/00	10/2/00	10/10/00		
AMENDMENT (BC)	10/12/00	10/13/00	10/19/00		
AMENDMENT (BC)	12/6/00	12/7/00	12/7/00		
AMENDMENT (BC)	12/22/00	12/27/00	12/29/00		
AMENDMENT (AC)	1/4/01	1/5/01	1/9/01		
AMENDMENT (AC) ¹	2/2/01	2/5/01	2/5/01		
AMENDMENT (BC) ¹	2/20/01	2/22/01	2/28/01		
AMENDMENT (BC) ¹	2/26/01	2/26/01 ²	2/27/01		

¹Subject of the current CR#7; ²As telephone facsimile.

NAME & ADDRESS OF APPLICANT:

GlaxoSmithKline
 Five Moore Drive
 P.O. Box 13398
 Research Triangle Park, NC 27709

DRUG PRODUCT NAME

Proprietary:
Nonproprietary/USAN:
Code Name/#:
Chem.Type/Ther.Class:

Ventolin[®] HFA Inhalation Aerosol
 albuterol sulfate HFA inhalation aerosol*
 AH3365F
 3S

PHARMACOL. CATEGORY/INDICATION:

For treatment or prevention of bronchospasm in patients 4 yrs. and older with reversible obstructive airway disease and for prevention of exercise-induced bronchospasm

DOSAGE FORM: inhalation aerosol

STRENGTHS: 108 µg albuterol sulfate (90 µg base)/act from actuator (120 µg of albuterol sulfate/act from valve), 75 mg suspension/act

ROUTE OF ADMINISTRATION:

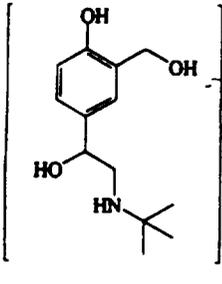
Inhalation

DISPENSED:

Rx OTC

SPECIAL PRODUCTS:

Yes No

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

Albuterol Sulfate, α^1 -[*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene- α, α' -diol sulfate (2:1) (salt); Molecular Formula: $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$;
Molecular Weight: 576.72 (base 239.32)

$\cdot H_2SO_4$

APPEARS THIS WAY
ON ORIGINAL

SUPPORTING DOCUMENTS:

DMFs:

DMF No. (type)	Holder Name	Subject	Status	Dates Reviewed	Reference In Reviews
		GR106642X, HFA-134a propellant manufacture	Adequate	8/3/98 4/21/99	p. 28 of CR#1 p. 19 of CR#2
		Pharmacology and Toxicological Information for Propellant HFA-134a coating of canisters	-	-	See consult review from Pharm/Tox
		Metered Dose Inhaler Cans Internally Coated with Fluoropolymer	Inadequate	9/2/98	p. 65 of CR#1, DMF replaces p. 56 of CR#2
		TEFLON® Topcoat 3200-100, canister coating formulation	Adequate	11/24/98 4/26/99	p. 56 of CR#2
		uncoated aluminum alloy canister	Adequate	9/2/98 4/13/00	p. 65 of CR#1, p. 57 of CR#2 p. 40 of CR#3
		DF-60 Mk12 Valve	Adequate	9/3/98	p. 65 of CR#1
		Zytel E 101 L NC-10 Polyamide	Adequate	9/9/98 6/10/99 1/28/00	p. 71 of CR#1 p. 75 of CR#2 p. 46 of CR#3
		gaskets	Adequate	5/26/99	See DMF review dated 6/10/99
		actuator	Adequate	8/31/98 4/12/99 1/4/00	p. 71 of CR#1 p. 75 of CR#2 p. 46 of CR#3
		actuator strap-cap	Inadequate	9/10/98	p. 73 of CR#1 DMF replaces
		actuator	Adequate	3/3/00	p. 76 of CR#2 p. 47 of CR#3
		actuator	Inadequate	9/10/98	p. 73 of CR#1, DMF replaces
		actuator	Adequate	4/30/99 1/4/00	p. 76 of CR#2 p. 47 of CR#3
		Pro-Fax 6331 polypropylene homopolymer resin for actuator	Adequate	9/14/92	p. 73 of CR#1
		Pro-Fax SR548M propylene/ethylene copolymer for strap-caps	Adequate	9/15/98	p. 73 of CR#1
		silica gel desiccant	Adequate	9/10/97	p. 74 of CR#1
		silica gel desiccant	Adequate	11/4/92	p. 75 of CR#1
		overwrap	Adequate	9/2/98 4/28/99 10/2/00	p. 75 of CR#1 p. 80 of CR#2 p. 49 of CR#3 p. 28 of CR#4

Courtesy supplies only strap-caps for the actuators (DMF) and is no longer an actuator supplier. has been and will be the only supplier of actuators (DMF Comments of DMF 2/25/00 deficiency letter pertained to actuators only (see p. 47 of CR#3).

RELATED DOCUMENTS:

- NDA:**
- N18-473 Ventolin® (albuterol) Inhalation Aerosol (AP 5/81)
 - N19-112 Ventolin® (albuterol) Tablets (AP 7/86)
 - N19-269 Ventolin® (albuterol sulfate) Inhalation Solution (AP 1/87)
 - N19-489 Ventolin® (albuterol sulfate) Rotocaps for Inhalation (AP 5/88)
 - N19-621 Ventolin® (albuterol sulfate) Syrup (AP 6/87)
 - N19-773 Ventolin® (albuterol sulfate) Inhalation Solution (AP 4/92)

IND:

CONSULTS:

Consult	Date Forwarded	Status	Comments
EES	Forwarded on 8/31/98 Update forwarded 7/5/00 Update forwarded 2/22/01	-Acceptable -Acceptable -Acceptable	OC decision 6/25/99 OC decision 7/13/00 OC decision 2/26/01
Separate request for contract extractables laboratories (3)	Forwarded on 7/20/00	-Acceptable	OC decision 11/13/00
Microbiology	5/25/99	-Acceptable, 5/28/99	Requested comments on results of microorganism survivability studies performed as per comment 11 of the 10/26/98 Agency letter.
Pharmacology/Toxicology	-9/10/98 -10/9/98 -Updated request 6/21/99 ¹ -7/6/00 (response to comment 37) -6/22/99 -7/6/00 (response to comment 37) 10/19/00 -10/9/98 -11/16/98 -3/22/99 -4/16/99	-Acceptable, 2/4/99 -Unacceptable, 7/1/99 -Unacceptable, 8/23/00 -Acceptable, 10/19/00 -Unacceptable, 7/1/99 -Unacceptable, 8/23/00 -Acceptable, 10/19/00 -Unacceptable, 7/1/99 -Acceptable, 8/23/00 -Acceptable, 4/22/99 -Acceptable, 6/17/99 -Acceptable, 6/7/99	-HFA-134a Impurities Consult Gasket -Comment 37 of 7/1/99 AE -See p. 23 of CR#4 -Comment 37 of 7/1/99 AE -See p. 23 of CR#4 -Comments 4 & 36 of 7/1/99 AE
Method Validation	Not forwarded.		-Updated packages to be requested.
Labeling and Nomenclature Committee	Not forwarded.		-The trademark Ventolin® is already in use for six other albuterol or albuterol sulfate products from the applicant.
Biometrics	-12/7/00 -12/13/00 -10/18/00 -2/6/01	-See review for details and discussion p. 30 of CR#5 -Acceptable -See p. 14 of CR#6 -See p. 4 of CR#7	Expiry for Batches 6ZX012, 6ZX013, and 6ZX015 Expiry for Batch 7ZX027 for mean DCU (beg and end of can) -Request comments on stress test sampling plan response to comment 3.d of 8/17/00) -Request review of response to comments 3 and 4 of 1/26/01 Agency facsimile.

REMARKS/COMMENTS:

See chemist's review notes below, p. 7.

CONCLUSIONS & RECOMMENDATIONS: In terms of Chemistry, Manufacturing, and Controls information, the application is **approvable (AE)**. However, it will be necessary for the applicant to address the comments in the draft letter before approval can be recommended. The PM should forward the comments in the attached draft letter to the applicant. The applicant should also be reminded of their prior commitments and agreements when an action is taken on this application (see those attached after the draft letter).

cc:

Org. NDA 20-983

HFD-570/Division File

HFD-570/CBertha/3/1/01

HFD-570/PJani

HFD-570/GPoochikian

R/D Init by: _____

Craig M. Bertha, Ph.D.
Review Chemist

filename: 01-02-26.rev.doc

/s/

Craig Bertha
3/1/01 02:46:55 PM
CHEMIST

Guiragos Poochikian
3/1/01 04:10:31 PM
CHEMIST

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Manufacturing And Controls

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

<u>NDA #:</u>	20-983	<u>CHEM. REVIEW #</u>	6	<u>REVIEW DATE:</u>	1/23/01
<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>		
ORIGINAL	6/30/98	7/1/98	7/8/98		
AMENDMENT (BC)	7/10/98	7/13/98	7/15/98		
AMENDMENT (BC)	7/23/98	7/24/98	7/27/98		
AMENDMENT (BC)	7/27/98	7/28/98	8/6/98		
AMENDMENT (BC)	12/18/98	12/21/98	12/23/98		
AMENDMENT (BC)	2/26/99	3/2/99	3/8/99		
AMENDMENT (AC)	3/31/99	4/1/99	4/5/99		
AMENDMENT (BC)	6/2/99	6/3/99	6/14/99		
AMENDMENT (AC)	6/29/00	7/3/00	7/5/00		
AMENDMENT (BC)	7/19/00	7/20/00	7/25/00		
CORRESPONDENCE	8/25/00	8/28/00	8/29/00		
AMENDMENT (BC)	9/29/00	10/2/00	10/10/00		
AMENDMENT (BC)	10/12/00	10/13/00	10/19/00		
AMENDMENT (BC)	12/6/00	12/7/00	12/7/00		
AMENDMENT (BC) ¹	12/22/00	12/27/00	12/29/00		
AMENDMENT (AC) ¹	1/4/01	1/5/01	1/9/01		

¹Subject of the current CR#6

NAME & ADDRESS OF APPLICANT:

Glaxo Wellcome Inc.
 Five Moore Drive
 P.O. Box 13398
 Research Triangle Park, NC 27709

DRUG PRODUCT NAME

<u>Proprietary:</u>	Ventolin [®] HFA Inhalation Aerosol
<u>Nonproprietary/USAN:</u>	albuterol sulfate HFA inhalation aerosol*
<u>Code Name/#:</u>	AH3365F
<u>Chem.Type/Ther.Class:</u>	3S

PHARMACOL. CATEGORY/INDICATION: For treatment or prevention of bronchospasm in patients 4 yrs. and older with reversible obstructive airway disease and for prevention of exercise-induced bronchospasm

DOSAGE FORM: inhalation aerosol
STRENGTHS: 108 µg albuterol sulfate (90 µg base)/act from actuator (120 µg of albuterol sulfate/act from valve), 75 mg suspension/act

ROUTE OF ADMINISTRATION:

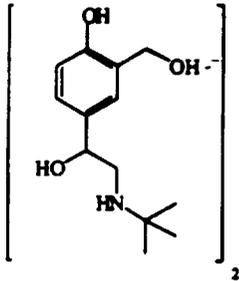
Inhalation

DISPENSED:

Rx OTC

SPECIAL PRODUCTS:

Yes No

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

Albuterol Sulfate, α^1 -[*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene- α, α' -diol sulfate (2:1) (salt); Molecular Formula: $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$; Molecular Weight: 576.72 (base 239.32)

$\cdot H_2SO_4$

SUPPORTING DOCUMENTS: DMFs:

DMF No. (type)	Holder Name	Subject	Status	Dates Reviewed	Reference in Reviews
		GR106642X, HFA-134a propellant manufacture	Adequate	8/3/98 4/21/99	p. 28 of CR#1 p. 19 of CR#2
		Pharmacology and Toxicological Information for Propellant HFA-134a	--	--	See consult review from Pharm/Tox
		coating of canisters	Inadequate	9/2/98	p. 65 of CR#1. DMF replaces p. 56 of CR#2
		Metered Dose Inhaler Cans Internally Coated with Fluoropolymer	Adequate	11/24/98 4/26/99	p. 56 of CR#2
		TEFLON [®] Topcoat 3200-100, canister coating formulation	Adequate	9/2/98 4/13/00	p. 65 of CR#1, p. 57 of CR#2 p. 40 of CR#3
		uncoated aluminum alloy canister	Adequate	9/3/98	p. 65 of CR#1
		DF60 Mk12 Valve	Adequate	9/9/98 6/10/99 1/28/00	p. 71 of CR#1 p. 75 of CR#2 p. 46 of CR#3
		Zytel E 101 L NC-10 Polyamide	Adequate	5/26/99	See DMF review dated 6/10/99
		gaskets	Adequate	8/31/98 4/12/99 1/4/00	p. 71 of CR#1 p. 75 of CR#2 p. 46 of CR#3
		actuator	Inadequate	9/10/98	p. 73 of CR#1, DMF replaces
		actuator strap-cap	Adequate*	3/3/00	p. 76 of CR#2 p. 47 of CR#3
		actuator	Inadequate	9/10/98	p. 73 of CR#1, DMF replaces
		actuator	Adequate	4/30/99 1/4/00	p. 76 of CR#2 p. 47 of CR#3
		Pro-Fax 6331 polypropylene homopolymer resin for actuator	Adequate	9/14/92	p. 73 of CR#1
		Pro-Fax SR549M propylene/ethylene copolymer for strap-caps	Adequate	9/15/98	p. 73 of CR#1
		silica gel desiccant	Adequate	9/10/97	p. 74 of CR#1
		silica gel desiccant	Adequate	11/4/92	p. 75 of CR#1
		overwrap	Adequate	9/2/98 4/28/99 10/2/00	p. 75 of CR#1 p. 80 of CR#2 p. 49 of CR#3 p. 28 of CR#4

*Courtesy supplies only strap-caps for the actuators (DMF) and is no longer an actuator supplier.
has been and will be the only supplier of actuators (DMF) Comments of DMF 2/25/00 deficiency letter pertained to actuators only (see p. 47 of CR#3).

RELATED DOCUMENTS:

NDA: N18-473 Ventolin® (albuterol) Inhalation Aerosol (AP 5/81)
 N19-112 Ventolin® (albuterol) Tablets (AP 7/86)
 N19-269 Ventolin® (albuterol sulfate) Inhalation Solution (AP 1/87)
 N19-489 Ventolin® (albuterol sulfate) Rotocaps for Inhalation (AP 5/88)
 N19-621 Ventolin® (albuterol sulfate) Syrup (AP 6/87)
 N19-773 Ventolin® (albuterol sulfate) Inhalation Solution (AP 4/92)

IND:**CONSULTS:**

Consult	Date Forwarded	Status	Comments
EES Separate request for contract extractables laboratories (3)	Forwarded on 8/31/98 Update forwarded 7/5/00	-Acceptable -Acceptable	OC decision 6/25/99 OC decision 7/13/00
	Forwarded on 7/20/00	-Acceptable	OC decision 11/13/00
Microbiology	5/25/99	-Acceptable, 5/28/99	Requested comments on results of microorganism survivability studies performed as per comment 11 of the 10/26/98 Agency letter.
	-9/10/98	-Acceptable, 2/4/99	-HFA-134a Impurities Consult
	-10/9/98	-Unacceptable, 7/1/99	Gasket -Comment 37 of 7/1/99 AE
	-Updated request 6/21/99 ¹	-Unacceptable, 8/23/00	
	-7/6/00 (response to comment 37)	-Acceptable, 10/19/00	-See p. 23 of CR#4
	-6/22/99	-Unacceptable, 7/1/99	-Comment 37 of 7/1/99 AE
	-7/6/00 (response to comment 37)	-Unacceptable, 8/23/00	
	10/19/00	-Acceptable, 10/19/00	-See p. 23 of CR#4
	-10/9/98	-Unacceptable, 7/1/99 -Acceptable, 8/23/00	-Comments 4 & 36 of 7/1/99 AE
	-11/18/98	-Acceptable, 4/22/99	
	-3/22/99	-Acceptable, 6/17/99	
	-4/16/99	-Acceptable, 6/7/99	
Method Validation	Not forwarded.		-Updated packages to be requested.
Labeling and Nomenclature Committee	Not forwarded.		-The trademark Ventolin® is already in use for six other albuterol or albuterol sulfate products from the applicant.
Biometrics	-12/7/00	-See review for details and discussion p. 30 of CR#5	Expiry for Batches 6ZX012, 6ZX013, and 6ZX015
	-12/13/00		Expiry for Batch 7ZX027 for mean

	-10/18/00	-Acceptable -See p. 15 of CR#6	DCU (beg and end of can) -Request comments on MDI stress test sampling plan (GW response to comment 3.d of 8/17/00)
--	-----------	-----------------------------------	--

APPEARS THIS WAY
ON ORIGINAL

REMARKS/COMMENTS:

See chemist's review notes below, p. 7.

CONCLUSIONS & RECOMMENDATIONS: In terms of Chemistry, Manufacturing, and Controls information, it is recommended that the application **not be approved (NA)**. The PM should forward the comments in the attached draft letter to the applicant. The applicant should also be reminded of their prior commitments and agreements when an action is taken on this application (see those attached after the draft letter).

cc:

Org. NDA 20-983

HFD-570/Division File

HFD-570/CBertha/1/23/01

HFD-570/PJani

HFD-570/GPoochikian

R/D Init by: _____

filename: 01-01-04.rev.doc

Craig M. Bertha, Ph.D.
Review Chemist

/s/

Craig Bertha
1/23/01 02:48:53 PM
CHEMIST

Guiragos Poochikian
1/23/01 03:54:45 PM
CHEMIST

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Manufacturing And Control

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

<u>NDA #:</u>	20-983	<u>CHEM. REVIEW #</u>	5	<u>REVIEW DATE:</u>	12/18/00
<u>SUBMISSION TYPE</u>		<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>	
ORIGINAL		6/30/98	7/1/98	7/8/98	
AMENDMENT (BC)		7/10/98	7/13/98	7/15/98	
AMENDMENT (BC)		7/23/98	7/24/98	7/27/98	
AMENDMENT (BC)		7/27/98	7/28/98	8/6/98	
AMENDMENT (BC)		12/18/98	12/21/98	12/23/98	
AMENDMENT (BC)		2/26/99	3/2/99	3/8/99	
AMENDMENT (AC)		3/31/99	4/1/99	4/5/99	
AMENDMENT (BC)		6/2/99	6/3/99	6/14/99	
AMENDMENT (AC)		6/29/00	7/3/00	7/5/00	
AMENDMENT (BC)		7/19/00	7/20/00	7/25/00	
CORRESPONDENCE		8/25/00	8/28/00	8/29/00	
AMENDMENT (BC)		9/29/00	10/2/00	10/10/00	
AMENDMENT (BC)		10/12/00	10/13/00	10/19/00	
AMENDMENT (BC) ¹		12/6/00	12/7/00	12/7/00	

¹Subject of the current CR#5

NAME & ADDRESS OF APPLICANT:

Glaxo Wellcome Inc.
 Five Moore Drive
 P.O. Box 13398
 Research Triangle Park, NC 27709

DRUG PRODUCT NAME

<u>Proprietary:</u>	Ventolin [®] HFA Inhalation Aerosol
<u>Nonproprietary/USAN:</u>	albuterol sulfate HFA inhalation aerosol*
<u>Code Name/#:</u>	AH3365F
<u>Chem.Type/Ther.Class:</u>	3S

*Note: See comment 7.b in the attached draft letter.

PHARMACOL. CATEGORY/INDICATION: For treatment or prevention of bronchospasm in patients 4 yrs. and older with reversible obstructive airway disease and for prevention of exercise-induced bronchospasm

DOSAGE FORM: inhalation aerosol

STRENGTHS: 108 µg albuterol sulfate (90 µg base)/act from actuator (120 µg of albuterol sulfate/act from valve), 75 mg suspension/act

ROUTE-OF ADMINISTRATION:

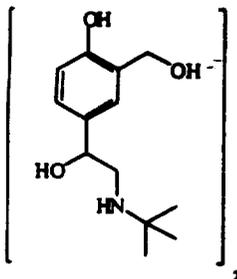
Inhalation

DISPENSED: -

Rx OTC

SPECIAL PRODUCTS:

Yes No

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

Albuterol Sulfate, α^1 -[*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene- α, α' -diol sulfate (2:1) (salt); Molecular Formula: $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$; Molecular Weight: 576.72 (base 239.32)

$\cdot H_2SO_4$

SUPPORTING DOCUMENTS:**DMFs:**

DMF No. (type)	Holder Name	Subject	Status	Dates Reviewed	Reference in Reviews
		GR106642X, HFA-134a propellant manufacture	Adequate	8/3/98 4/21/99	p. 28 of CR#1 p. 19 of CR#2
		Pharmacology and Toxicological Information for Propellant HFA-134a	-	-	See consult review from Pharm/Tox
		coating of canisters	Inadequate	9/2/98	p. 65 of CR#1, DMF replaces p. 56 of CR#2
		Metered Dose Inhaler Cans Internally Coated with Fluoropolymer	Adequate	11/24/98 4/26/99	p. 56 of CR#2
		TEFLON [®] Topcoat 3200-100, canister coating formulation	Adequate	9/2/98 4/13/00	p. 65 of CR#1, p. 57 of CR#2 p. 40 of CR#3
		uncoated aluminum alloy canister	Adequate	9/3/98	p. 65 of CR#1
		DF-80 Mk12 Valve	Adequate	9/9/98 6/10/99 1/28/00	p. 71 of CR#1 p. 75 of CR#2 p. 46 of CR#3
		Zytel E 101 L NC-10 Polyamide	Adequate	5/26/99	See DMF review dated 6/10/99
		Type gaskets	Adequate	8/31/98 4/12/99 1/4/00	p. 71 of CR#1 p. 75 of CR#2 p. 46 of CR#3
		actuator	Inadequate	9/10/98	p. 73 of CR#1, DMF replaces
		actuator strap-cap	Adequate*	3/3/00	p. 76 of CR#2 p. 47 of CR#3
		actuator	Inadequate	9/10/98	p. 73 of CR#1, DMF replaces
		actuator	Adequate	4/30/99 1/4/00	p. 76 of CR#2 p. 47 of CR#3
		Pro-Fax 6331 polypropylene homopolymer resin for actuator	Adequate	9/14/92	p. 73 of CR#1
		Pro-Fax SR549M propylene/ethylene copolymer for strap-caps	Adequate	9/15/98	p. 73 of CR#1
		silica gel desiccant	Adequate	9/10/97	p. 74 of CR#1
		silica gel desiccant	Adequate	11/4/92	p. 75 of CR#1
		overwrap	Adequate	9/2/98 4/28/99 10/2/00	p. 75 of CR#1 p. 80 of CR#2 p. 49 of CR#3 p. 28 of CR#4

*No longer an actuator supplier; will supply strap-caps to
letter pertained to actuators, not strap-caps.

DMF

Comments of 2/25/00 deficiency

**APPEARS THIS WAY
ON ORIGINAL**

RELATED DOCUMENTS:

- NDAs:** N18-473 Ventolin® (albuterol) Inhalation Aerosol (AP 5/81)
 N19-112 Ventolin® (albuterol) Tablets (AP 7/86)
 N19-269 Ventolin® (albuterol sulfate) Inhalation Solution (AP 1/87)
 N19-489 Ventolin® (albuterol sulfate) Rotocaps for Inhalation (AP 5/88)
 N19-621 Ventolin® (albuterol sulfate) Syrup (AP 6/87)
 N19-773 Ventolin® (albuterol sulfate) Inhalation Solution (AP 4/92)

IND: []

CONSULTS:

Consult	Date Forwarded	Status	Comments
EES Separate request for contract extractables laboratories (3)	Forwarded on 8/31/98 Update forwarded 7/5/00	-Acceptable -Acceptable	OC decision 6/25/99 OC decision 7/13/00
	Forwarded on 7/20/00	-Acceptable	OC decision 11/13/00
Microbiology	5/25/99	-Acceptable, 5/28/99	Requested comments on results of microorganism survivability studies performed as per comment 11 of the 10/26/98 Agency letter.
	-9/10/98	-Acceptable, 2/4/99	-HFA-134a Impurities Consult
	-10/9/98 -Updated request 6/21/99' -7/6/00 (response to comment 37)	-Unacceptable, 7/1/99 -Unacceptable, 8/23/00 -Acceptable, 10/19/00	-Gasket -Comment 37 of 7/1/99 AE -See p. 23 of CR#4
	-6/22/99 -7/6/00 (response to comment 37) 10/19/00	-Unacceptable, 7/1/99 -Unacceptable, 8/23/00 -Acceptable, 10/19/00	-Comment 37 of 7/1/99 AE -See p. 23 of CR#4
	-10/9/98	-Unacceptable, 7/1/99 -Acceptable, 8/23/00	-Comments 4 & 36 of 7/1/99 AE
	-11/16/98	-Acceptable, 4/22/99	
	-3/22/99	-Acceptable, 6/17/99	
	-4/16/99	-Acceptable, 6/7/99	
Method Validation	Not forwarded.		-Updated packages to be requested.
Labeling and Nomenclature Committee	Not forwarded.		-The trademark Ventolin® is already in use for six other albuterol or albuterol sulfate products from the applicant.
Biometrics	-12/7/00	-See review for details and discussion p. 31	Expiry for Batches 6ZX012, 6ZX013, and 6ZX015
	-12/13/00		Expiry for Batch 7ZX027 for mean DCU (beg and end of can)

	-10/18/00	-Acceptable -See p. 13	-Request comments on stress test sampling plan response to comment 3.d of 8/17/00)
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APPEARS THIS WAY
ON ORIGINAL

REMARKS/COMMENTS:

See chemist's review notes below, p. 8.

CONCLUSIONS & RECOMMENDATIONS: In terms of Chemistry, Manufacturing, and Controls information, the application is considered **approvable**. The comments in the attached deficiency letter and the previous commitments from the applicant listed in CR#4 (and also attached after the draft letter of this review) should be forwarded to the applicant with the action.

cc:

Org. NDA 20-983

HFD-570/Division File

HFD-570/CBertha/12/18/00

HFD-570/PJani

HFD-570/GPoochikian

R/D Init by: _____

filename: 00-12-06.rev.doc

Craig M. Bertha, Ph.D.
Review Chemist

/s/

Craig Bertha
12/20/00 02:10:02 PM
CHEMIST

Guiragos Poochikian
12/20/00 03:14:08 PM
CHEMIST

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Manufacturing And Control

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

<u>NDA #:</u>	20-983	<u>CHEM. REVIEW #</u>	4	<u>REVIEW DATE:</u>	10/20/00
<u>SUBMISSION TYPE</u>		<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>	
ORIGINAL		6/30/98	7/1/98	7/8/98	
AMENDMENT (BC)		7/10/98	7/13/98	7/15/98	
AMENDMENT (BC)		7/23/98	7/24/98	7/27/98	
AMENDMENT (BC)		7/27/98	7/28/98	8/6/98	
AMENDMENT (BC)		12/18/98	12/21/98	12/23/98	
AMENDMENT (BC)		2/26/99	3/2/99	3/8/99	
AMENDMENT (AC)		3/31/99	4/1/99	4/5/99	
AMENDMENT (BC)		6/2/99	6/3/99	6/14/99	
AMENDMENT (AC)		6/29/00	7/3/00	7/5/00	
AMENDMENT (BC)		7/19/00	7/20/00	7/25/00	
CORRESPONDENCE ¹		8/25/00	8/28/00	8/29/00	
AMENDMENT (BC) ¹		9/29/00	10/2/00	10/10/00	
AMENDMENT (BC) ²		10/12/00	10/13/00	10/19/00	

¹Subject of the current CR#4; ²See p. 23 for details (pharm/tox related).

NAME & ADDRESS OF APPLICANT:

Glaxo Wellcome Inc.
 Five Moore Drive
 P.O. Box 13398
 Research Triangle Park, NC 27709

DRUG PRODUCT NAME

Proprietary:

Nonproprietary/USAN:

Code Name/#:

Chem.Type/Ther.Class:

Ventolin[®] HFA Inhalation Aerosol
 albuterol sulfate HFA inhalation aerosol*
 AH3365F

3S

*Note: See remarks section comment 3, p. 5.

PHARMACOL. CATEGORY/INDICATION:

For treatment or prevention of bronchospasm in patients 4 yrs. and older with reversible obstructive airway disease and for prevention of exercise-induced bronchospasm

DOSAGE FORM:

inhalation aerosol

STRENGTHS:

108 µg albuterol sulfate (90 µg base)/act from actuator (120 µg of albuterol sulfate/act from valve), 75 mg suspension/act

ROUTE OF ADMINISTRATION:

Inhalation

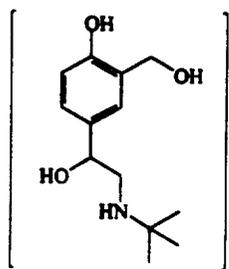
DISPENSED:

Rx OTC

SPECIAL PRODUCTS:

Yes No

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



.H₂SO₄

Albuterol Sulfate, α¹-[*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol sulfate (2:1) (salt);
 Molecular Formula: (C₁₃H₂₁NO₃)₂·H₂SO₄;
 Molecular Weight: 576.72 (base 239.32)

SUPPORTING DOCUMENTS:

DMFs:

DMF No. (type)	Holder Name	Subject	Status	Dates Reviewed	Reference in Reviews
		GR106642X, HFA-134a propellant manufacture	Adequate	8/3/98 4/21/99	p. 28 of CR#1 p. 19 of CR#2
		Pharmacology and Toxicological Information for Propellant HFA-134a	-	-	See consult review from Pharm/Tox regarding HFA-134a impurities specifications.
		coating of canisters	Inadequate	9/2/98	p. 65 of CR#1, Note DMF replaces p. 56 of CR#2
		Metered Dose Inhaler Cans Internally Coated with Fluoropolymer	Adequate	11/24/98 4/26/99	p. 56 of CR#2
		TEFLON Topcoat 3200-100, canister coating formulation	Adequate	9/2/98 4/13/00	p. 65 of CR#1, p. 57 of CR#2 p. 40 of CR#3
		uncoated aluminum alloy canister	Adequate	9/3/98	p. 65 of CR#1
		DF60 Mk12 Valve	Adequate	9/9/98 8/10/99 1/28/00	p. 71 of CR#1 p. 75 of CR#2 p. 46 of CR#3
		Zytel E 101 L NC-10 Polyamide	Adequate	5/26/99	See DMF review dated 6/10/99
		Type gaskets	Adequate	8/31/98 4/12/99 1/4/00	p. 71 of CR#1 p. 75 of CR#2 p. 46 of CR#3
		actuator	Inadequate	9/10/98	p. 73 of CR#1, Note DMF replaces
		actuator strap-cap	Adequate*	3/3/00	p. 76 of CR#2 p. 47 of CR#3
		actuator	Inadequate	9/10/98	p. 73 of CR#1, Note DMF replaces
		actuator	Adequate	4/30/99 1/4/00	p. 76 of CR#2 p. 47 of CR#3
		Pro-Fax 6331 polypropylene homopolymer resin for actuator	Adequate	9/14/92	p. 73 of CR#1
		Pro-Fax SR549M propylene/ethylene copolymer for strap-caps	Adequate	9/15/98	p. 73 of CR#1
		silica gel desiccant	Adequate	9/10/97	p. 74 of CR#1
		silica gel desiccant	Adequate	11/4/92	p. 75 of CR#1
		overwrap	Adequate	9/2/98 4/28/99 10/2/00	p. 75 of CR#1 p. 80 of CR#2 p. 49 of CR#3 p. 28 of CR#4

*No longer an actuator supplier, but will supply strap-caps to 2/25/00 deficiency letter pertained to actuators, not strap-caps.

(DMF) Comments of

RELATED DOCUMENTS:

NDAs: N18-473 Ventolin® (albuterol) Inhalation Aerosol (AP 5/81)
 N19-112 Ventolin® (albuterol) Tablets (AP 7/86)
 N19-269 Ventolin® (albuterol sulfate) Inhalation Solution (AP 1/87)
 N19-489 Ventolin® (albuterol sulfate) Rotocaps for Inhalation (AP 5/88)
 N19-621 Ventolin® (albuterol sulfate) Syrup (AP 6/87)
 N19-773 Ventolin® (albuterol sulfate) Inhalation Solution (AP 4/92)

IND:**CONSULTS:**

Consult	Date Forwarded	Status	Comments
EES Separate request for contract extractables laboratories (3)	Forwarded on 8/31/98 Update forwarded 7/5/00	-Acceptable -Acceptable	OC decision 8/25/99 OC decision 7/13/00
	Forwarded on 7/20/00	-Pending	
Microbiology	8/25/99	-Acceptable, 5/28/99	Requested comments on results of microorganism survivability studies performed as per comment 11 of the 10/26/98 Agency letter.
	-8/10/98 -10/9/98 -Updated request 8/21/99' -7/6/00 (response to comment 37)	-Acceptable, 2/4/99 -Unacceptable, 7/1/99 -Unacceptable, 8/23/00 -Acceptable, 10/19/00	-HFA-134a Impurities Consult Gasket -Comment 37 of 7/1/99 AE -See p. 23
	-8/22/99 -7/6/00 (response to comment 37) 10/19/00	-Unacceptable, 7/1/99 -Unacceptable, 8/23/00 -Acceptable, 10/19/00	-Comment 37 of 7/1/99 AE -See p. 23
	-10/9/98 -11/16/98 -3/22/99 -4/16/99	-Unacceptable, 7/1/99 -Acceptable, 8/23/00 -Acceptable, 4/22/99 -Acceptable, 6/17/99 -Acceptable, 8/7/99	-Comments 4 & 36 of 7/1/99 AE
Labeling and Nomenclature Committee	Not forwarded.		-The trademark Ventolin® is already in use for six other albuterol or albuterol sulfate products from the applicant.
Biometrics	Not forwarded.		-Consult on expiration dating period will be sent once DP specifications finalized with applicant.
	-10/18/00	-Pending	-Request comments on MDI stress test sampling plan (GW response to comment 3.d of 8/17/00)

REMARKS/COMMENTS:

See chemist's review notes below, p. 5.

CONCLUSIONS & RECOMMENDATIONS: In terms of Chemistry, Manufacturing, and Controls information, it is recommended that the application be **not approved**. The comments in the attached letter should be forwarded to the applicant by the PM. Issues listed under remark 3 on p. 5 and remark 6 on p. 5 of this review need to be resolved within the team prior to approval of the product. Any final action should include a list of commitments from the firm (see p. 33).

cc:

Org. NDA 20-983

HFD-570/Division File

HFD-570/CBertha/10/20/00

HFD-570/PJani

HFD-570/GPoochikian

R/D Init by: _____

filename: 00-09-29.rev.doc

Craig M. Bertha, Ph.D.
Review Chemist

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Manufacturing And Controls

Jani

AUG 16 2000

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

NDA #: 20-983 **CHEM. REVIEW #** 3 **REVIEW DATE:** 8/15/00

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	6/30/98	7/1/98	7/8/98
AMENDMENT (BC)	7/10/98	7/13/98	7/15/98
AMENDMENT (BC)	7/23/98	7/24/98	7/27/98
AMENDMENT (BC)	7/27/98	7/28/98	8/6/98
AMENDMENT (BC)	12/18/98	12/21/98	12/23/98
AMENDMENT (BC)	2/26/99	3/2/99	3/8/99
AMENDMENT (AC)	3/31/99	4/1/99	4/5/99
AMENDMENT (BC)	6/2/99	6/3/99	6/14/99
AMENDMENT (AC)*	6/29/00	7/3/00	7/5/00
AMENDMENT (BC)*	7/19/00	7/20/00	7/25/00

*Subject of the current CR#3.

NAME & ADDRESS OF APPLICANT:

Glaxo Wellcome Inc.
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

DRUG PRODUCT NAME

Proprietary:

Nonproprietary/USAN:

Code Name/##:

Chem. Type/Ther. Class:

*Note: See remarks section comment 3.

Ventolin® HFA Inhalation Aerosol
albuterol sulfate HFA inhalation aerosol*
AH3365F
3S

PHARMACOL. CATEGORY/INDICATION:

For treatment or prevention of bronchospasm in patients 4 yrs. and older with reversible obstructive airway disease and for prevention of exercise-induced bronchospasm

DOSAGE FORM:

inhalation aerosol

STRENGTHS:

108 µg albuterol sulfate (90 µg base)/act from actuator (120 µg of albuterol sulfate/act from valve), 75 mg suspension/act

ROUTE OF ADMINISTRATION:

Inhalation

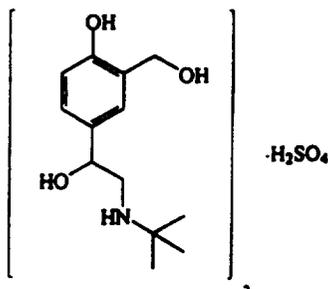
DISPENSED:

Rx OTC

SPECIAL PRODUCTS:

Yes No

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



Albuterol Sulfate, α^1 -[*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene- α, α' -diol sulfate (2:1) (salt);
Molecular Formula: $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$;
Molecular Weight: 576.72 (base 239.32)

SUPPORTING DOCUMENTS:**DMFs:**

DMF No. (type)	Holder Name	Subject	Status	Dates Reviewed	Reference in Reviews
		GR106642X, HFA-134a propellant manufacture	Adequate	8/3/98 4/21/99	p. 28 of CR#1 p. 19 of CR#2
		Pharmacology and Toxicological Information for Propellant HFA-134a	-	-	See consult review from Pharm/Tox regarding HFA-134a impurities specifications.
		coating of canisters	Inadequate	9/2/98	p. 65 of CR#1, Note DMF replaces p. 56 of CR#2
		Metered Dose Inhaler Cans Internally Coated with Fluoropolymer	Adequate	11/24/98 4/26/99	p. 56 of CR#2
		TEFLON® Topcoat 3200-100, canister coating formulation	Adequate	9/2/98 4/13/00	p. 65 of CR#1, p. 57 of CR#2 p. 40 of CR#3
		uncoated aluminum alloy canister	Adequate	9/3/98	p. 65 of CR#1
		DF60 Mk12 Valve	Adequate	9/9/98 6/10/99 1/28/00	p. 71 of CR#1 p. 75 of CR#2 p. 46 of CR#3
		Zytel E 101 L NC-10 Polyamide	Adequate	5/26/99	See DMF review dated 8/10/99
		gaskets	Adequate	8/31/98 4/12/99 1/4/00	p. 71 of CR#1 p. 75 of CR#2 p. 46 of CR#3
		actuator	Inadequate	9/10/98	p. 73 of CR#1, Note DMF replaces
		actuator strap-cap	Inadequate Adequate*	3/3/00	p. 76 of CR#2 p. 47 of CR#3
		actuator	Inadequate	9/10/98	p. 73 of CR#1, Note DMF replaces
		actuator	Adequate	4/30/99 1/4/00	p. 76 of CR#2 p. 47 of CR#3
		Pro-Fax 6331 polypropylene homopolymer resin for actuator	Adequate	9/14/92	p. 73 of CR#1
		Pro-Fax SR549M propylene/ethylene copolymer for strap-caps	Adequate	9/15/98	p. 73 of CR#1
		silica gel desiccant	Adequate	9/10/97	p. 74 of CR#1
		silica gel desiccant	Adequate	11/4/92	p. 75 of CR#1
		overwrap	Inadequate	9/2/98 4/28/99	p. 75 of CR#1 p. 80 of CR#2 p. 49 of CR#3

*No longer an actuator supplier, but will supply strap-caps to 2/25/00 deficiency letter pertained to actuators, not strap-caps.

DMF Comments of

RELATED DOCUMENTS:**NDAs:**

- N18-473 Ventolin® (albuterol) Inhalation Aerosol (AP 5/81)
- N19-112 Ventolin® (albuterol) Tablets (AP 7/86)
- N19-269 Ventolin® (albuterol sulfate) Inhalation Solution (AP 1/87)
- N19-489 Ventolin® (albuterol sulfate) Rotocaps for Inhalation (AP 5/88)
- N19-621 Ventolin® (albuterol sulfate) Syrup (AP 6/87)
- N19-773 Ventolin® (albuterol sulfate) Inhalation Solution (AP 4/92)

IND:

CONSULTS:

Consult	Date Forwarded	Status	Comments
EES Separate request for contract extractables laboratories (3)	Forwarded on 8/31/98 Update forwarded 7/5/00 Forwarded on 7/20/00	-ACCEPTABLE -ACCEPTABLE -Pending	OC decision 6/25/99 OC decision 7/13/00
Microbiology	5/25/99	-Final, 5/26/99	Requested comments on results of microorganism survivability studies performed as per comment 11 of the 10/26/98 Agency letter.
	-9/10/98 -10/9/98 -Updated request 6/21/99 -8/22/99 -10/9/98 -11/16/98 -3/22/99 -4/16/99 -7/5/00	-Final, 2/4/99 -Final, 7/1/99 -Final, 7/1/99 -Final, 7/1/99 -Final, 4/22/99 -Final, 6/17/99 -Final, 6/7/99 -Pending	-HFA-134a Impurities Consult Gasket -Comment 37 of 7/1/99 AE -Comments 4 & 36 of 7/1/99 AE
Labeling and Nomenclature Committee	Not forwarded.		The trademark Ventolin® is already in use for six other albuterol or albuterol sulfate products from the applicant.
Biometrics	Not forwarded.		Will be sent once DP specifications finalized with applicant.

REMARKS/COMMENTS:

See chemist's review notes below.

CONCLUSIONS & RECOMMENDATIONS: In terms of Chemistry, Manufacturing, and Controls information, it is recommended that the application be not approved. The deficiency comments in the attached letter should be forwarded to the applicant by the PM. PM should note remark 13 with regard to the future action letter.

cc:

Org. NDA 20-983

HFD-570/Division File

HFD-570/CBertha/8/15/00

HFD-570/PJani

HFD-570/GPoochikjan

R/D Init by *CB* 8/16/00

filename: 00-06-29.rev.doc

CB

Craig M. Bertha, Ph.D.
Review Chemist

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Manufacturing And Controls

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

NDA #: 20-983 **CHEM. REVIEW #** 2 **REVIEW DATE:** 6/25/99

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

ORIGINAL	6/30/98	7/1/98	7/8/98
AMENDMENT (BC)	7/10/98	7/13/98	7/15/98
AMENDMENT (BC)	7/23/98	7/24/98	7/27/98
AMENDMENT (BC)	7/27/98	7/28/98	8/6/98
AMENDMENT (BC)*	12/18/98	12/21/98	12/23/98
AMENDMENT (BC)*	2/26/99	3/2/99	3/8/99
AMENDMENT (AC)*	3/31/99	4/1/99	4/5/99
AMENDMENT (BC)*	6/2/99	6/3/99	6/14/99

*Subject of the current CR#2.

NAME & ADDRESS OF APPLICANT:

Glaxo Wellcome Inc.
 Five Moore Drive
 P.O. Box 13398
 Research Triangle Park, NC 27709

DRUG PRODUCT NAME

Proprietary:

Nonproprietary/USAN:

Code Name/#:

Chem. Type/Ther. Class:

Ventolin® HFA Inhalation Aerosol
 albuterol sulfate inhalation aerosol*
 AH3365F
 3S

*Note: See remarks section comment 3.

PHARMACOL. CATEGORY/INDICATION:

For treatment or prevention of bronchospasm in patients 4 yrs. and older with reversible obstructive airway disease and for prevention of exercise-induced bronchospasm

DOSAGE FORM:

inhalation aerosol

STRENGTHS:

108 µg albuterol sulfate (90 µg base)/act from actuator (120 µg of albuterol sulfate/act from valve), 75 mg suspension/act

ROUTE OF ADMINISTRATION:

Inhalation

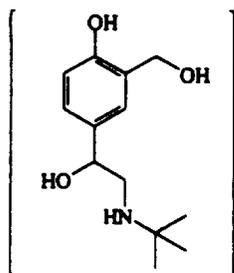
DISPENSED:

Rx OTC

SPECIAL PRODUCTS:

Yes No

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



·H₂SO₄

Albuterol Sulfate, α¹-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol sulfate (2:1) (salt);
 Molecular Formula: (C₁₃H₂₁NO₃)₂·H₂SO₄;
 Molecular Weight: 576.72 (base 239.32)

SUPPORTING DOCUMENTS:**DMFs:**

DMF No. (type)	Holder Name	Subject	Status	Dates Reviewed	Reference in Reviews
		GR106642X, HFA-134a propellant manufacture	Adequate	8/3/98 4/21/99	p. 28 of CR#1 p. 19 of CR#2
		Pharmacology and Toxicological Information for Propellant HFA-134a	-	-	See consult review from Pharm/Tox regarding HFA-134a impurities specifications.
		coating of canisters	Inadequate	9/2/98	p. 65 of CR#1, Note DMF replaces p. 56 of CR#2
		Metered Dose Inhaler Cans Internally Coated with Fluoropolymer	Adequate	11/24/98 4/28/99	p. 56 of CR#2
		TEFLON® Topcoat 3200-100, canister coating formulation	Inadequate	9/2/98	p. 65 of CR#1, p. 57 of CR#2
		uncoated aluminum alloy canister	Adequate	9/3/98	p. 65 of CR#1
		DF60 Mk12 Valve	Inadequate	9/9/98 6/10/99	p. 71 of CR#1, p. 75 of CR#2
		Zytel E 101 L NC-10 Polyamide	Adequate	5/26/99	See DMF review dated 6/10/99
		gaskets	Inadequate	8/31/98 4/12/99	p. 71 of CR#1, p. 75 of CR#2
		actuator	Inadequate	9/10/98	p. 73 of CR#1, Note DMF replaces
		actuator	Inadequate	4/30/99	p. 76 of CR#2
		actuator	Inadequate	9/10/98	p. 73 of CR#1, Note DMF replaces
		actuator	Inadequate	4/30/99	p. 76 of CR#2
		Pro-Fax 6331 polypropylene homopolymer resin for actuator	Adequate	9/14/92	p. 73 of CR#1
		Pro-Fax SR549M propylene/ethylene copolymer for strap-caps	Adequate	9/15/98	p. 73 of CR#1
		silica gel desiccant	Adequate	9/10/97	p. 74 of CR#1
		silica gel desiccant	Adequate	11/4/92	p. 75 of CR#1
		overwrap	Inadequate	9/2/98 4/28/99	p. 75 of CR#1, p. 80 of CR#2

RELATED DOCUMENTS:

- NDA:**
- N18-473 Ventolin® (albuterol) Inhalation Aerosol (approved 5/81)
 - N19-112 Ventolin® (albuterol) Tablets (approved 7/86)
 - N19-269 Ventolin® (albuterol sulfate) Inhalation Solution (approved 1/87)
 - N19-489 Ventolin® (albuterol sulfate) Rotocaps for Inhalation (approved 5/88)
 - N19-621 Ventolin® (albuterol sulfate) Syrup (approved 6/87)
 - N19-773 Ventolin® (albuterol sulfate) Inhalation Solution (approved 4/92)

IND:

CONSULTS:

Consult	Date Forwarded	Status	Comments
EES	Forwarded on 8/31/98	-ACCEPTABLE	Overall compliance decision provided on 6/25/99
Microbiology	5/25/99	-Final, 5/28/99	Requested comments on results of microorganism survivability studies performed as per comment 11 of the 10/26/98 Agency letter.
	-9/10/98 -10/9/98 -Updated request 6/21/99 ¹ -6/22/99	-Final, 2/4/99 -Pending -Pending	-HFA-134a Impurities Consult Gasket Extractables Consult
	-10/9/98 -11/16/98 -3/22/99 -4/16/99	-Pending -Final, 4/22/99 -Final, 6/17/99 -Final, 6/7/99	-Safety Evaluation of Applicant's Proposed Limits
Labeling and Nomenclature Committee	Not forwarded.		The trademark Ventolin® is already in use for six other albuterol or albuterol sulfate products from the applicant.
Biometrics	Not forwarded.		Applicant will be asked to revise various specification limits before expiry can be calculated. See response to comment 12.d.

¹The updated gasket extractables limits proposed in the applicant response to comment 10.e(4) of the 2/26/99 amendment were forwarded in a consult dated 6/21/99. The pharmacologist was informed that a review was not needed by the due date of 6/30/99 as the recommendation from CMC would be that the application be not approved.

REMARKS/COMMENTS:

See chemist's review notes below.

CONCLUSIONS & RECOMMENDATIONS: In terms of Chemistry, Manufacturing, and Controls information, it is recommended that the application be **not approved**. The deficiency comments in the attached letter should be forwarded to the applicant by the PM.

cc:

Org. NDA 20-983

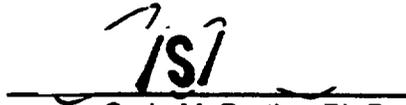
HFD-570/Division File

HFD-570/CBertha

HFD-570/PJani

HFD-570/GPoochikjan

R/D Init by: CB 6/28/99


Craig M. Bertha, Ph.D.
Review Chemist

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Manufacturing And Controls

OCT 19 1998

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

NDA #: 20-983 **CHEM. REVIEW #** 1 **REVIEW DATE:** 10/14/98

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	6/30/98	7/1/98	7/8/98
AMENDMENT (BC)	7/10/98	7/13/98	7/15/98
AMENDMENT (BC)	7/23/98	7/24/98	7/27/98
AMENDMENT (BC)	7/27/98	7/28/98	8/6/98

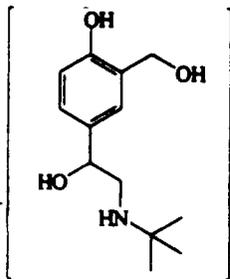
NAME & ADDRESS OF APPLICANT: Glaxo Wellcome Inc.
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

DRUG PRODUCT NAME
Proprietary: Ventolin® HFA Inhalation Aerosol
Nonproprietary/USAN: albuterol sulfate inhalation aerosol*
Code Name/#: AH3365F
Chem. Type/Ther. Class: 3S
*Note: See remarks section.

PHARMACOL. CATEGORY/INDICATION: For treatment or prevention of bronchospasm in patients 4 yrs. and older with reversible obstructive airway disease and for prevention of exercise-induced bronchospasm

DOSAGE FORM: inhalation aerosol
STRENGTHS: 120 µg of albuterol sulfate/act from valve, 108 µg albuterol sulfate(90 µg base)/act from actuator, 75 mg suspension/act
ROUTE OF ADMINISTRATION: Inhalation
DISPENSED: Rx OTC
SPECIAL PRODUCTS: Yes No

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



$\cdot\text{H}_2\text{SO}_4$ Albuterol Sulfate, α^1 -[*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene- α,α' -diol sulfate (2:1) (salt);
Molecular Formula: $(\text{C}_{13}\text{H}_{21}\text{NO}_3)_2\cdot\text{H}_2\text{SO}_4$;
Molecular Weight: 576.72 (base 239.32)

SUPPORTING DOCUMENTS:

DMFs:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1 review
		GR108642X, HFA-134a propellant manufacture	Inadequate	8/3/98	p. 28
		Pharmacology and Toxicological Information for Propellant HFA-134a	-	-	See pending consult to Pharm/Tox regarding HFA-134a impurities specifications.
		coating of canisters	Inadequate	9/2/98	p. 65
		TEFLON® Topcoat 3200-100, canister coating formulation	Inadequate	9/2/98	p. 65
		uncoated aluminum alloy canister	Adequate	9/3/98	p. 65
		DF60 Mk12 Valve	Inadequate	9/9/98	p. 71
		gaskets	Inadequate	8/31/98	p. 71
		actuator	Inadequate	9/10/98	p. 73
		actuator	Inadequate	9/10/98	p. 73
		Pro-Fax 6331 polypropylene homopolymer resin for actuator	Adequate	9/14/92	p. 73
		Pro-Fax SR549M propylene/ethylene copolymer for strap-caps	Adequate	9/15/98	p. 73
		silica gel desiccant	Adequate	9/10/97	p. 74
		silica gel desiccant	Adequate	11/4/92	p. 75
		overwrap	Inadequate	9/2/98	p. 75

RELATED DOCUMENTS:

- NDA:**
- N18-473 Ventolin® (albuterol) Inhalation Aerosol (approved 5/81)
 - N19-112 Ventolin® (albuterol) Tablets (approved 7/86)
 - N19-269 Ventolin® (albuterol sulfate) Inhalation Solution (approved 1/87)
 - N19-489 Ventolin® (albuterol sulfate) Rotocaps for Inhalation (approved 5/88)
 - N19-621 Ventolin® (albuterol sulfate) Syrup (approved 6/87)
 - N19-773 Ventolin® (albuterol sulfate) Inhalation Solution (approved 4/92)

IND:

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CONSULTS:

Consult	Date Forwarded	Status	Comments
EES	Forwarded on Aug. 31, 1998		
Microbiology	Not forwarded.		Pending method revisions by applicant.
	-Sept. 10, 1998 -Oct. 9, 1998 -Not forwarded.	-Pending -Pending	-HFA-134a Impurities Consult Gasket Extractables Consult -Consult not forwarded due to absence of proposals from applicant for acceptance specifications.
	-Oct. 9, 1998	-Pending	-Safety Evaluation of Applicant's Proposed Limits
Labeling and Nomenclature Committee	Not forwarded.		The trademark Ventolin® is already in use for six other albuterol or albuterol sulfate products from the applicant.
Biometrics	Not forwarded.		Applicant will be asked to revise various specification limits before expiry can be calculated. Consult for expiration dating period evaluation will also be withheld pending the applicant's submission of updated 18 month stability data.

REMARKS/COMMENTS:

See chemist's review notes below.

CONCLUSIONS & RECOMMENDATIONS: In terms of Chemistry, Manufacturing, and Controls information, the application is not approvable. The deficiency comments in the attached letter should be forwarded to the applicant.

cc:
Org. NDA 20-983
HFD-570/Division File
HFD-570/CBertha
HFD-570/PJani
HFD-570/GPoochikian

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Review Chemist

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