

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-433

CHEMISTRY REVIEW(S)

ESTABLISHMENT EVALUATION REQUEST

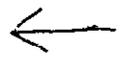
SUMMARY REPORT

Application : NDA 21433/000 Sponsor: GLAXO GRP LTD
Org Code : 570 1 FRANKLIN PLAZA
Priority : 3S PHILADELPHIA, PA 19101

Stamp Date : 27-FEB-2002 Brand Name : FLOVENT HFA (FLUTICASONE
PDUFA Date : 14-MAY-2004 PROPIONATE) INH
Action Goal : Estab. Name:
District Goal: 15-MAR-2004 Generic Name: FLUTICASONE PROPIONATE
INHALATION AEROSO
Dosage Form: (AEROSOL)
Strength : 44, 110 AND 220 MCG/INH

FDA Contacts: L. JAFARI Project Manager (HFD-570) 301-827-1050
A. SCHROEDER Review Chemist (HFD-570) 301-827-1068
C. BERTHA Team Leader (HFD-570) 301-827-1050

Overall Recommendation: ACCEPTABLE on 05-JAN-2004 by J. D AMBROGIO (HFD-322) 301-827-9049
ACCEPTABLE on 16-DEC-2002 by S. ADAMS (HFD-322) 301-827-9051



Establishment : CFN : — FEI : —

DMF No: /

Responsibilities: /

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 05-JAN-04
cision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 9610789 FEI : 3002806712

DMF No:

AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 05-JAN-04
Decision : ACCEPTABLE
Reason : BASED ON FILE REVIEW

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

BASED ON PROFILE

Establishment : CFN : 9610411 FEI : 1000291018
 GLAXO OPERATIONS UK LTD
 PRIORITY STREET
 WARE, HERTFORDSHIRE, UK

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MICRONIZER
 DRUG SUBSTANCE RELEASE TESTER

Profile : CSN OAI Status: NONE
 st Milestone: OC RECOMMENDATION
Milestone Date: 05-JAN-04
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI :
 GLAXO WELLCOME RESEARCH & DEVELOPMENT
 SG12 ODP
 WARE, HERTFORSHIRE, UK

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
 ilestone Date: 05-JAN-04
Decision : ACCEPTABLE
Reason : BASED ON FILE REVIEW

Establishment : CFN : 9610419 FEI : 3002807080

GLAXOCHEM LTD
COBDEN STREET
MONTROSE ANGUS, , UK DD108EA

F No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 05-JAN-04
Decision : ACCEPTABLE
Reason : BASED ON FILE REVIEW

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

BASED ON PROFILE

Establishment : CFN : 9611905 FEI : 3002807436
 LABORATOIRES GLAXO
 27000
 EVREUX, CEDEX, FR

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MICRONIZER
 DRUG SUBSTANCE RELEASE TESTER
 FINISHED DOSAGE LABELER
 FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE OTHER TESTER
 FINISHED DOSAGE PACKAGER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

Profile : ADM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 05-JAN-04
Decision : ACCEPTABLE
Reason : BASED ON FILE REVIEW

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

BASED ON PROFILE

Establishment : CFN : — FEI : —

DMF No: / AADA:

Responsibilities: —

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 05-JAN-04

cision : ACCEPTABLE

Reason : BASED ON FILE REVIEW

NDA 21-433

CR#2

**Flovent HFA Inhalation Aerosol
(fluticasone propionate 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 21-433
2. REVIEW #2:
3. REVIEW DATE: May 13, 2004
4. REVIEWER: Alan C. Schroeder, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original NDA	2/26/02
Amendment (Letter of Authorization)	2/26/02
BC Amendment (site information, answers to questions)	5/21/02
BC Amendment (repeats 5/21/02 amend. and other answers)	5/31/02
BC Amendment (update on actuation counter development)	7/24/02
BC Amendment (stability update & other information)	9/5/02
BC Amendment (drug product samples)	10/3/02

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
AZ Amendment (Resubmission)	11/13/03
BL Amendment	4/2/2004
BC Amendment	4/2/2004
BC Amendment	4/16/2004
BC Amendment	4/20/2004
BL Amendment	4/26/2004
Amendment	5/7/2004
Amendment	5/11/2004

7. NAME & ADDRESS OF APPLICANT:

Name: Glaxo Group Limited d/b/a GlaxoSmithKline

CHEMISTRY REVIEW

Chemistry Review Data Sheet – NDA 21-433

Address: One Franklin Plaza,
P.O. Box 7929,
Philadelphia, PA 19101

Representative: Lorna C. Wilson
Director, Regulatory Affairs

Telephone: 919-483-5121

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Flovent HFA x mcg Inhalation Aerosol
- b) Non-Proprietary Name (USAN): fluticasone propionate HFA x mcg inhalation aerosol
- c) Code Name/# (ONDC only): CCI18781
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Section 505(b)(1) of the FD&C Act

10. PHARMACOL. CATEGORY: anti-inflammatory corticosteroid

11. DOSAGE FORM: Aerosol, metered (code 339)

12. STRENGTH/POTENCY: 3 strengths: fluticasone propionate, 44, 110 and 220 mcg/inhalation from the mouthpiece.

13. ROUTE OF ADMINISTRATION: respiratory (inhalation), code 136

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

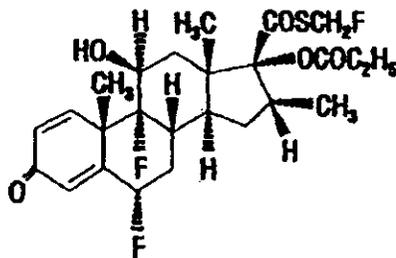
Not a SPOTS product

CHEMISTRY REVIEW

Chemistry Review Data Sheet – NDA 21-433

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

having the chemical name **S-(fluoromethyl)6 α ,9-difluoro-11 β ,17-dihydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -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 $C_{25}H_{31}F_3O_5S$.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
-	IV	/	/	1	Adequate	11/20/2003 (Dr. Arthur Shaw)	[IR letter to be sent 4/04 for clarifications]
-	III			1	Adequate for N21-433	4/30/2004	
-	III			1	Adequate for N21-433	4/30/2004	
-	FIII			7	Adequate	10/1/01	See 10/1/01 review. 10/16/01 amend. provides COAs; 11/2/01 amend. provides updated drawings; 6/27/02 amendment is an annual update.
-	III	/	/	7	Adequate	8/22/02	See 8/22/02 review. 11/01/02 revision of DMF provides clarifications, small changes in some procedures, not viewed as major.

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						11/1/03 amendment – change in firm name.
—	III			3	Adequate	4/13/00 One LOA submitted since last review. Update request letter sent 02/24/2004
—	III			7	Adequate	12/11/02 DMF holder has satisfactorily responded in a 5/5/04 fax to IR letter dated 4/19/2004: response to be submitted officially to DMF.
/	III			3	Adequate	10/30/00
—	III			3	Adequate	10/04/01 See notes on pg. 9 of Chem. Rev. 2 for N21254. Nothing but LOAs have been submitted since 10/4/01 review
—	III			3, 4	Adequate	9/10/97 Same — is specified as for — See — Response — amendment). LOA of 1/14/03 indicates that the 12/7/95 amendment contains the information on the — which was found to be adequate in the 9/10/97 review. No new submissions amending info. for this
—	III			3	adequate	1/10/01 Same — Sec —
—	III			3	adequate	10/2/00 (C.Bertha) This pertains to — identified by specification — of the DMF). Clarifications requested in CR#1 of N21433. (no change in — nfo.

CHEMISTRY REVIEW

Chemistry Review Data Sheet – NDA 21-433

	III		1	Adequate	2/11/04	since last review) This is a supporting DMF for DMF
	III		3	Adequate	12/10/02	This is a supporting DMF for DMF
	III		7	Adequate	(none)	This DMF supports DMF (above). DMF is adequate because it provides the (no change in DMF info)
	III		7	Adequate	(none)	This DMF supports DMF (above). DMF is adequate because it provides the (no change in DMF info)

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)

CR# = Chemistry Review Number

Note: Dr. Craig Bertha kindly reviewed DMFs 11817, 13859, 1500 for this application, and checked that there were no relevant amendments received for the other DMFs since they were last reviewed.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	53,502	fluticasone propionate HFA inhalation aerosol

The Chemistry Review for NDA 21-433

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA may be approved from a CMC perspective.

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

A number of post-approval agreements have been accepted by the applicant and the Agency. These include the following:

Work will continue to improve the cascade impactor assay for particle size distribution of the drug product by decreasing the number of actuations required per analysis. The applicant will continue to investigate the phenomenon of atypically high results at the end of inhaler use when tested by a different testing regimen than is routinely used: i.e., for manual sample collection after automated discharge of waste actuations. The reason for this is to understand whether there is a potential product problem. Data will be collected to allow re-evaluation of the acceptance criteria for

corrected as necessary. The robustness of the will be investigated and

The active drug in the drug product appears to interfere with the measurement of preventing the development of acceptance criteria. The applicant will continue to investigate this and resolve the problem so they can then submit appropriate drug product acceptance criteria for ISK will work with their to reevaluate the methodology for measuring and to see whether they have missed any Acceptance criteria for quantitative mass balance will be proposed as part of the aerodynamic particle size distribution (APSD) specification for the drug product.

These agreements are designed to ensure the continued quality and consistency of the drug product and to

Some of these agreements were developed because additional data are needed to understand whether any trends may exist in certain parameters, and to determine appropriate final acceptance criteria. The applicant should be reminded of their post-approval agreements in the final approval letter.

CHEMISTRY REVIEW

Executive Summary Section – NDA 21-433

II. Summary of Chemistry Assessments

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

The **drug substance** is micronized fluticasone propionate. CMC information on the drug substance is referenced to GSK's approved NDA# 20-121 (see under "drug substance" in the review notes section of this current review).

Control of particle size distribution is critical in both drug substance and drug product, since it affects drug delivery to appropriate sites of the patient's lungs.

The **drug product** is Flovent (fluticasone propionate) HFA Inhalation Aerosol. The drug product is a suspension MDI, to be produced in three strengths of fluticasone propionate as; 44, 110 and 220 mcg/inhalation, through the mouthpiece. These three to-be-marketed non-proportional formulations are made up solely of the one micronized drug substance and HFA-134a propellant (1,1,1,2-tetrafluoroethane). The targets of the specifications are (for the 44 mcg strength product) and (for the 110 mcg and 220 mcg strength products). The drug product is packaged with a desiccant in a foil laminate overwrap pouch

All strengths of the drug product will be labeled for 120 actuations.

to maintain sufficient formulation to insure the labeled number of full strength actuations at the end of shelf life

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

The drug product uses

for the 110 µg and 220 µg products and the used for the 44 µg product. The materials used in used for

include the following materials:

The aluminum cans are to the same as those

CHEMISTRY REVIEW

Executive Summary Section – NDA 21-433

The desiccant pack and foil laminate overwrap are — The actuators and strapcaps are identical to those used for Flovent Inhalation Aerosol (CFC product). The overwrap (secondary protective packaging, along with desiccant packets inside the overwrap) is designed to protect the drug product against excessive moisture uptake.

/

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 with a particular particle and droplet size distribution 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 deliver metered amounts of micronized drug substance 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 to be shaken before each actuation. Each dosing actuation is to be inhaled in a coordinated manner by the patient. The patient is instructed to prime the new MDI, one that has been left unused for 7 days, and one that has been dropped.

The proposed maximum recommended dosage is 880 mcg, twice daily. The proposed expiration dating period for the drug product is 18 months with storage at 25°C (excursions permitted to 15°-30°C), and it has been found to be satisfactory based upon stability data provided.

C. Basis for Approvability or Not-Approval Recommendation

All issues related to drug product performance which impact approvability have been adequately resolved. Data provided on split batches of drug product (into — portions) do not demonstrate any consistent, substantive effect of —

— A non-use period of 7 days has been established for the drug product, after which it must be reprimed (with a single actuation) before using it again.

— 100% of the canisters will be employed during manufacture of commercial batches of Flovent HFA Inhalation Aerosol. —

/

in-use.

— Up to 18 months stability data have been provided for — NDA batches, three batches of each strength and pack size of FLOVENT HFA.

Agreement has been reached on acceptable acceptance criteria for delivered dose uniformity for the drug product, which were deficient in CR #1. Dose proportionality among the three strengths of drug product has been sufficiently demonstrated —

CHEMISTRY REVIEW

Executive Summary Section – NDA 21-433

The medical officer feels that this is adequate for this product, rather than requiring

This is an important issue, since once on the market, dose proportionality among the product strengths will be assumed by health care professionals.

The applicant has provided post-approval agreements to improve certain methods for

Specifications are now in place for from two different sources which are found on the The specifications for interim specifications and final specifications are to be proposed post approval.

The particle size distribution of the drug product affects the amount of drug inhaled by the patient as well as its distribution within the patient's lungs.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Alan C. Schroeder, Ph.D./Date
Richard Lostritto, Ph.D./Date

C. CC Block

Ladan Jafari, HFD-570, project manager

Ladan Jafari, HFD-570, project manager

219 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

**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
5/14/04 10:42:02 AM
CHEMIST

Richard Lostritto
5/14/04 10:53:35 AM
CHEMIST

NDA 21-433

*Please
update*

**Flovent HFA Inhalation Aerosol
(fluticasone propionate HFA inhalation aerosol)**

GlaxoSmithKline

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

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Chemistry Review Data Sheet – NDA 21-433

Chemistry Review Data Sheet

1. NDA 21-433
2. REVIEW #1:
3. REVIEW DATE: December 20, 2002
4. REVIEWER: Alan C. Schroeder, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

none

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA
Amendment (Letter of Authorization)
BC Amendment (site information, answers to questions)
BC Amendment (repeats 5/21/02 amend. and other answers)
BC Amendment (update on — development)
BC Amendment (stability update & other information)
BC Amendment (drug product samples)

Document Date

2/26/02
2/26/02
5/21/02
5/31/02
7/24/02
9/5/02
10/3/02

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:	Lorna C. Wilson Director, Regulatory Affairs
Telephone:	919-483-5121

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Chemistry Review Data Sheet – NDA 21-433

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Flovent HFA Inhalation Aerosol
- b) Non-Proprietary Name (USAN): fluticasone propionate HFA inhalation aerosol
- c) Code Name/# (ONDC only): CC118781
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Section 505(b)(1) of the FD&C Act

10. PHARMACOL. CATEGORY: anti-inflammatory corticosteroid

11. DOSAGE FORM: Aerosol, metered (code 339)

12. STRENGTH/POTENCY: 3 strengths: fluticasone propionate, 44, 110 and 220 mcg/inhalation from the mouthpiece.

13. ROUTE OF ADMINISTRATION: respiratory (inhalation), code 136

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note22]:

SPOTS product – Form Completed

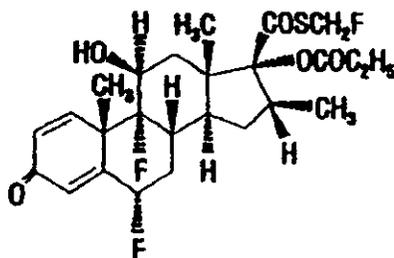
Not a SPOTS product

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

CHEMISTRY REVIEW

Chemistry Review Data Sheet – NDA 21-433

having the chemical name **S-(fluoromethyl)6 α ,9-difluoro-11 β ,17-dihydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -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 $C_{25}H_{31}F_3O_5S$.

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	
/	III			1	Inadequate	12/10/02	
/	III			7	Adequate	10/1/01	See 10/1/01 review. 10/16/01 amend. provides COAs; 11/2/01 amend. provides updated drawings; 6/27/02 amendment is an annual update.
/	III			7	Adequate	8/22/02	See 8/22/02 review. 11/01/02 revision of DMF provides clarifications, small changes in some procedures, not viewed as major.
/	III			3	Adequate	4/13/00	



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III	1	Inadequate	12/11/02	
III	3	Adequate	10/30/00	
III	3	Adequate	10/04/01 See notes on pg. 9 of Chem. Rev. 2 for N21254.	
III	3, 4	Adequate		Same amendment).
III	3	adequate	10/2/01	Same See
III	3	adequate	10/2/00 (C.Bertha)	This pertains to identified by specification (section of the DMF). Clarifications requested in CR#1 of N21433.
III	5	unknown	5/26/99	This is a supporting DMF for DMF The holder of DMF is not listed in DMF update amendment dated 9/24/02 as authorized to reference DMF
III	1	Adequate	12/10/02	This is a supporting DMF for DMF
III	7	Adequate	(none)	This DMF supports DMF (above). DMF is adequate because it provides the
III	7	Adequate	(none)	This DMF supports DMF (above).

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Biopharm	N.A.		
LNC	N.A. since the name was approved in previous applications		
Methods Validation	Deferred pending agreement on methods and acceptance criteria.		
OPDRA	N.A.		
EA	Satisfactory claim of categorical exclusion based upon 21 CFR Part 25.31(b).	12/18/02	Alan C. Schroeder, Ph.D.
Microbiology	Evaluation of: — method and its validation, as well as the — test – Recommended for Approval	11/27/2002	Bryan S. Riley, Ph.D.

**APPEARS THIS WAY
ON ORIGINAL**

The Chemistry Review for NDA 21-433

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

This recommendation is deferred at the present time, pending responses to the deficiencies indicated in this review.

II. Summary of Chemistry Assessments

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

The drug substance is micronized fluticasone propionate. CMC information on the drug substance is referred to GSK's approved NDA# 20-121 (see under "drug substance" in the review notes section of this current review).

Final agreement on the acceptance criteria for particle size distribution of the drug substance has not yet been reached. Control of particle size distribution is critical, since it affects drug delivery to appropriate sites of the patient's lungs.

The drug product is Flovent (fluticasone propionate) HFA Inhalation Aerosol. The drug product is a suspension MDI and it will be produced in three strengths of fluticasone propionate: fluticasone propionate, 44, 110 and 220 mcg/inhalation, through the mouthpiece. The formulation is made up solely of the one micronized drug substance and one propellant (GR106642X, which is 1,1,1,2-tetrafluoroethane, which is the same chemical structure as HFA-134a). For amounts of the drug delivered through the valve for each strength product, see the drug product composition section in this current review. The _____ of the _____ specifications _____ are _____ mg (for the 44 mcg strength product) and _____ mg (for the 110 mcg and 220 mcg strength products). All strengths of the drug product will be labeled for 120 actuations, and _____

_____ to maintain sufficient formulation to insure the labeled number of full strength actuations at the end of shelf life. The target

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number of actuations to be added to each presentation at the time of manufacture, _____, are as follows: _____ actuations (44 mcg/120 labeled actuation product), _____, and _____ actuations (110 mcg/120 labeled actuation and 220 mcg/120 labeled actuation products).

target and range as for venonin

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

The drug product uses _____ depending on the strength of the product.

The desiccant pack and foil laminate are identical to those _____. The actuators and strapcaps are identical to those used for Flovent Inhalation Aerosol (CFC product).

The applicant states that the overwrap (secondary protective packaging, along with desiccant packets inside the overwrap) protects the drug product against moisture uptake.

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 with a particular particle and droplet size distribution that is created each time the drug product is used.

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

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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: fluticasone propionate, 44, 110 and 220 mcg/inhalation, through the mouthpiece. Each strength product is labeled for 120 actuations,

The proposed maximum recommended dosage is 880 mcg, twice daily. The proposed expiration dating period for the drug product is 18 months. The Agency has not yet reached agreement on this proposal for expiry, pending additional data.

C. Basis for Approvability or Not-Approval Recommendation

There are a number of critical areas related to drug product performance that lack information or may not be well understood by the applicant. These need to be resolved to insure that the patient receives the proper dose (in both drug content and in particle size distribution) over the shelf life of the drug product and over the usage life of the product (from beginning to end). In addition, the drug product's performance must remain linked to drug product used for critical clinical trials. Examples of these problem areas are included below.

- There appear to be more "out of specification" results for _____ (especially for accelerated storage conditions).
- Data provided so far have not definitively established a non-use period for the drug product, after which it must be reprimed before using it again.

This is contrary to the normal

Deficiencies pertaining to the proposed _____, in the manufacturing process for the drug product still exist. A stability study _____ Flovent HFA canisters is underway. Updates of the stability study, and certain stability summaries, have been requested. Additional stability data may be needed if a different _____ procedure is approved, relative to that used for

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NDA “primary stability” batches do not include the _____ proposed for the 110 mcg and 220 mcg strengths, nor were the “primary stability” batches _____ during manufacture. Therefore a second stability study using _____ of drug product, was initiated, and it is still ongoing, with _____ of data to date. Based on available data for the _____ stability samples, modification of some of the label claim values may be indicated for drug delivered per actuation.

There is considerable variability between delivered dose uniformity at the beginning of use, with that at the end of use of the drug product unit. This has led to the applicant’s request for delivered dose acceptance criteria that are wider than the standard for MDIs. Agreement has not been reached on this issue.

Dose proportionality among the three strengths of drug product still needs to be more fully demonstrated for particle size distribution. This is an important issue, since once on the market, dose proportionality among the product strengths will be assumed by health care professionals.

Certain specific stability data summaries and statistical analyses are requested to permit a better understanding and evaluation of the stability data.

Several supporting DMFs remain deficient.

Agreement has not been reached for the _____ in the drug product, which can adversely affect the _____. A correlation between _____ has not been fully established.

The issue of control of the _____ has not been fully resolved. This was shown _____ to affect the particle size distribution of the drug product when the _____. This is important not only because of concern for the effect of impurities on a very sensitive patient population when delivered by the pulmonary route, but also because of the effect of _____. The particle size distribution of the drug product affects the amount of drug inhaled by the patient as well as its distribution within the patient’s lungs.

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

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

Labeling should be considered in the final review cycle, to warn against dropping the canister, based upon studies showing an increase in delivered drug, particularly in the first actuation after dropping. Review of labeling will be done in the last review cycle.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Alan C. Schroeder, Ph.D./Date: December 20, 2002
Guirag Poochikian, Ph.D./Date

C. CC Block

Ladan Jafari, HFD-570, project manager

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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/s/

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12/20/02 11:08:33 AM
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