CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-254

CHEMISTRY REVIEW(S)

ADVAIR HFA
(FLUTICASONE PROPIONATE AND SALMETEROL)
INHALATION AEROSOL
NDA 21-254

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: GlaxoSmithKline
One Franklin Plaza
Philadelphia, PA 19101

Indication: ADVAIR HFA is indicated for long-term, twice-daily maintenance treatment of asthma in patients 12 years of age and older.

Presentation: 3 strengths. Fluticasone propionate, 45, 115 and 230 mcg/inhalation (previously 44, 110, and 220), each with salmeterol xinafoate 21 mcg/inhalation (expressed as salmeterol base), from the mouthpiece of actuator

EER Status: Pending

Consults: EA – categorical exclusion provided
Biometrics – No consult forwarded but expiry period of 12 months found acceptable.
Methods Validation – Forwarded to Agency laboratory on 04-MAY-2006.

Original Submission: 20-DEC-2000
Re-submissions: 07-DEC-2005 (response to AE letter)

Post-Approval Agreements:

In addition to the stability commitment, the following post-approval agreements were made with the applicant:

1. Agree that efforts will be made to examine the [redacted] and to minimize it if possible, file any associated changes according to Agency guidance, and provide brief summaries of any progress in annual reports.

2. Agree to re-evaluate the Parametric Tolerance Interval Test approach for dose content uniformity once an adequate database is available (i.e., approximately 18 months after product launch), and [redacted]

3. Agree to submit the s [redacted]

4. Agree that post-approval agreements and subsequent changes and filing mechanisms outlined in the May 14, 2004, approval letter for the Flovent HFA Inhalation Aerosol application (N21-433) will also apply to the Advair HFA application in cases where there is commonality of the chemistry, manufacturing, and controls.

   a. (Commitment 1). [redacted] issues will be addressed for fluticasone propionate and fluticasone [redacted]

   b. (Commitment 2). Implementation of a [redacted] will occur [redacted]

   c. (Commitment 11). You will submit a prior approval supplement to implement final acceptance criteria for quantitative mass balance within 18 months of product launch.

Drug Substances:

Fluticasone propionate, a corticosteroid, has the chemical name S-(fluoromethyl) 6α,9–difluoro-11β, 17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β–carbothioate, 17–propionate. Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6 Daltons and the empirical formula is $C_{25}H_{31}F_3O_5S$. CMC information for fluticasone propionate is referenced to NDA 20-121 (Flonase Nasal Spray), except for particle size distribution for micronized drug substance, which is referenced to NDA 20-833 (Flovent Diskus Inhalation Powder).

Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy-α^1-[[[6-(4-phenylbutoxy) hexyl] aminomethyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate. Salmeterol xinafoate is a white to off-white powder with a molecular weight of 603.8 Daltons and the empirical formula $C_{25}H_{37}NO_4$-$C_{11}H_8O_3$. CMC information is referenced to NDA 20-236 (Serevent Inhalation Aerosol), except for the specification for drug related impurities, which is referenced to Advair Diskus (NDA 21-077).

Conclusion: Drug substances are acceptable.

Drug Product: The drug product is a suspension metered dose inhaler (MDI) and will be produced in three strengths of fluticasone propionate combined with one strength of salmeterol xinafoate: fluticasone propionate, 45, 115 and 230 mcg/inhalation, each with salmeterol xinafoate 30.45 mcg/inhalation (21 mcg expressed as salmeterol base), from

the mouthpiece. The formulation is made up solely of the two micronized drug substances and the propellant (1,1,1,2-tetrafluoroethane or HFA-134a).

The midpoint (apparent target) of the weight per actuation specification (valve delivery) is Each canister is to be labeled for 120 actuations (this applies to trade and sample presentations), but overfilled to a target of at the time of manufacture to maintain sufficient formulation to insure 120 full strength actuations at the end of shelf life.

The container closure system for Advair HFA consists of an aluminum can a metering valve; and a actuator with a strapcap. A overwrap, containing a silica gel desiccant, is used as a secondary pack to provide additional protection against moisture ingress prior to use. Under accelerated storage conditions of 40°C/75%RH,

The drug product uses a metering valve that delivers (target) of drug formulation. The valve components are composed of the following materials:

The formulation, valve and actuator/mouthpiece are critical components in determining the properties of the delivered dose, which is the aerosol cloud of drug formulation that is created each time the drug product is used.

Conclusion: Drug product is satisfactory.

Additional Items:

Adequate stability data were provided to support a **12 month expiration dating period**.

All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion:

From a CMC perspective, the application is recommended for **approval**, pending an acceptable recommendation from the Office of Compliance.

Blair A. Fraser, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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/s/

Blair Fraser
5/23/2006 01:25:35 PM
CHEMIST

NDA 21-254

Advair HFA Inhalation Aerosol
(fluticasone propionate and salmeterol xinafoate HFA inhalation aerosol)

GlaxoSmithKline

Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment, Division 1

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Chemistry Review Data Sheet

1. NDA 21-254

2. REVIEW #5

3. REVIEW DATE: 22-MAY-2006

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	12/20/2000
Amendment (site addresses)	2/9/2001
Amendment (product samples)	2/22/2001
Amendment (site addresses)	2/23/2001
IR letter	3/9/2001
Amendment (site addresses)	3/14/2001
Amendment (site addresses)	3/15/2001
Amendment (pre-meeting package)	3/21/2001
Amendment [redacted] valve)	3/26/2001
Amendment (extractable methods)	3/30/2001
Amendment (pre-meeting package)	4/17/2001
Memo to file – minutes (4/4/2001 industry meeting)	5/7/2001
Amendment (revised stability protocol)	6/5/2001
Amendment (6-8-01 meeting overheads)	6/12/2001
Amendment [redacted]	6/12/2001
Amendment (CMC table of contents)	6/12/2001
Amendment (stability update, IR letter responses) – partial review	6/29/2001
Chem. Review #1	8/01/2001
Correspondence [redacted] specification)	8/10/2001
DR letter	8/13/2001
Memo to file – minutes (6/8/2001 industry meeting)	8/17/2001
Correspondence ([redacted] protocol)	9/4/2001
Correspondence [redacted] protocol minutes)	9/18/2001
Telecon memo (date 8/22/2001)	9/24/01
Amendment [redacted] protocols)	10/3/2001
Correspondence (update [redacted] protocol)	10/11/2001
Faxed comments to applicant re: [redacted]	10/16/2001
Chem. Review #2	10/18/2001
Action Letter (AE)	10/19/2001
Amendment [redacted] stability update)	11/07/2001 (in part)
CMC Meeting Minutes (meeting date 2/4/2002) – fax	2/28/02
IR Letter	3/25/02
IR Letter	6/14/02
IR Letter	8/2/02
Amendment (stability update)	6/29/01
Amendment [redacted] profiles)	9/04/01
Amendment (info. re: foreign recall)	10/30/01
Amendment ([redacted] stability update)	11/07/01
Amendment [redacted] leachables)	11/14/01
Amendment (test site clarification)	11/26/01
Amendment (response to action letter)	4/15/02
Amendment (stability update)	4/25/02
Amendment (responses to IR letter)	5/15/02
Amendment (addit. responses to IR letter)	7/31/02
Amendment, BL	2/17/06
Amendment, BC	9/12/02
Amendment (complete response to 16-OCT-2002, AE letter), AZ	12/7/05
Amendment, BC	6/7/05

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	5/2/06 (assigned 5/11/06)
Amendment	4/14/06 (assigned 4/24/06)
Amendment (post-approval agreements)	5/18/06 (assigned 5/22/06)

7. NAME & ADDRESS OF APPLICANT:

Name:	Glaxo Group Limited d/b/a GlaxoSmithKline
Address:	One Franklin Plaza P.O. Box 7929 Philadelphia, PA 19101
Representative:	Tracy L. Fischer Manager US Regulatory Affairs
Telephone:	919-483-4223

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Advair HFA Inhalation Aerosol
b) Non-Proprietary Name (USAN): fluticasone propionate and salmeterol xinafoate HFA inhalation aerosol
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Section 505(b) of the Food, Drug and Cosmetic Act.

10. PHARMACOL. CATEGORY:

Anti-inflammatory corticosteroid and beta$_2$-adrenergic bronchodilator

11. DOSAGE FORM:

Aerosol, metered (code 339)

12. STRENGTH/POTENCY:

3 strengths. Fluticasone propionate, 45, 115 and 230 mcg/inhalation (previously 44, 110, and 220), each with salmeterol xinafoate 21 mcg/inhalation (expressed as salmeterol base), from the mouthpiece of actuator

13. ROUTE OF ADMINISTRATION:

respiratory (inhalation), code 136

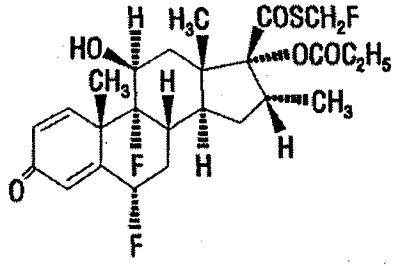
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed
___x___ Not a SPOTS product

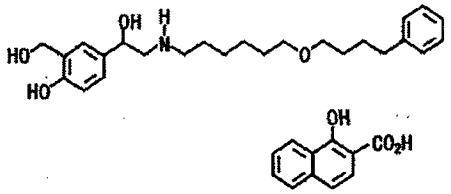
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

"One active component of ADVAIR HFA is fluticasone propionate, a corticosteroid having the chemical name S-(fluoromethyl)6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$."

The other active component of ADVAIR HFA is salmeterol xinafoate, a highly selective beta$_2$-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate, and it has the following chemical structure:



Salmeterol xinafoate is a white to off-white powder with a molecular weight of 603.8 and the empirical formula $C_{25}H_{37}NO_4 \bullet C_{11}H_8O_3$."

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	IV	[redacted]		7	Adequate	11/20/03 (A. Shaw, Ph.D.)	IR letter to be sent for clarification
	III			1	Adequate	2/14/06 4/26/06	
	III			7	N/A		Replaced by DMF [redacted]
	III			7	N/A		Replaced by DMF [redacted]
	III			1	Adequate	2/7/06	
	III			7	N/A		Replaced by DMF [redacted]
	III			3	Adequate	1/18/03	
	III			1	Adequate	1/26/06	IR letter
	III			7	N/A		Replaced by DMF [redacted]
	III			3	Adequate	8/28/03	
	III			1	Adequate	1/26/06 3/21/06	
	III			3	Adequate	10/04/01	See notes on pg. 9 of Chem. Rev. 2 for N21254.
	III			7	Adequate		This DMF supports DMF [redacted] (above). DMF is adequate because it provides the chemical composition and CFR references for the [redacted]
	III			4	N/A		See CR#1 pg. 73; see CR#3 – Response 9 (4-15-2002 amendment).
	III			3	Adequate	10/2/01	
	III			7	N/A		Replaced by DMF [redacted]
	III			3	Adequate	5/26/99	This is a supporting DMF for DMF [redacted]
	III			1	Adequate	2/7/2006	This is a supporting DMF for DMF [redacted] Deficiency letter
	III			7	N/A		No longer used, see DMF [redacted]
	III				Adequate	2/7/06 3/23/06	
[redacted]	III	[redacted]		1	Adequate	2/8/06 4/25/06	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 57,151	GlaxoSmithKline's Advair HFA Inhalation Aerosol

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	No consult forwarded. See p. 98 of CR#4.		
EES	Acceptable Pending	4/9/01 Resubmitted to OC on 28-DEC-2005	
Pharm/Tox (leachables)	Leachables issues addressed in conjunction with Flovent HFA. Current proposed leachables acceptance criteria are consistent or more stringent than those approved for Flovent HFA such that a pharm/tox consult is not needed. New leachable – [redacted] See review of comment 11 response in CR#5.	6/20/01 2/22/06	Lawrence Sancilio, Ph.D. Lawrence Sancilio, Ph.D.
Biopharm	N.A.		
DDMAC/DMETS	Corrections to labeling have been taken into consideration in conjunction with DPAP/ONDQA/OCP review of labeling.	5/16/2006 (DDMAC)	Michele Safarik
Methods Validation	Pending.	5/4/06 (forwarded)	
OPDRA	N.A.		
EA	N.A. (acceptable claim of categorical exclusion)		
Microbiology (microbial limits test, microbial challenge test)	satisfactory	6/21/01	Neal Sweeney, Ph.D.

The Chemistry Review for NDA 21-254

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for **approval (AP)** from a CMC perspective, pending an acceptable recommendation from the Office of Compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The PM should attach the CMC agreements that are included in the 18-MAY-2006, amendment (see attachment at end of review) to the action letter.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substances are fluticasone propionate and salmeterol xinafoate (salt). CMC information for both drug substances is referred to other approved NDAs from this applicant (see review notes of Chemistry Review #1).

The drug product is Advair (fluticasone propionate and salmeterol xinafoate) HFA Inhalation Aerosol (hereafter referred to as Advair HFA). The drug product is a suspension MDI and it will be produced in three strengths of fluticasone propionate combined with one strength of salmeterol xinafoate: fluticasone propionate, 45, 115 and 230 mcg/inhalation, each with salmeterol xinafoate 30.45 mcg/inhalation (21 mcg expressed as salmeterol base), from the mouthpiece. The formulation is made up solely of the two micronized drug substances and the propellant (GR106642X, which is 1,1,1,2-tetrafluoroethane or HFA-134a). For amounts of each drug delivered through the valve, see the composition section of the drug product review in Chemistry Review #1. The midpoint (apparent target) of the weight per actuation specification (valve delivery) is Each canister

is to be labeled for 120 actuations (this applies to trade and sample presentations), but overfilled to a target of actuations at the time of manufacture to maintain sufficient formulation to insure 120 full strength actuations at the end of shelf life. Individual canisters will be rejected and discarded from the batch during the manufacturing process after the canisters are filled, if the total fill weights are outside of the range . The jet hole ("orifice") diameter of the actuator is mm (the same orifice diameter range as for GSK's Ventolin HFA Inhalation Aerosol).

The container closure system (CCS) for Advair HFA consists of an aluminum can metering valve, and a actuator with a strapcap. A overwrap containing a silica gel desiccant is used as a secondary pack to provide additional protection against moisture ingress prior to use. It was found that under accelerated storage conditions of 40°C/75%RH,

The drug product uses a that delivers target) of drug formulation. The valve components are composed of the following materials: It is important to note that the original application included data using a similar but distinct valve.

The formulation, valve and actuator/mouthpiece are critical components in determining the properties of the delivered dose, which is the aerosol cloud of drug formulation that is created each time the drug product is used.

B. Description of How the Drug Product is Intended to be Used

This drug product is a multiple dose suspension metered dose inhaler and is designed to meter amounts of micronized drug substances suspended in HFA-134a propellant and to create a directed aerosol cloud of very fine droplets/particles, for each of the 120 labeled inhalations (all three strengths). The drug product is produced in three strengths of fluticasone propionate combined with one strength of salmeterol xinafoate: fluticasone propionate, 45, 115 and 230 mcg/inhalation, each with salmeterol xinafoate 30.45 mcg/inhalation (21 mcg expressed as salmeterol base), through the mouthpiece. The recommended dosage for each of the strengths is 2 inhalations twice daily. The **expiration dating period is 12 months.**

C. Basis for Approvability or Not-Approval Recommendation

Not applicable.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D./ONDQA/DIV 1/5/22/2006
Blair Fraser, Ph.D./ ONDQA/DIV 1/Branch Chief_____

C. CC Block

Orig. NDA 21-254
OND/DPAP/Division File
ONDQA/DIV 1/CBertha
ONDQA/DIV 1/BFraser
ONDQA/DIV 1/PPeri
OND/DPAP/LJafari
OND/DPAP/SBarnes
R/D Init. by: BFraser_____
Filename and Location:
c:\data\mydocuments\reviews etc\NDA\21254\Review 4\06-05-18_rev.doc

34 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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/s/

Craig Bertha
5/23/2006 07:52:11 AM
CHEMIST

Blair Fraser
5/23/2006 08:10:34 AM
CHEMIST

NDA 21-254

Advair HFA Inhalation Aerosol
(fluticasone propionate and salmeterol xinafoate HFA inhalation aerosol)

GlaxoSmithKline

Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment, Division 1

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C. CC Block 13

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Chemistry Review Data Sheet

1. NDA 21-254

2. REVIEW #4

3. REVIEW DATE: 07-MAR-2006

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	12/20/2000
Amendment (site addresses)	2/9/2001
Amendment (product samples)	2/22/2001
Amendment (site addresses)	2/23/2001
IR letter	3/9/2001
Amendment (site addresses)	3/14/2001
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Amendment (pre-meeting package)	3/21/2001
Amendment ([redacted] valve)	3/26/2001
Amendment (extractable methods)	3/30/2001
Amendment (pre-meeting package)	4/17/2001
Memo to file – minutes (4/4/2001 industry meeting)	5/7/2001
Amendment (revised stability protocol)	6/5/2001
Amendment (6-8-01 meeting overheads)	6/12/2001
Amendment ([redacted]	6/12/2001
Amendment (CMC table of contents)	6/12/2001
Amendment (stability update, IR letter responses) – partial review	6/29/2001
Chem. Review #1	8/01/2001
Correspondence ([redacted] specification)	8/10/2001
DR letter	8/13/2001
Memo to file – minutes (6/8/2001 industry meeting)	8/17/2001
Correspondence ([redacted] protocol)	9/4/2001
Correspondence ([redacted] protocol minutes)	9/18/2001
Telecon memo (date 8/22/2001)	9/24/01
Amendment ([redacted] protocols)	10/3/2001
Correspondence (updated [redacted] protocol)	10/11/2001
Faxed comments to applicant re: [redacted]	10/16/2001
Chem. Review #2	10/18/2001
Action Letter (AE)	10/19/2001
Amendment ([redacted] stability update)	11/07/2001 (in part)
CMC Meeting Minutes (meeting date 2/4/2002) – fax	2/28/02
IR Letter	3/25/02
IR Letter	6/14/02
IR Letter	8/2/02
Amendment (stability update)	6/29/01
Amendment ([redacted] profiles)	9/04/01
Amendment (info. re: foreign recall)	10/30/01
Amendment ([redacted] stability update)	11/07/01
Amendment ([redacted] leachables)	11/14/01
Amendment (test site clarification)	11/26/01
Amendment (response to action letter)	4/15/02
Amendment (stability update)	4/25/02
Amendment (responses to IR letter)	5/15/02
Amendment (addit. responses to IR letter)	7/31/02

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment, BL	17-FEB-2006 (assigned 02-MAR-2006)
Amendment, BC	12-SEP-2002 (assigned 12-JAN-2006)
Amendment (complete response to 16-OCT-2002, AE letter), AZ	07-DEC-2005 (assigned 12-JAN-2006)
Amendment, BC	07-JUN-2005 (assigned 12-JAN-2006)

7. NAME & ADDRESS OF APPLICANT:

Name:	Glaxo Group Limited d/b/a GlaxoSmithKline
Address:	One Franklin Plaza P.O. Box 7929 Philadelphia, PA 19101
Representative:	Tracy L. Fischer Manager US Regulatory Affairs
Telephone:	919-483-4223

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Advair HFA Inhalation Aerosol
b) Non-Proprietary Name (USAN): fluticasone propionate and salmeterol xinafoate HFA inhalation aerosol
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Section 505(b) of the Food, Drug and Cosmetic Act.

10. PHARMACOL. CATEGORY:

Anti-inflammatory corticosteroid and beta$_2$-adrenergic bronchodilator

11. DOSAGE FORM:

Aerosol, metered (code 339)

12. STRENGTH/POTENCY:

3 strengths. Fluticasone propionate, 45, 115 and 230 mcg/inhalation (previously 44, 110, and 220), each with salmeterol xinafoate 21 mcg/inhalation (expressed as salmeterol base), through the mouthpiece

13. ROUTE OF ADMINISTRATION:

respiratory (inhalation), code 136

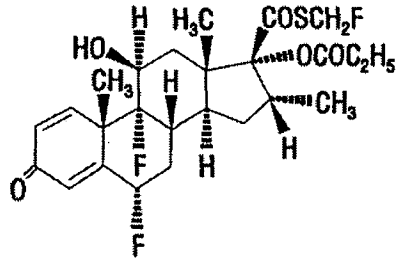
14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
___x___Not a SPOTS product

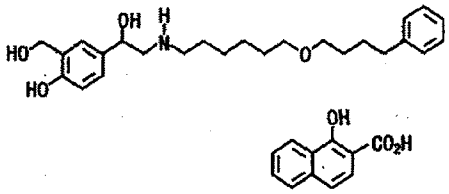
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

"One active component of ADVAIR HFA is fluticasone propionate, a corticosteroid having the chemical name S-(fluoromethyl)6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$."

The other active component of ADVAIR HFA is salmeterol xinafoate, a highly selective beta$_2$-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate, and it has the following chemical structure:



Salmeterol xinafoate is a white to off-white powder with a molecular weight of 603.8 and the empirical formula $C_{25}H_{37}NO_4 \bullet C_{11}H_8O_3$."

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	IV			7	Adequate	11/20/03 (A. Shaw, Ph.D.)	IR letter to be sent for clarification
	III			1	Inadequate	2/14/06	Inadequate due to inadequacy of DMF
	III			7	N/A		Replaced by DMF
	III			7	N/A		Replaced by DMF
	III			1	Adequate	2/7/06	
	III			7	N/A		Replaced by DMF
	III			3	Adequate	1/18/03	
	III			1	Adequate	1/26/06	IR letter
	III			7	N/A		Replaced by DMF 9988
	III			3	Adequate	8/28/03	
	III			1	Inadequate	1/26/06	Deficiency letter
	III			3	Adequate	10/04/01	See notes on pg. 9 of Chem. Rev. 2 for N21254.
	III			7	Adequate		This DMF supports DMF (above). DMF is adequate because it provides the chemical composition and CFR references for the
	III			4	N/A		See CR#1 pg. 73; see CR#3 – Response 9 (4-15-2002 amendment).
	III			3	Adequate	10/2/01	
	III			7	N/A		Replaced by DMF
	III			3	Adequate	5/26/99	This is a supporting DMF for DMF
	III			1	Adequate	2/7/2006	This is a supporting DMF for DMF Deficiency letter
	III			7	N/A		No longer used, see DMF
	III				Inadequate	2/7/06	Deficiency letter, supports DMF
	III			1	Inadequate	2/8/06	Deficiency letter

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 57,151	GlaxoSmithKline's Advair HFA Inhalation Aerosol

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	No consult forwarded. See p. 98 of review.		
EES	Acceptable Pending	4/9/01 Resubmitted to OC on 28-DEC-2005	
Pharm/Tox (leachables)	Leachables issues addressed in conjunction with Flovent HFA. Current proposed leachables acceptance criteria are consistent or more stringent than those approved for Flovent HFA such that a pharm/tox consult is not needed. New leachable –	6/20/01 2/22/06	Lawrence Sancilio, Ph.D. Lawrence Sancilio, Ph.D.
Biopharm	N.A.		
LNC	N.A. since the name "Advair" was approved in another NDA		
Methods Validation	Will be requested upon receipt of updated MV package (see attached draft DR letter comment).		
OPDRA	N.A.		
EA	N.A. (acceptable claim of categorical exclusion)		
Microbiology (	satisfactory	6/21/01	Neal Sweeney, Ph.D.

The Chemistry Review for NDA 21-254

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is **approvable (AE)** from a CMC perspective. The PM should draft a discipline review letter from the attached draft letter to be forwarded to the applicant.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant has made revisions to the valve and actuator components of the container closure system that were to improve [redacted]

As a result of the changes there was some improvement in the [redacted] but there was also an [redacted] r. As a result, the applicant will be asked to agree to undertake further studies of the product so that [redacted] can be lessened or eliminated. In addition, the applicant will be asked to agree to adopt the Parametric Tolerance Interval Test (PTIT) approach once the Agency and the industry representatives from IPAC-RS (International Pharmaceutical Aerosol Consortium on Regulation and Science) come to agreement on the specifics of this testing scheme.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substances are fluticasone propionate [redacted] and salmeterol xinafoate (salt). CMC information for both drug substances is referred to other approved NDAs from this applicant (see review notes of Chemistry Review #1) [redacted]

The drug product is Advair (fluticasone propionate and salmeterol xinafoate) HFA Inhalation Aerosol (hereafter referred to as Advair HFA). The drug product is a suspension MDI and it will be produced in three strengths of fluticasone propionate combined with one strength of salmeterol xinafoate: fluticasone propionate, 45, 115 and 230 mcg/inhalation, each with salmeterol xinafoate 30.45 mcg/inhalation (21 mcg expressed as salmeterol base), through the mouthpiece. The formulation is made up solely of the two micronized drug substances and the propellant (GR106642X, which is 1,1,1,2-tetrafluoroethane or HFA-134a). For amounts of each drug delivered through the valve, see the composition section of the drug product review in Chemistry Review #1. The midpoint (apparent target) of the weight per actuation specification (valve delivery) is [redacted]. Each canister is to be labeled for 120 actuations (this applies to trade and sample presentations), but overfilled to a target of [redacted] actuations at the time of manufacture to maintain sufficient formulation to insure 120 full strength actuations at the end of shelf life. Individual canisters will be rejected and discarded from the batch during the manufacturing process after the canister is filled, if the total fill weight is outside of the range [redacted]. The jet hole ("orifice") diameter of the actuator is [redacted] the same orifice diameter range as for GSK's Ventolin HFA Inhalation Aerosol).

The container closure system (CCS) for Advair HFA consists of an aluminum [redacted] can [redacted] a metering valve, and a [redacted] actuator with a strapcap. A [redacted] overwrap containing a silica gel desiccant is used as a secondary pack to provide additional protection against moisture ingress prior to use. It was found that under accelerated storage conditions of 40°C/75%RH, [redacted]

The drug product uses a [redacted] metering valve [redacted] that delivers [redacted] (target) of drug formulation. The valve components are composed of the following materials: [redacted]. It is important to note that the original application included data using a similar but distinct [redacted] valve. [redacted]

The formulation, valve and actuator/mouthpiece are critical components in determining the properties of the delivered dose, which is the aerosol cloud of drug formulation that is created each time the drug product is used.

B. Description of How the Drug Product is Intended to be Used

This drug product is a multiple dose suspension metered dose inhaler and is designed to meter amounts of micronized drug substances suspended in HFA-134a propellant and to create a directed aerosol cloud of very fine droplets/particles, each time that it is used for inhalation. The drug product is produced in three strengths of fluticasone propionate combined with one strength of salmeterol xinafoate: fluticasone propionate, 45, 115 and 230 mcg/inhalation, each with salmeterol xinafoate 30.45 mcg/inhalation (21 mcg expressed as salmeterol base), through the mouthpiece. Each canister is labeled for 120 actuations. The recommended dosage for each of the strengths is 2 inhalations twice daily. The proposed expiration dating period for the drug product is — — and — of stability data are included in the resubmission. There was

C. Basis for Approvability or Not-Approval Recommendation

Agreements will be sought from the applicant regarding the undesirable —

The currently proposed — expiration dating period is not supported by the — of stability data currently included in the resubmission. A 12 month expiry is reasonably justified.

Three drug master files pertaining to the — are inadequate and deficiencies will need to be addressed by the holders of each of these files.

Labeling negotiations will be necessary. Also a response from the pharmacology/toxicology team regarding the consult on the safety of the — — leachable in the drug product formulation is pending. Additionally, the issue of —), as covered in the applicant's response to comment 3 of the last AE letter, is still under discussion within the clinical team.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D./ONDQA/DIV 1/3/7/2006
Blair Fraser, Ph.D./ ONDQA/DIV 1/Branch Chief_____

C. CC Block

Orig. NDA 21-254
OND/DPAP/Division File
ONDQA/DIV 1/CBertha
ONDQA/DIV 1/BFraser
OND/DPAP/LJafari
OND/DPAP/SBarnes
R/D Init. by: BFraser_____
Filename and Location:
c:\data\mydocuments\reviews etc\NDA\21254\Review 4\05-12-07_rev.doc

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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
3/7/2006 10:56:06 AM
CHEMIST

Blair Fraser
3/7/2006 02:27:14 PM
CHEMIST

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: August 19, 2004

FROM: Alan C. Schroeder, Ph.D.

SUBJECT: Stability Protocol in Correspondence from GSK dated August 2, 2004 (Pre-meeting package)

TO: NDA 21-254 (GlaxoSmithKline's Advair HFA Inhalation Aerosol)

Preliminary Review of Stability Protocol in GSK's 8/2/2004 submission to N21-254 (Advair HFA Inhalation Aerosol).

The stability protocol will be implemented after a number of proposed changes in the drug product have been made. The applicant has requested our rapid evaluation of the stability protocol. These comments are limited to the stability protocol, and they do not constitute complete review of the 8/2/2004 pre-meeting package.

Comments for the applicant:

This is a preliminary review of your proposed new stability protocol. It was not performed with consideration of all outstanding issues for this NDA, which should be considered before proceeding with the stability study.

Explain the following comment pertaining to the proposed core stability protocol (pg. 20): "This protocol may be modified in view of the data as they are generated."

Acceptance criteria for leachables in the drug product should be based upon your stability data. If your long term stability studies for leachables are conducted at [redacted], then the acceptance criteria should be based upon stability data obtained after storing under these conditions. Similarly, a safety assessment should be provided for these data, and an extractables/leachables correlation should be established.

Measure the parameter, foreign particulates, at the [redacted] time point for storage at [redacted] as well as at the proposed time points.

Add leachables testing at the [redacted] time point [redacted] conditions) and at the [redacted] time point [redacted] conditions).

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

/s/

Alan Schroeder
8/20/04 08:53:06 AM
CHEMIST
Project manager is requested to send comments to applicant.
comments re: stability protocol to cover proposed product changes

Richard Lostritto
8/20/04 05:12:16 PM
CHEMIST

NDA 21-254

Advair HFA Inhalation Aerosol
(fluticasone propionate and salmeterol xinafoate HFA inhalation aerosol)

GlaxoSmithKline

Alan C. Schroeder, Ph.D.
Division of Pulmonary and Allergy Drug Products

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Chemistry Review Data Sheet

1. NDA 21-254

2. REVIEW #3

3. REVIEW DATE: October 8, 2002

4. REVIEWER: Alan C. Schroeder, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	12/20/2000
Amendment (site addresses)	2/9/2001
Amendment (product samples)	2/22/2001
Amendment (site addresses)	2/23/2001
IR letter	3/9/2001
Amendment (site addresses)	3/14/2001
Amendment (site addresses)	3/15/2001
Amendment (pre-meeting package)	3/21/2001
Amendment [redacted] valve)	3/26/2001
Amendment (extractable methods)	3/30/2001
Amendment (pre-meeting package)	4/17/2001
Memo to file – minutes (4/4/2001 industry meeting)	5/7/2001
Amendment (revised stability protocol)	6/5/2001
Amendment (6-8-01 meeting overheads)	6/12/2001
Amendment [redacted]	6/12/2001
Amendment (CMC table of contents)	6/12/2001
Amendment (stability update, IR letter responses) – partial review	6/29/2001
Chem. Review #1	8/01/2001
Correspondence [redacted] specification)	8/10/2001
DR letter	8/13/2001
Memo to file – minutes (6/8/2001 industry meeting)	8/17/2001
Correspondence [redacted] protocol)	9/4/2001
Correspondence [redacted] protocol minutes)	9/18/2001
Telecon memo (date 8/22/2001)	9/24/01
Amendment [redacted] protocols)	10/3/2001
Correspondence (updated [redacted] rotocol)	10/11/2001
Faxed comments to applicant re: [redacted]	10/16/2001
Chem. Review #2	10/18/2001
Action Letter (AE)	10/19/2001
Amendment ([redacted] ability update)	11/07/2001 (in part)
CMC Meeting Minutes (meeting date 2/4/2002) – fax	2/28/02
IR Letter	3/25/02
IR Letter	6/14/02
IR Letter	8/2/02

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (stability update)	6/29/01
Amendment (profiles)	9/04/01
Amendment (info. re: foreign recall)	10/30/01
Amendment (stability update)	11/07/01
Amendment (eachables)	11/14/01
Amendment (test site clarification)	11/26/01
Amendment (response to action letter)	4/15/02
Amendment (stability update)	4/25/02
Amendment (responses to IR letter)	5/15/02
Amendment (addit. responses to IR letter)	7/31/02

7. NAME & ADDRESS OF APPLICANT:

Name:	Glaxo Group Limited d/b/a GlaxoSmithKline
Address:	One Franklin Plaza P.O. Box 7929 Philadelphia, PA 19101
Representative:	Sue M. Holmes, M.S. Asst. Dir. US CMC Regulatory Affairs
Telephone:	919-483-4411

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Advair HFA Inhalation Aerosol
b) Non-Proprietary Name (USAN): fluticasone propionate and salmeterol xinafoate HFA inhalation aerosol
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Section 505(b) of the Food, Drug and Cosmetic Act.

10. PHARMACOL. CATEGORY:

Anti-inflammatory corticosteroid and beta$_2$-adrenergic bronchodilator

11. DOSAGE FORM:

Aerosol, metered (code 339)

12. STRENGTH/POTENCY:

3 strengths. Fluticasone propionate, 44, 110 and 220 mcg/inhalation, each with salmeterol xinafoate 21 mcg/inhalation (expressed as salmeterol base), through the mouthpiece

13. ROUTE OF ADMINISTRATION:

respiratory (inhalation), code 136

14. Rx/OTC DISPENSED: _X__Rx ___OTC

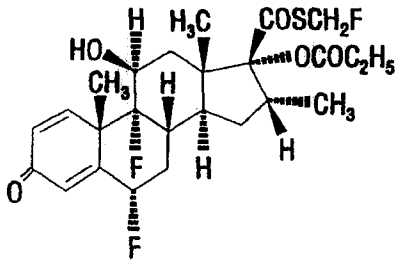
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note25]:

_____SPOTS product – Form Completed

___x___Not a SPOTS product

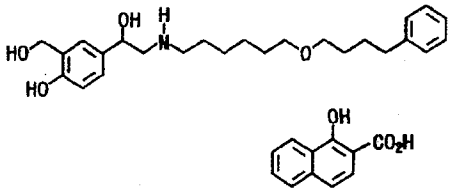
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

"One active component of ADVAIR HFA is fluticasone propionate, a corticosteroid having the chemical name S-(fluoromethyl)6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$.

The other active component of ADVAIR HFA is salmeterol xinafoate, a highly selective beta$_2$-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate, and it has the following chemical structure:



Salmeterol xinafoate is a white to off-white powder with a molecular weight of 603.8 and the empirical formula $C_{25}H_{37}NO_4 \bullet C_{11}H_8O_3$."

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	IV			7	Adequate	8/17/2001	6/26/02 amend. since last review; updates manuf. process description; no change in operations
	III			1	Inadequate	8/14/2002	Deficiency letter
	III			1	Inadequate	8/20/02	Deficiency letter
	III			7	Adequate	10/1/01	10/16/01 amend. provides COAs; 11/2/01 amend. provides updated drawings; no change in
	III			1	Adequate	8/22/02	
	III			3	Adequate	4/13/00	
	III			1	Inadequate	8/22/02	Deficiency letter
	III			3	Adequate	10/30/00	
	III			3	Adequate	10/04/01	See notes on pg. 9 of Chem. Rev. 2 for N21254.
	III			4			See CR#1 pg. 73; see CR#3 – Response 9 (4-15-2002 amendment).
	III			3	adequate	10/2/01	
	III			3	adequate	10/2/00	This pertains to (section 125 of the DMF)
	III			3	Adequate	5/26/99	This is a supporting DMF for DMF
	III			1	Inadequate	8/20/2002	This is a supporting DMF for DMF Deficiency letter
	III			1	Inadequate	8/20/02	This is a supporting DMF for DMF Deficiency letter
	III			7	Adequate		This DMF supports DMF above). DMF is

							adequate because it provides the chemical composition and CFR references for the —

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 57,151	GlaxoSmithKline's Advair HFA Inhalation Aerosol

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Consult request for statistical evaluation of expiry is withheld pending agreement on acceptance criteria. Also, evaluation of — — stability data will be performed.		
EES	Acceptable	4/9/01	M. Egas; Needs an update before AP action.
Pharm/Tox (leachables)[1]	Acceptable (for one year after manufacture). Additional consult will be needed once leachable deficiencies are adequately addressed and data provided. This also will include assessment of — on valve components.	6/20/01	Lawrence Sancilio, Ph.D.
Biopharm	N.A.		
LNC	N.A. since the name "Advair"		

	was approved in another NDA		
Methods Validation	not requested yet pending resolution of specification issues		
OPDRA	N.A.		
EA	N.A. (acceptable claim of caterorical exclusion)		
Microbiology (microbial limits test, microbial challenge test)	satisfactory	6/21/01	Neal Sweeney, Ph.D.

[1] Overall pharm/tox assessment of the safety of the Renoclean and Mergital LM115 residues present on valve components is deferred (along with the issues in responses 12h(1) and (2) in the 4/15/02 amendment) at this time pending the additional information requested about these residues. Note our IR requests dated June 14, 2002 and August 2, 2002, for which we have not yet received a response.

The Chemistry Review for NDA 21-254

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is approvable from a CMC perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Applicant should provide a stability commitment to study the [redacted] in all of the post-approval commitment batches, at all the usual time points and provide a comparison of the stability data between the [redacted]

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substances are fluticasone propionate and salmeterol xinafoate. CMC information for both drug substances is referred to other approved NDAs owned by this applicant (see under "drug substance" in review notes of Chemistry Review #1). [redacted]

The drug product is Advair (fluticasone propionate and salmeterol xinafoate) HFA Inhalation Aerosol. The drug product is a suspension MDI and it will be produced in three strengths of fluticasone propionate combined with one strength of salmeterol xinafoate: fluticasone propionate, 44, 110 and 220 mcg/inhalation, each with salmeterol xinafoate 21 mcg/inhalation (expressed as salmeterol base), through the mouthpiece. The formulation is made up solely of the two micronized drug substances and the propellant (GR106642X, which is 1,1,1,2-tetrafluoroethane, which is the same chemical structure as HFA-134a). For amounts of each drug delivered through the valve, see the composition section of the drug product review in Chemistry Review #1. Note that when salmeterol

xinafoate is expressed as the salt, 21 mcg of the base is equivalent to 30.45 mcg of the xinafoate salt. The midpoint (apparent target) of the weight per actuation specification (valve delivery) is . Each canister is to be labeled for 120 actuations (this applies to trade, sample and institutional presentations), but overfilled to a target of actuations at manufacture to maintain sufficient formulation to insure 120 full strength actuations at the end of shelf life. Individual canisters will be rejected and discarded from the batch during the manufacturing process after the canister is filled if the total fill weight is outside of the range The jet hole ("orifice") diameter of the actuator is mm (the same orifice diameter range as for Ventolin HFA Inhalation Aerosol).

"The container/closure system for ADVAIR consists of an aluminum can , metering valve and a actuator with a strapcap. A overwrap containing a desiccant is used as a secondary pack to provide additional protection against moisture ingress."

The drug product uses a metering valve and its materials of manufacture are said to be identical to those used for Ventolin HFA (except for . The valve delivers (target) of drug formulation. The valve components are composed of the following materials: The aluminum can are indicated to be identical to those employed for Ventolin HFA Inhalation Aerosol (except that the can is shorter, resulting in smaller volume). . The desiccant pack and are identical to those used for Ventolin HFA Inhalation Aerosol. The actuators and strapcaps are said to be identical to those used for Serevent Inhalation Aerosol and Flovent Inhalation Aerosol, except for a used in Advair.

The following reason is giving for overwrapping the drug product and placing desiccant packets inside the overwrap, along with the drug product. "Studies conducted on unprotected product at 40C/75% RH have shown

The formulation, valve and actuator/mouthpiece are critical components in determining the properties of the dosage unit, which is the aerosol cloud of drug formulation that is created each time the drug product is used.

B. Description of How the Drug Product is Intended to be Used

This drug product, a multiple dose suspension metered dose inhaler, is designed to meter amounts of micronized drug substances suspended in HFA-134a propellant and to create a directed aerosol cloud of very fine droplets/particles, each time

that it is used for inhalation. The drug product is produced in three strengths of fluticasone propionate combined with one strength of salmeterol xinafoate: fluticasone propionate, 44, 110 and 220 mcg/inhalation, each with salmeterol xinafoate 21 mcg/inhalation (expressed as salmeterol base), through the mouthpiece. Each canister is labeled for 120 actuations. The maximum recommended dosage is 2 inhalations of ADVAIR HFA 220/21 twice daily. The proposed expiration dating period for the drug product is ⟶ The Agency has not yet reached agreement on this proposal, pending additional data.

C. Basis for Approvability or Not-Approval Recommendation

NDA primary stability batches do not include the product overage proposed for the 44/21 strength. Even when the product overage is the same as that proposed for marketing, the target values for all strengths are not the same as the label claim values and therefore the label claims for product strength need to be modified somewhat.

There has been inadequate stability data to define the stability of the drug product

There is considerable

Several supporting DMFs remain deficient.

Agreement has not been reached for the control of extractables and leachables in the drug product, which can adversely affect the sensitive patient. A correlation between extractables and leachables has not been fully established. Such a correlation is essential since leachables in the drug product are usually controlled by control of extractables in the container closure components.

A number of specification issues remain deficient, including acceptance criteria, analytical procedures and methods validation data.

Note that review of leachable issues including the extractable/leachable correlation are deferred pending additional information, requested in the IR letters dated June 14 and August 2, 2002. This deferred review also includes various information, including Appendix 8 of the 11/7/01 amendment and Appendix 14 of the 4/25/02 submission. See also information discussed beginning on page 103 of chemistry review #1.

Review of the proposed expiration dating period (using statistical analysis of the stability data) is deferred, pending agreement on the — procedure during — - manufacture, agreement on the acceptance criteria and adequate response to stability deficiencies.

See discussion of Response 18 in the 4/15/02 amendment, pertaining to the effect of dropping the canister. Labeling should be considered in the final review cycle, to — —. Review of labeling will be done in the last review cycle.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Alan Schroeder, Ph.D./10-08-2002
Guirag Poochikian, Ph.D./Date
Ladan Jafari – project manager

C. CC Block

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/s/

Alan Schroeder
10/8/02 04:11:16 PM
CHEMIST

Chem. Review #3 (Advair HFA)

Guiragos Poochikian
10/15/02 09:58:55 AM
CHEMIST

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

NDA #: 21-254 **CHEM. REVIEW #:** 2 **REVIEW DATE:** October 17, 2001

RECOMMEND ACTION: **Not Approvable**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	12/20/2000	12/20/2000	1/9/2001
Amendment (site addresses)	2/9/01	2/12/01	2/13/01
Amendment (product samples)	2/22/01	2/23/01	2/28/01
Amendment (site addresses)	2/23/01	2/26/01	2/28/01
Amendment (site addresses)	3/14/01		
Amendment (site addresses)	3/15/01	3/16/01	3/19/01
Amendment (pre-meeting package)	3/21/01	3/23/01	
Amendment (disassembled valve)	3/26/01	3/27/01	
Amendment (extractable methods)	3/30/01	4/3/01	4/9/01
Amendment (pre-meeting package)	4/17/01	4/18/01	
Amendment (revised stability protocol)	6/5/01	6/6/01	6/6/01
Amendment (6-8-01 meeting overheads)	6/12/01	6/13/01	6/15/01
Amendment (acrylonitrile monomer)	6/12/01	6/13/01	7/17/01
Amendment (CMC table of contents)	6/12/01	6/13/01	
Amendment* (stability update, IR letter responses)	6/29/01	7/2/01	
Correspondence* (acrylonitrile monomer specification)	8/10/91	8/14/01	
Correspondence* (mis-use protocol)	9/4/2001		
Amendment* (equilibrium and quarantine protocols)	10/3/2001		

***subject of this review**

NAME & ADDRESS OF APPLICANT:
GlaxoSmithKline
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709-3398
ATTN: Lorna C. Wilson, Associate Director,
CMC Regulatory Affairs

DRUG PRODUCT NAME:

Proprietary: Advair HFA Inhalation Aerosol

Nonproprietary/USAN: fluticasone propionate and salmeterol xinafoate HFA inhalation aerosol

Code Name/#:

Chem. Type/Ther. Class:

PHARMACOL. CATEGORY/INDICATION: anti-inflammatory corticosteroid, and $beta_2$-adrenergic bronchodilator

DOSAGE FORM: inhalation aerosol

STRENGTHS: fluticasone propionate, 44, 110 and 220 mcg/inhalation each with salmeterol xinafoate 21 mcg/inhalation (expressed as salmeterol base), through the mouthpiece

ROUTE OF ADMINISTRATION: inhalation

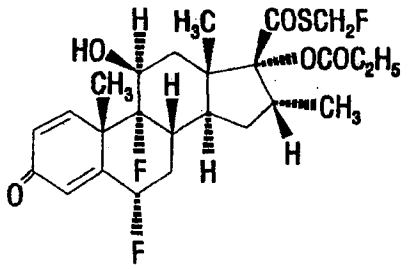
DISPENSED: X Rx _ OTC

SPECIAL PRODUCTS: x_ YES _ NO (clarifying information about specific biological source of starting material to be sought from referenced NDA in drug substance section)

(If yes, fill out the form for special products and deliver to the TIA through the team leader for data entry)

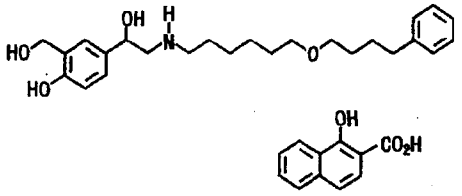
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

"One active component of ADVAIR HFA is fluticasone propionate, a corticosteroid having the chemical name S-(fluoromethyl)6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$.

The other active component of ADVAIR HFA is salmeterol xinafoate, a highly selective beta$_2$-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate, and it has the following chemical structure:



Salmeterol xinafoate is a white to off-white powder with a molecular weight of 603.8 and the empirical formula $C_{25}H_{37}NO_4 \bullet C_{11}H_8O_3$."

SUPPORTING DOCUMENTS:

DMFs

DMF No.	Holder Name	Subject	Status	Date Reviewed or date found adequate*	Reference in Reviews
			Adequate	8/17/2001	pp. 18-19 in Chem. Rev. #1 pp. 8-10 in Chem. Rev. #2
			Adequate	8/16/2001	pp. 8-10 in Chem. Rev. #2
			Inadequate	9/28/2001 (letter sent 10-2-01)	pp. 8-10 in Chem. Rev. #2
			Adequate	10/1/01	pp. 8-10 in Chem. Rev. #2
			not reviewed pending clarification	no review - letter sent 9/28/01	pp. 8-10 in Chem. Rev. #2
			Adequate	4/13/00	pp. 8-10 in Chem. Rev. #2
			Inadequate LOA	not reviewed (comment for applicant)	pp. 8-10 in Chem. Rev. #2
			Adequate	10/30/00	pp. 8-10 in Chem. Rev. #2
			Adequate	10/04/01	pp. 8-10 in Chem. Rev. #2
			Inadequate LOA	not reviewed (comment for applicant)	pp. 8-10 in Chem. Rev. #2
			adequate	10/2/01	pp. 8-10 in Chem. Rev. #2
			adequate	10/2/00	pp. 8-10 in Chem. Rev. #2
			Adequate	5/26/99	See CR#5 of DMF
			Inadequate LOA	not reviewed	See CR#5 of DMF
			Inadequate LOA	not reviewed	See CR#5 of DMF

*see inside this review

RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject
IND	57,151	GlaxoSmithKline	Advair HFA Inhalation Aerosol

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	4/5/01	found acceptable by Compliance on 4/9/01	
Microbiology, HFD-805	3/19/2001 5/10/01	satisfactory (6/21/01 micro. review) satisfactory (6/21/01 micro. review)	informal consult re:
Pharmacology	5/18/01	acceptable	Since no new impurities or degradation products are observed for the drug product, compared to those in approved drug products, a pharm/tox evaluation should not be necessary to evaluate drug related impurities and degradants which are present in the drug product. Safety evaluation of leachables in the drug product was requested. Daily exposure of extractables/leachables from the drug product is acceptable for one year from the date of drug product manufacture (per current stability data).
Biometrics, HFD-710		delayed pending stability update (for product)	
Environmental Assessment		no EA needed	Applicant claims a categorical exclusion under 21 CFR 25.31(b). Acceptable.
Labeling & Nomenclature Committee		no consult necessary.	Consult not necessary, since "Advair" was previously approved in another NDA (Advair Diskus).

CONCLUSIONS AND RECOMMENDATIONS:

This NDA may be considered to be **NOT APPROVABLE** from a CMC perspective, pending resolution of the issues listed at the end of this review. Review of all stability data and information in the 6/29/01 amendment is deferred at this time, since a new stability study is underway, beginning at the end of May, 2001, on drug product manufactured utilizing the proposed process, and since initial data from that study will not become available until late October or early November. An update of other stability data has also been requested. CMC labeling comments are also withheld at this time. The amendment dated October 11, 2001 is not reviewed at this time.

cc:
Orig. NDA 21-254
HFD-570/Division File
HFD-570/Aschroeder/10-17-2001
HFD-570/CSO
HFD-570/GPoochikian

Alan C. Schroeder, Ph.D., Review Chemist

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/s/

Alan Schroeder
8/1/01 04:33:46 PM
CHEMIST

Initial CMC review - Advair HFA Inhalation Aerosol

Guiragos Poochikian
8/1/01 04:38:40 PM
CHEMIST

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

NDA #: 21-254 **CHEM. REVIEW #:** 1 **REVIEW DATE:** July 31, 2001

RECOMMEND ACTION: DR Letter

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	12/20/2000	12/20/2000	1/9/2001
Amendment (site addresses)	2/9/01	2/12/01	2/13/01
Amendment (product samples)	2/22/01	2/23/01	2/28/01
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Amendment (	6/12/01	6/13/01	7/17/01
Amendment (CMC table of contents)	6/12/01	6/13/01	

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GlaxoSmithKline
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709-3398
ATTN: Lorna C. Wilson, Associate Director,
CMC Regulatory Affairs

DRUG PRODUCT NAME:

Proprietary: Advair HFA Inhalation Aerosol

Nonproprietary/USAN: fluticasone propionate and salmeterol xinafoate HFA inhalation aerosol

Code Name/#:

Chem. Type/Ther. Class:

PHARMACOL. CATEGORY/INDICATION: anti-inflammatory corticosteroid, and $beta_2$-adrenergic bronchodilator

DOSAGE FORM: inhalation aerosol

STRENGTHS: fluticasone propionate, 44, 110 and 220 mcg/inhalation each with salmeterol xinafoate 21 mcg/inhalation (expressed as salmeterol base), through the mouthpiece

ROUTE OF ADMINISTRATION:

DISPENSED: X Rx _ OTC

SPECIAL PRODUCTS:
(If yes, fill out the form for special products and deliver to the TIA through the team leader for data entry)

x_ YES _ NO (clarifying information about specific biological source of starting material to be sought from referenced NDA in drug substance section)

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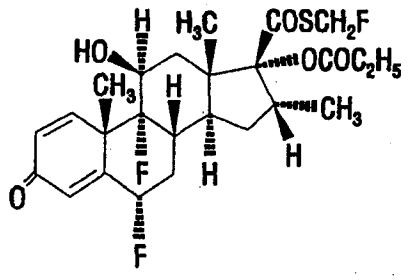

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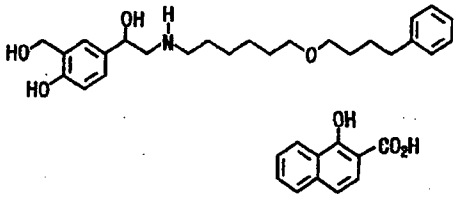

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SUPPORTING DOCUMENTS:

DMFs

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in Reviews
			[need to check 2000 amendment]	4/21/99 by Dr. Bertha	Found adequate for inhalation aerosol in — by Dr. Bertha. (see B.3.B.2 in current review)
			to be reviewed		
			to be reviewed		
			to be reviewed		
			to be reviewed		
			to be reviewed		
			to be reviewed		
			to be reviewed		
			to be reviewed		
			to be reviewed		
			to be reviewed		
			to be reviewed		

RELATED DOCUMENTS (if applicable)

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CONSULT	DATE FORWARDED	STATUS	COMMENTS
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Biometrics, HFD-710		delayed pending stability update	
Environmental Assessment		no EA needed	Applicant claims a categorical exclusion under 21 CFR 25.31(b). Acceptable.
Labeling & Nomenclature Committee		no consult necessary.	Consult not necessary, since "Advair" was previously approved in another NDA (Advair Diskus).

CONCLUSIONS AND RECOMMENDATIONS:

Comments at the end of this review should be forwarded to the applicant in a Discipline Request letter.

cc:
Orig. NDA 21-254
HFD-570/Division File
HFD-570/Aschroeder/7-31-01
HFD-570/CSO PJani
HFD-570/GPoochikian
HFD-570/medical reviewer
R/D Init. by: _____
filename: N21254R1.doc

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Alan C. Schroeder, Ph.D., Review Chemist

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/s/

Alan Schroeder
8/1/01 04:33:46 PM
CHEMIST

Initial CMC review - Advair HFA Inhalation Aerosol

Guiragos Poochikian
8/1/01 04:38:40 PM
CHEMIST