

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-247

CHEMISTRY REVIEW(S)

**NDA 21-247
Review 6**

Aerospan HFA (flunisolide inhalation aerosol)

Forest Laboratories, Inc.

**Brian Rogers
Division of Pulmonary and Allergy Drug Products
and
Office of New Drug Quality Assessment**



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1. NDA 21-247
2. REVIEW #6
3. REVIEW DATE: 1/23/06
4. REVIEWER: Brian Rogers

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5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
ORIGINAL	27-APR-2000
Amendment	02-JUN-2000
Amendment	13-JUN-2000
Amendment	21-SEP-2000
Amendment	22-SEP-2000
Amendment	02-OCT-2000
Amendment	09-NOV-2000
Amendment	26-DEC-2000
Review #1	03-MAY-2001
Action Letter (AE)	07-MAY-2001
Amendment	07-MAR-2001
Amendment	28-AUG-2001
Amendment	24-OCT-2001
Amendment	07-DEC-2001
Review #2	05-JUN-2002
Action Letter (AE)	11-JUN-2002
Amendment	05-FEB-2003
Amendment	05-FEB-2003
Review #3	05-MAY-2003
Disc. Rev. Letter	08-MAY-2003
Amendment	01-MAY-2003
Amendment	05-JUN-2003
Amendment	10-JUN-2003
Amendment	01-JUL-2003
Review #4	23-JUL-2003
Action Letter (AE)	30-JUL-2003
Amendment	20-OCT-2003
Amendment	17-DEC-2003
Amendment	12-JAN-2004
Amendment	14-JAN-2004



CHEMISTRY REVIEW



Chemistry Review Data Sheet

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	26-JUL-2004
Amendment	26-JUL-2005
Amendment	11-AUG-2005

7. NAME & ADDRESS OF APPLICANT:

Name: Forest Laboratories
Harborside Financial Center
Address: Plaza Three, Suite 602
Jersey City, NJ 07311
Representative: David A. Lust
Associate Director, Regulatory Affairs
Telephone: 201-386-2024

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Aerospan HFA (flunisolide inhalation aerosol)
- b) Non-Proprietary Name (USAN): flunisolide inhalation aerosol
- c) Code Name/#:
- d) Chem. Type/Submission Priority:
 - Chem. Type: 6
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

505(b)(1)

10. PHARMACOL. CATEGORY: Treatment of asthma as prophylactic therapy in adult/pediatric patients four years of age and older/for patients requiring oral corticosteroid therapy for asthma.

11. DOSAGE FORM: Inhalation Aerosol

12. STRENGTH/POTENCY: Claimed by the applicant to deliver 139 µg flunisolide hemihydrate per actuation from the valve, and 80 µg flunisolide hemihydrate (equivalent to 78 µg of flunisolide) from the spacer (using 30 L/min for 4 sec). Valve delivery is 58 mg/ — , per actuation.

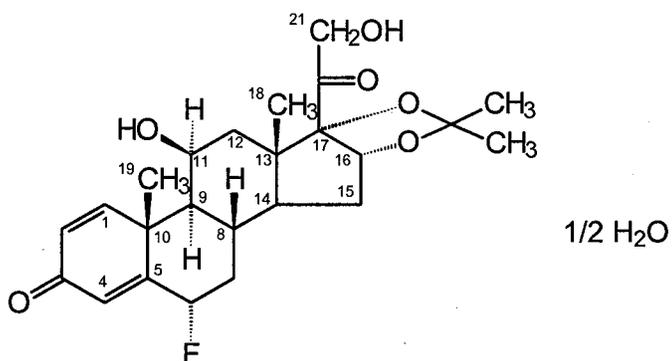
13. ROUTE OF ADMINISTRATION: Oral Inhalation; 1 act. bid; max. —

Chemistry Review Data Sheet

 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:


Flunisolide hemihydrate
 $C_{24}H_{31}O_6F \cdot 1/2 H_2O$
 MW 443.51

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Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting Documents:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1	II			7	Adequate	4/17/03	Holder has withdrawn sites from application.
	V			3	Adequate	10/15/99 by KSwiss	
	V			3	Adequate	2/27/97 by MChun	
	III	3M Pharmaceuticals, Inc.	Valve	1	Adequate	1/19/06 by Rogers	
	III	3M Pharmaceuticals, Inc.	Container Closure Extractables	1	Adequate	6/2/02 by Rogers	
	III			1	Adequate	1/10/06 by Rogers	Supports DMF
	III			1	Adequate	1/10/06 by Rogers	Supports DMF
	III			1	Adequate	1/9/06	Supports DMF
III	Bespak	Actuator/Spacer	1	Adequate	5/28/02 by Rogers		

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 Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N/A					

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	51,456	Forest Laboratories	Aerobid (flunisolide hemihydrate in HFA-134a)
IND			
NDA	18-340	Forest Laboratories	Aerobid (flunisolide hemihydrate inhalation aerosol)



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Chemistry Review Data Sheet

18. CONSULTS/ CMC RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics			None necessary	
EES		FUR 2/13/03 FUR 11/24/03 FUR 8/24/05	Acceptable	All sites are acceptable 1/17/06
Pharm/Tox		10/27/00 3/4/04 3/12/04	Completed 5/21/02 Completed 4/9/04 Completed 4/9/04	Consult for related impurities Consult for acceptable leachables level Consult for acceptable leachables level
Biopharm			N/A	
LNC			Completed 5/8/03	DMETS has no objections to the use of the proprietary name. DDMAC finds the proprietary name acceptable from a promotional perspective.
Methods Validation			To be submitted	Methods validation will be accomplished in FDA laboratories once the analytical methods have been finalized.
OPDRA			Acceptable Hye-Joo Kim 2/13/02	Update may be needed once application is approvable from a CMC perspective
EA			N/A	Applicant has applied for a categorical exclusion.
Microbiology			N/A	No Microbiological consult will be issued owing to having previously accepted specs

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The Chemistry Review for NDA 21-247

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application as submitted may be APPROVED from the standpoint of chemistry, manufacturing and controls.

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

See list of post-approval agreements at the end of this review.

II. Summary of Chemistry Assessments

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

Drug Substance Description

All information pertaining to the flunisolide hemihydrate drug substance is referenced to the content of _____, DMF _____. DMF _____ includes _____ for manufacture of the drug substance, the _____ site and Syntex _____. The _____ site was not inspected and is considered unacceptable since it has been shut down, is unable to be inspected, and will no longer produce drug substance. The _____ site is currently being used as drug substance release tester. Currently, there is no approved drug substance manufacturing site.

DMF _____ for drug substance manufacture has been reviewed and is adequate to support this application. The holder has been requested to provide complete results of drug substance release testing to DMF _____.

A Follow-Up Request was issued 8/24/05 for all sites. All sites are acceptable in recommendation dated 1/17/06.

In the 12/7/01 amendment, the applicant has withdrawn both the _____, and the _____ sites from the application as drug substance manufacturing sites. The drug substance stored in _____ was manufactured by _____, and will be used for the commercial batches once satisfactory identity, quality, and purity are shown. They have also been informed that we expect them to submit a separate and complete DMF for the _____ site. The applicant has agreed to submit a prior-approval supplement, after approval of this application, to support the manufacture of flunisolide hemihydrate at _____.

Drug substance used in all the toxicological, clinical and stability lots has been manufactured at the _____ using the same _____ process.

Forest Laboratories will provide the results of extensive drug substance characterization studies on each container of flunisolide hemihydrate stored in _____.

The PSD is not controlled as a profile since the drug product is a _____.

Drug Product Description – Drug product is a pressurized metered-dose inhaler



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Flunisolide hemihydrate HFA contains a solution of 0.24% flunisolide hemihydrate in Dehydrated Alcohol, USP and a hydrofluorocarbon propellant (HFA-134a) in a aluminum can fitted with a valve. The device includes a mouthpiece/actuator/spacer.

Pack Sizes proposed are 120-actuation and 60-actuation sizes using identical canister and valve. Both of these presentations deliver 139 µg flunisolide hemihydrate from the valve and 80 µg flunisolide hemihydrate (equivalent to 78 µg of flunisolide) from the spacer at a flow rate of 30 L/min for 4 sec. These correspond to a shot weight of approximately 58 mg.

The excipient Dehydrated Alcohol USP is used for the drug substance. The formulation has valve mechanism.

COMPONENTS / COMPOSITION (p. 4: 31)

Raw Material	60-Act. g/Unit*	120-Act. g/Unit*	% w/w
Flunisolide hemihydrate, USP			
Dehydrated alcohol, USP			
Propellant HFA-134a			

*The g/unit values are based on target fill weight ().

The formulation density is , at .

Target fill weights are , for 60 and 120 actuation units, respectively. The ranges of fill weight are , during filling, respectively. The net fill-weights post-fill (acceptance criteria for stability and release testing) are 5.1 g, and 8.9 g, respectively.

Fill weight necessary to deliver 60 and 120 actuations based on shot weight are , (taking into account the mean leak rate over 2 years). These calculate to overfills of , respectively at the label claim, and at the current minimum fill weight.

The solubility of the drug substance in the formulation is adequate to prevent precipitation of the drug substance under the recommended storage conditions. Solubility of flunisolide in 10% ethanol in HFA-134a was found to be . The solubility of flunisolide in the formulation at is equal to its concentration in the drug product. The labeling shows the recommended storage temperature range is 15 - 30°C. All labeling should show the recommended storage temperature as 25°C since the real-world storage conditions will exceed the recommendations by a wide margin. The narrowest possible range should be specified on the labels to alert shippers and patients to the need for careful storage.

Interpolation of the solubility data show the expected solubility of the drug substance in 10% alcohol/HFA-134a is at 15°C, the lowest allowed storage temp. This allows a deficiency of solvent or overage of drug substance before the solubility limit is reached. Although some propellant is apt to leak from the container, it is likely the solubility of the drug substance in the remaining formulation is increased by this change. It is likely that storage conditions under real-world shipping will cause precipitation of the drug substance from the formulation. For this reason, it is necessary to keep the shippers and patients advised that the recommended storage conditions are to be 25°C.

Batch formulae (as manufactured at) are provided on page 4: 56 and are listed in the following table:



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G29 Ingredients	60 Actuations per Unit (Unit Batch)	120 Actuations per Batch (Unit Batch)
Flunisolide hemihydrate, USP	_____	_____
Dehydrated Alcohol, USP	_____	_____
1,1,1,2-Tetrafluoroethane	_____	_____
Total	_____	_____

Early development lots contained _____ in order to be similar to the current Aerobid and Aerobid M CFC products. Tox studies and initial PK clinical study used solution formulations containing _____.

The _____ are probably not an issue taken alone. There is a potential change in flunisolide bioavailability and absorption rate brought about by inclusion of the _____ when the tox formulation is compared with the to-be-marketed formulation. There may or may not be a change in absorption attributable to this addition.

Container/Closure Development History

- Three actuators were tested during the PK study program (see pages 3: 102-105).

_____ (1st PK study)
 _____ actuator (PK study ANC-PK1-97-004-000)
 Bespak actuator/spacer (to be marketed configuration, PK study ANC-PK1-97-004-000 and all subsequent clinical trials and stability studies)

- Three _____ modifications were incorporated

The original _____ s only used in tox and PK studies

The first modification included _____

_____ (see Table 8 on page 4: 42). This modification was incorporated into all _____ used in NDA stability batches and Phase III clinical studies batches.

The second modification incorporated an _____

_____. The applicant reports that _____ with the above modification were used in the Phase III clinical trials.

Third modification to the _____

_____. The applicant states that no changes were made in the material or manufacturing process for the _____ . The change was reportedly made _____

_____. The _____ was evaluated (see Table 9 on page 4: 43) before and after the change in the _____ . This study showed the change caused a _____ , and almost doubled the _____

- Three canisters were used in developmental work, differing in modifications to _____

First canister was not used in the critical clinical trials.

The first two modifications were reportedly implemented to _____

The first modification was to change the _____



The second modification: _____

The results of _____ studies were provided on page 4:44 in Table 10. It is obvious from the data that the change in _____

The third modification was to _____ The canisters used in the Phase III clinical trials contained all above modifications.



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

According to the applicant, the drug product delivers 139 µg of flunisolide hemihydrate per actuation from the valve and 80 µg of flunisolide hemihydrate from the spacer (using a flow rate of 30 L/min for 4 sec). Valve delivery is 58 mg _____ . The maximum daily dose is _____ µg.

The formulation density is _____ at _____

Target fill weights are _____ for 60 and 120 actuation units, respectively. The ranges of fill weights are _____ during filling, respectively. The net fill-weights post-fill (acceptance criteria for stability and release testing) are _____, respectively.

Fill weight necessary to deliver 60 and 120 actuations based on shot weight are _____ (taking into account the mean leak rate over 2 years). This calculates to overfills of _____ respectively at the label claim, and _____ at the current minimum fill weight.

Solubility of flunisolide in 10% ethanol in HFA-134a was found to be _____ The solubility of flunisolide in the formulation at _____ is equal to its concentration in the drug product. The labeling shows the recommended storage temperature range is 15 - 30°C. All labeling should show the recommended storage temperature as _____ 25°C since the real-world storage conditions will exceed the recommendations by a wide margin. The narrowest possible range should be specified on the labels to alert shippers and patients to the need for careful storage.

Route of Administration is Oral Inhalation; minimum dose is 1 actuation bid; maximum _____

Proposed expiration dating period is 24 months for both presentations. This proposal is deemed acceptable based upon the provided stability data.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided adequate information pertaining to drug product quality to permit approval from a CMC standpoint.

**D. Remarks/Comments:****Drug Substance**

1. All information pertaining to the flunisolide hemihydrate drug substance is referenced to DMF _____. The sites supported by this DMF are _____. The _____ site has been removed from DMF _____ and a separate DMF will be submitted for this site.
2. Drug substance used in all the toxicological, clinical and stability lots has been manufactured at the _____ using the same _____ process.
3. The _____ was not inspected since it has been shut down and will no longer produce drug substance. A Follow-Up Request was issued 8/24/05 for all sites. All sites were deemed acceptable by OC in their recommendation dated 1/17/06.
4. In the 12/7/01 amendment, the applicant has withdrawn _____ from the application. The drug substance stored in _____ was manufactured by _____ and will be used for the commercial batches once satisfactory identity, quality, and purity are shown. They have also been informed that we expect them to submit a separate and complete DMF for the _____. The applicant has agreed to submit a prior-approval supplement, after approval of this application, to support the manufacture of flunisolide hemihydrate at _____.
5. We have not received data from drug product manufactured from flunisolide hemihydrate made at the proposed site for flunisolide hemihydrate manufacture _____.
6. The applicant must submit to the NDA the test results for all flunisolide hemihydrate containers stored in the _____ facility in _____. They agree to perform acceptance testing of drug substance batches no more than 90 days prior to formulation.
7. The applicant should reevaluate the _____ acceptance criterion once the applicant manufactures _____ additional drug substance batches at the _____. Forest has committed to reevaluate the _____ levels and revise the acceptance criteria based upon the results obtained from analysis of the first three production-scale batches.
8. The proposed acceptance criteria for related substances in the drug substance are on an interim basis until Forest submits the _____ to the application for approval. The drug substance acceptance criteria will be specific to and distinguished by the manufacturing site for the drug substance. For the flunisolide hemihydrate from _____ the applicant must amend the NDA to include revised acceptance specifications wherein the applicant commits to adopt the _____ specifications. After the applicant has manufactured three full-scale batches at the _____ and Forest must submit test results for review and reevaluation of the acceptance criteria. This agreement must be communicated to the applicant in the AP letter.

Drug Product

1. Flunisolide hemihydrate HFA contains a solution of 0.24% flunisolide hemihydrate in Dehydrated Alcohol, USP and a _____ fluorohydrocarbon propellant (HFA-134a) in a _____, aluminum _____ can fitted with a _____ valve. The device includes a _____ mouthpiece/actuator/spacer.
2. Pack Sizes proposed are 120-actuation and 60-actuation sizes using identical canister and valve. Both of these presentations deliver 139 µg of flunisolide hemihydrate from the valve and 80 µg from the spacer at a flow rate of 30 L/min for 4 sec (2 L volume). These correspond to a shot weight of _____ ng when the concentration of drug substance in the formulation is used for calculations. The formulation density is _____ at _____. The density, when combined with the nominal valve metering chamber volume of _____, indicates the valve delivery should be 58 mg per actuation.



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3. The amount of drug delivered at the mouthpiece and the fine particle mass are directly dependent on the flow rate.
- [
4. Fill weight necessary to deliver 60 and 120 actuations based on shot weight are _____ (taking into account the mean leak rate over 2 years). This calculates to overfills of _____, respectively at the label claim, and _____ at the current minimum fill weight. The canister has a nominal volume of _____ mL. The formulation density is _____ at _____.
5. The Bepak actuator/spacer is a two-piece assembly with an orifice diameter of _____ mm. The spacer has an internal capacity of _____ mL.
6. _____
7. An FUR was issued 8/24/05 for all sites. All sites are acceptable as recommended on 1/17/06 by OC.
8. The applicant has withdrawn the Forest Pharmaceuticals Inc. _____ site from the application in the 11/9/00 amendment.
9. Forest has submitted the following two testing facilities for periodic testing of container-closure components to evaluate the results from 3M COA:
- _____
- _____
10. Forest has committed to repeat the tests given by _____ on the Certificate of Compliance for the first three lots intended for commercialization. Thereafter, Forest commits to test every _____ lot manufactured by _____ annually. In addition, Forest commits to testing the first three commercial lots for extractables using Forest test procedure _____ and for product performance measured by _____, and medication delivery/through life (test methods _____). Forest must be reminded of these agreements in the AP letter.
11. [
12. Forest commits to review the fill weight data with 3M after one year of production and revise these specifications if appropriate. The applicant must be reminded of this agreement in the AP letter.
13. Forest has made a commitment in the November 20, 2002 meeting, to institute changes in their manufacturing process to minimize oxidation of flunisolide drug substance. This agreement must be reflected in the AP letter once issued.
14. Forest states that they commit to perform acceptance testing of flunisolide hemihydrate no more than 90 days prior to its use in the formulation. This agreement must be captured in the AP letter once issued.
15. Forest has agreed that the proposed acceptance criteria for related substances in the drug substance are on an interim basis until the _____ is submitted to the application for approval. They have stated that _____ will file a new DMF for the drug substance and Forest will file a post-approval supplement to support the use of the drug substance from the _____ prior to its use in the manufacturing of the drug product. This agreement needs to be reflected in the AP letter once issued.

16. A microbiology consult is not needed since the proposed acceptance criteria have been previously allowed in other applications.
17. A description of the investigational and stability batches is provided in the 6/13/00 amendment. No other formulations were used in IND studies.
18. The applicant has applied for a categorical exclusion under 21 CFR 25.31(b) and is justified in doing so.
19. Methods validation will be accomplished in FDA laboratories post-approval.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Brian Rogers/1/23/06
Richard Lostritto
Ladan Jafari

C. CC Block

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21 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

/s/

Brian Rogers
1/23/2006 04:15:42 PM
CHEMIST

Richard Lostritto
1/23/2006 05:13:13 PM
CHEMIST

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**NDA 21-247
Review 5**

Aerospan HFA (flunisolide inhalation aerosol)

Forest Laboratories, Inc.

**Brian Rogers
Division of Pulmonary and Allergy Drug Products**



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C. CC Block	14
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Chemistry Review Data Sheet

1. NDA 21-247
2. REVIEW #5
3. REVIEW DATE: 4/14/04
4. REVIEWER: Brian Rogers

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CHEMISTRY REVIEW



Chemistry Review Data Sheet

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
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Amendment	10-JUN-2003
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Action Letter (AE)	30-JUL-2003

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<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	20-OCT-2003
Amendment	17-DEC-2003
Amendment	12-JAN-2004
Amendment	14-JAN-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Forest Laboratories
Harborside Financial Center
Address: Plaza Three, Suite 602
Jersey City, NJ 07311



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Representative: David A. Lust
Associate Director, Regulatory Affairs
Telephone: 201-386-2024

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Aerospan HFA (flunisolide inhalation aerosol)
- b) Non-Proprietary Name (USAN): flunisolide inhalation aerosol
- c) Code Name/#:
- d) Chem. Type/Submission Priority:
 - Chem. Type: 6
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Treatment of asthma as prophylactic therapy in adult/pediatric patients four years of age and older/for patients requiring oral corticosteroid therapy for asthma.

11. DOSAGE FORM: Inhalation Aerosol

12. STRENGTH/POTENCY: Claimed by the applicant to deliver 139 μg flunisolide hemihydrate per actuation from the valve, and 80 μg flunisolide hemihydrate (equivalent to 78 μg of flunisolide) from the spacer (using 30 L/min for 4 sec). Valve delivery is 58 mg/

13. ROUTE OF ADMINISTRATION: Oral Inhalation; 1 act. bid; max.

14. Rx/OTC DISPENSED: X Rx OTC

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

 SPOTS product – Form Completed

 X Not a SPOTS product

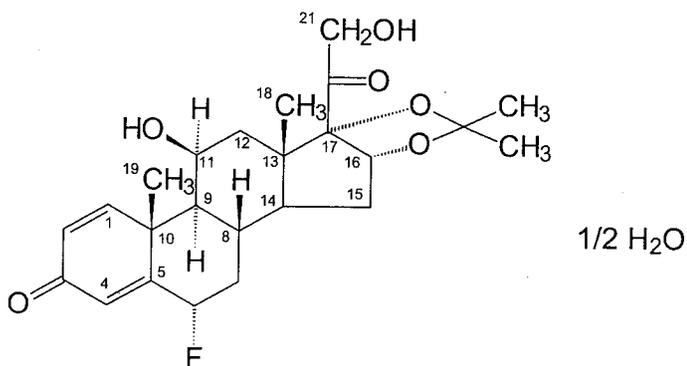
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:



CHEMISTRY REVIEW



Chemistry Review Data Sheet



Flunisolide hemihydrate
C₂₄H₃₁O₆F · 1/2 H₂O
MW 443.51

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting Documents:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
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	V	_____	_____	3	Adequate	2/27/97 by MChun	
	III	3M Pharmaceuticals, Inc.	Valve	1	Inadequate	4/13/04 by Rogers	Inadequate for extractable method and toxicity data
	III	3M Pharmaceuticals, Inc.	Container Closure Extractables	1	Adequate	6/2/02 by Rogers	
	III	_____	_____	1	Inadequate	1/5/04 by Rogers	Supports DMF
	III	_____	_____	1	Inadequate	12/18/03 by Rogers	Supports DMF
	III	Bespak	Actuator/Spacer	1	Adequate	5/28/02 by Rogers	

¹ Action codes for DMF Table:

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Other codes indicate why the DMF was not reviewed, as follows:

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4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N/A					

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	51,456	Forest Laboratories	Aerobid (flunisolide hemihydrate in HFA-134a)
IND			
NDA	18-340	Forest Laboratories	Aerobid (flunisolide hemihydrate inhalation aerosol)

18. CONSULTS/ CMC RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics			None necessary	
EES		FUR 2/13/03 FUR 11/24/03	Acceptable	All sites are acceptable 3/5/04
Pharm/Tox		10/27/00 3/4/04 3/12/04	Completed 5/21/02 Completed 4/9/04 Completed 4/9/04	Consult for related impurities Consult for acceptable leachables level Consult for acceptable leachables level
Biopharm			N/A	
LNC			Completed 5/8/03	DMETS has no objections to the use of the proprietary name. DDMAC finds the proprietary name acceptable from a promotional perspective.
Methods Validation			To be submitted	Methods validation will be accomplished in FDA laboratories once the analytical methods have been finalized.
OPDRA			Acceptable Hye-Joo Kim 2/13/02	Update may be needed once application is approvable from a CMC perspective
EA			N/A	Applicant has applied for a categorical exclusion.
Microbiology			N/A	No Microbiological consult will be issued owing to having previously accepted specs

Appears This Way
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The Chemistry Review for NDA 21-247

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application as submitted is approvable from the standpoint of chemistry, manufacturing and controls, pending resolution of the deficiencies in DMF _____. Deficiencies related to the NDA are detailed in the accompanying review notes and summarized in the attached draft letter to the applicant, chemistry portion.

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

Several commitments and agreements are listed in the Remarks/Comments section that need to be included in the final letter.

II. Summary of Chemistry Assessments

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

Drug Substance Description

All information pertaining to the flunisolide hemihydrate drug substance is referenced to the content of _____. DMF _____ DMF _____ includes _____ for manufacture of the drug substance, the _____ The _____ was not inspected and is considered unacceptable since it has been shut down, is unable to be inspected, and will no longer produce drug substance. The _____ is currently being used as drug substance release tester. Currently, there is no approved drug substance manufacturing site.

DMF _____ for drug substance manufacture has been reviewed and is adequate to support this application. The holder has been requested to provide complete results of drug substance release testing to DMF _____.

A Follow-Up Request was issued 11/24/03 for all sites. All sites are acceptable in recommendation dated 3/5/04. In the 12/7/01 amendment, the applicant has withdrawn both the _____ sites from the application as drug substance manufacturing sites. The drug substance stored in _____ was manufactured by _____ and will be used for the commercial batches once satisfactory identity, quality, and purity are shown. They have also been informed that we expect them to submit a separate and complete DMF for the _____ site. The applicant has agreed to submit a prior-approval supplement, after approval of this application, to support the manufacture of flunisolide hemihydrate at _____.

Drug substance used in all the toxicological, clinical and stability lots has been manufactured at the _____ using the same _____ process.

Forest Laboratories will provide the results of extensive drug substance characterization studies on each container of flunisolide hemihydrate stored in _____.

The PSD is not controlled as a profile since the drug product is _____.

Drug Product Description – Drug product is a pressurized metered-dose inhaler



CHEMISTRY REVIEW



Flunisolide hemihydrate HFA contains a solution of 0.24% flunisolide hemihydrate in Dehydrated Alcohol, USP and a hydrofluorocarbon propellant (HFA-134a) in a aluminum can fitted with a valve. The device includes a mouthpiece/actuator/spacer.

Pack Sizes proposed are 120-actuation and 60-actuation sizes using identical canister and valve. Both of these presentations deliver 139 µg flunisolide hemihydrate from the valve and 80 µg flunisolide hemihydrate (equivalent to 78 µg of flunisolide) from the spacer at a flow rate of 30 L/min for 4 sec. These correspond to a shot weight of approximately 58 mg.

The excipient Dehydrated Alcohol USP is used for the drug substance. The formulation has valve mechanism.

COMPONENTS / COMPOSITION (p. 4: 31)

Raw Material	60-Act. g/Unit*	120-Act. g/Unit*	% w/w
Flunisolide hemihydrate, USP			
Dehydrated alcohol, USP			
Propellant HFA-134a			

*The g/unit values are based on target fill weight ().

The formulation density is at

Target fill weights are for 60 and 120 actuation units, respectively. The ranges of fill weight are during filling, respectively. The net fill-weights post-fill (acceptance criteria for stability and release testing) are 5.1 g, and 8.9 g, respectively.

Fill weight necessary to deliver 60 and 120 actuations based on shot weight are ; (taking into account the mean leak rate over 2 years). These calculate to overfills of , respectively at the label claim, and at the current minimum fill weight.

The solubility of the drug substance in the formulation is adequate to prevent precipitation of the drug substance under the recommended storage conditions. Solubility of flunisolide in 10% ethanol in HFA-134a was found to be . The solubility of flunisolide in the formulation at is equal to its concentration in the drug product. The labeling shows the recommended storage temperature range is 15 - 30°C. All labeling should show the recommended storage temperature as 25°C since the real-world storage conditions will exceed the recommendations by a wide margin. The narrowest possible range should be specified on the labels to alert shippers and patients to the need for careful storage.

Interpolation of the solubility data show the expected solubility of the drug substance in 10% alcohol/HFA-134a is at 15°C, the lowest allowed storage temp. This allows a % deficiency of solvent or overage of drug substance before the solubility limit is reached. Although some propellant is apt to leak from the container, it is likely the solubility of the drug substance in the remaining formulation is increased by this change. It is likely that storage conditions under real-world shipping will cause precipitation of the drug substance from the formulation. For this reason, it is necessary to keep the shippers and patients advised that the recommended storage conditions are to be 25°C.

Batch formulae (as manufactured at) are provided on page 4: 56 and are listed in the following table:



CHEMISTRY REVIEW



G29 Ingredients	60 Actuators per Unit (— Unit Batch)	120 Actuators per Batch (— Unit Batch)
Flunisolide hemihydrate, USP	_____	_____
Dehydrated Alcohol, USP	_____	_____
1,1,1,2-Tetrafluoroethane	_____	_____
Total	_____	_____

Early development lots contained _____ in order to be similar to the current Aerobid and Aerobid M CFC products. Tox studies and initial PK clinical study used solution formulations containing _____

The _____ are probably not an issue taken alone. There is a potential change in flunisolide bioavailability and absorption rate brought about by inclusion of the _____ in the tox formulation is compared with the to-be-marketed formulation. There may or may not be a change in absorption attributable to this addition.

Container/Closure Development History

- Three actuators were tested during the PK study program (see pages 3: 102-105).

_____ (1st PK study)

_____ actuator (PK study ANC-PK1-97-004-000)

Bespak actuator/spacer (to be marketed configuration, PK study ANC-PK1-97-004-000 and all subsequent clinical trials and stability studies)

- Three _____ modifications were incorporated

The original _____ configuration was only used in tox and PK studies

The first modification included _____

_____ (see Table 8 on page 4: 42). This modification was incorporated into all _____ used in NDA stability batches and Phase III clinical studies batches.

The second modification incorporated an _____

_____. The applicant reports that _____ with the above modification were used in the Phase III clinical trials.

Third modification to the _____

_____. The applicant states that no changes were made in the material or manufacturing process for the _____

_____. The change was reportedly made _____

_____. The _____ was evaluated (see Table 9 on page 4: 43) before and after the change in the _____

_____. This study showed the change caused _____ mg/year, and almost doubled _____

- Three canisters were used in developmental work, differing in modifications to _____

First canister was not used in the critical clinical trials.

The first two modifications were reportedly implemented to _____

The first modification was to change the _____



The second modification _____

The results of _____ studies were provided on page 4:44 in Table 10. It is obvious from the data that the change in _____

The third modification was to _____ The canisters used in the Phase III clinical trials contained all above modifications.



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

According to the applicant, the drug product delivers 139 µg of flunisolide hemihydrate per actuation from the valve and 80 µg of flunisolide hemihydrate from the spacer (using a flow rate of 30 L/min for 4 sec). Valve delivery is 58 mg _____
_____. The maximum daily dose is _____ µg.

The formulation density is _____ at _____

Target fill weights are _____ for 60 and 120 actuation units, respectively. The ranges of fill weights are _____ during filling, respectively. The net fill-weights post-fill (acceptance criteria for stability and release testing) are _____ respectively.

Fill weight necessary to deliver 60 and 120 actuations based on shot weight are _____ (taking into account the mean leak rate over 2 years). This calculates to overfills of _____ respectively at the label claim, and _____ at the current minimum fill weight.

Solubility of flunisolide in 10% ethanol in HFA-134a was found to be _____. The solubility of flunisolide in the formulation at _____ is equal to its concentration in the drug product. The labeling shows the recommended storage temperature range is 15 - 30°C. All labeling should show the recommended storage temperature as _____ 25°C since the real-world storage conditions will exceed the recommendations by a wide margin. The narrowest possible range should be specified on the labels to alert shippers and patients to the need for careful storage.

Route of Administration is Oral Inhalation; minimum dose is 1 actuation bid; maximum _____

Proposed expiration dating period is 24 months for both presentations. This proposal is deemed acceptable based upon the provided stability data.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has not provided adequate information pertaining to drug product specifications, testing, and labeling.



D. Remarks/Comments:

Drug Substance

1. All information pertaining to the flunisolide hemihydrate drug substance is referenced to DMF _____. The sites supported by this DMF are _____. The _____ site has been removed from DMF _____ and a separate DMF will be submitted for this site.
2. Drug substance used in all the toxicological, clinical and stability lots has been manufactured at the _____ using the same _____ process.
3. The _____ was not inspected since it has been shut down and will no longer produce drug substance. A Follow-Up Request was issued 11/24/03 for all sites. All sites were deemed acceptable by OC in their recommendation dated 3/5/04.
4. In the 12/7/01 amendment, the applicant has withdrawn _____ from the application. The drug substance stored in _____ was manufactured by _____ and will be used for the commercial batches once satisfactory identity, quality, and purity are shown. They have also been informed that we expect them to submit a separate and complete DMF for the _____. The applicant has agreed to submit a prior-approval supplement, after approval of this application, to support the manufacture of flunisolide hemihydrate at _____.
5. We have not received data from drug product manufactured from flunisolide hemihydrate made at the proposed site for flunisolide hemihydrate manufacture _____.
6. The applicant must submit to the NDA the test results for all flunisolide hemihydrate containers stored in the _____ facility in _____. They agree to perform acceptance testing of drug substance batches no more than 90 days prior to formulation.
7. The applicant should reevaluate the _____ acceptance criterion once the applicant manufactures additional drug substance batches at the _____. Forest has committed to reevaluate the _____ levels and revise the acceptance criteria based upon the results obtained from analysis of the first three production-scale batches.
8. The proposed acceptance criteria for related substances in the drug substance are on an interim basis until Forest submits the _____ to the application for approval. The drug substance acceptance criteria will be specific to and distinguished by the manufacturing site for the drug substance. For the flunisolide hemihydrate from _____ the applicant must amend the NDA to include revised acceptance specifications wherein the applicant commits to adopt the _____ specifications. After the applicant has manufactured three full-scale batches at the _____ and Forest must submit test results for review and reevaluation of the acceptance criteria. This agreement must be communicated to the applicant in the AP letter.

Drug Product

1. Flunisolide hemihydrate HFA contains a solution of 0.24% flunisolide hemihydrate in Dehydrated Alcohol, USP and a _____ fluorohydrocarbon propellant (HFA-134a) in a _____ aluminum _____ can fitted with a _____ valve. The device includes a _____ mouthpiece/actuator/spacer.
2. Pack Sizes proposed are 120-actuation and 60-actuation sizes using identical canister and valve. Both of these presentations deliver 139 μg of flunisolide hemihydrate from the valve and 80 μg from the spacer at a flow rate of 30 L/min for 4 sec (2 L volume). These correspond to a shot weight of _____ g when the concentration of drug substance in the formulation is used for calculations. The formulation density is _____ at _____. The density, when combined with the nominal valve metering chamber volume of _____ indicates the valve delivery should be 58 mg per actuation.



CHEMISTRY REVIEW



3. The amount of drug delivered at the mouthpiece and the fine particle mass are directly dependent on the flow rate. []
4. Fill weight necessary to deliver 60 and 120 actuations based on shot weight are _____ (taking into account the mean leak rate over 2 years). This calculates to overfills of _____ respectively at the label claim, and _____, at the current minimum fill weight. The canister has a nominal volume of _____. The formulation density is _____ at _____.
5. The Bepak actuator/spacer is a two-piece assembly with an orifice diameter of _____ mm. The spacer has an internal capacity of _____ L.
6. _____
7. An FUR was issued 11/24/03 for all sites. All sites are acceptable as recommended on 3/5/04 by OC.
8. The applicant has withdrawn the Forest Pharmaceuticals Inc. _____ site from the application in the 11/9/00 amendment.
9. Forest has submitted the following two testing facilities for periodic testing of container-closure components to evaluate the results from 3M COA:

Both of the above sites were issued ACCEPTABLE EERs on 3/5/04 by the OC.

10. Forest has committed to repeat the tests given by _____ in the Certificate of Compliance for the first three lots intended for commercialization. Thereafter, Forest commits to test every _____ lot manufactured by _____ annually. In addition, Forest commits to testing the first three commercial lots for extractables using Forest test procedure _____ and for product performance measured by _____ and medication delivery/through life (test methods _____). Forest must be reminded of these agreements in the AP letter.
11. []
12. Forest commits to review the fill weight data with 3M after one year of production and revise these specifications if appropriate. The applicant must be reminded of this agreement in the AP letter.
13. Forest has made a commitment in the November 20, 2002 meeting, to institute changes in their manufacturing process to minimize oxidation of flunisolide drug substance. This agreement must be reflected in the AP letter once issued.
14. Forest states that they commit to perform acceptance testing of flunisolide hemihydrate no more than 90 days prior to its use in the formulation. This agreement must be captured in the AP letter once issued.
15. Forest has agreed that the proposed acceptance criteria for related substances in the drug substance are on an interim basis until the _____ is submitted to the application for approval. They have stated that Roche will file a new DMF for the drug substance and Forest will file a post-approval supplement to support the use of the drug substance from the _____ prior to its use in the manufacturing of the drug product. This agreement needs to be reflected in the AP letter once issued.

16. A microbiology consult is not needed since the proposed acceptance criteria have been previously allowed in other applications.
17. A description of the investigational and stability batches is provided in the 6/13/00 amendment. No other formulations were used in IND studies.
18. The applicant has applied for a categorical exclusion under 21 CFR 25.31(b) and is justified in doing so.
19. Methods validation will be accomplished in FDA laboratories once the drug product specifications have been agreed to.
20. Forest must be made responsible for extractables and leachables testing and drug product specifications.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Brian Rogers/4/12/04
Richard Lostritto
Ladan Jafari

C. CC Block

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29 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

/s/

Brian Rogers
4/14/04 09:56:12 AM
CHEMIST

Richard Lostritto
4/14/04 02:27:47 PM
CHEMIST

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CHEMISTRY REVIEW

**NDA 21-247
Review 4**

Aerospan (flunisolide HFA) Inhalation Aerosol

Forest Laboratories, Inc.

**Brian Rogers
Division of Pulmonary and Allergy Drug Products**



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Chemistry Review Data Sheet

1. NDA 21-247
2. REVIEW #4
3. REVIEW DATE: 7/23/03
4. REVIEWER: Brian Rogers
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
ORIGINAL	27-APR-2000
Amendment	02-JUN-2000
Amendment	13-JUN-2000
Amendment	21-SEP-2000
Amendment	22-SEP-2000
Amendment	02-OCT-2000
Amendment	09-NOV-2000
Amendment	26-DEC-2000
Review #1	03-MAY-2001
Action Letter (AE)	07-MAY-2001
Amendment	07-MAR-2001
Amendment	28-AUG-2001
Amendment	24-OCT-2001
Amendment	07-DEC-2001
Review #2	05-JUN-2002
Action Letter (AE)	11-JUN-2002
Amendment	05-FEB-2003
Amendment	05-FEB-2003
Review #3	05-MAY-2003
Disc. Rev. Letter	08-MAY-2003



CHEMISTRY REVIEW



Chemistry Review Data Sheet

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	01-MAY-2003
Amendment	05-JUN-2003
Amendment	10-JUN-2003
Amendment	01-JUL-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Forest Laboratories
Harborside Financial Center
Address: Plaza Three, Suite 602
Jersey City, NJ 07311
Representative: David A. Lust
Associate Director, Regulatory Affairs
Telephone: 201-386-2024

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Aerospan (Flunisolide HFA) Inhaler System
- b) Non-Proprietary Name (USAN): flunisolide hemihydrate inhalation aerosol
- c) Code Name/#:
- d) Chem. Type/Submission Priority:
 - Chem. Type: 6
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

505(b)(1)

10. PHARMACOL. CATEGORY: Treatment of asthma as prophylactic therapy in adult/pediatric patients four years of age and older/for patients requiring oral corticosteroid therapy for asthma.

11. DOSAGE FORM: Inhalation Aerosol

12. STRENGTH/POTENCY: Claimed by the applicant to deliver 139 μ g flunisolide hemihydrate per actuation from the valve, and 80 μ g flunisolide hemihydrate (equivalent to 78 μ g of flunisolide) from the spacer (using 30 L/min for 4 sec). Valve delivery is 58 mg/ —

Chemistry Review Data Sheet

13. ROUTE OF ADMINISTRATION: Oral Inhalation; 1 act. bid; max. _____

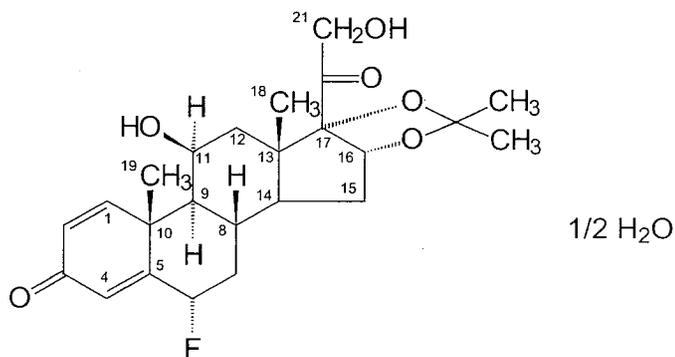
14. Rx/OTC DISPENSED: Rx OTC

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

_____ SPOTS product – Form Completed

Not a SPOTS product

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



Flunisolide hemihydrate
C₂₄H₃₁O₆F · 1/2 H₂O
MW 443.51

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CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting Documents:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1	II	_____	_____	7	Adequate	4/17/03	Holder has withdrawn sites from application.
	V	_____	_____	3	Adequate	10/15/99 by KSwiss	
	V	_____	_____	3	Adequate	2/27/97 by MChun	
	III	3M Pharmaceuticals, Inc.	Valve	1	Inadequate	4/15/03 by Rogers	Inadequate for extractable method
	III	3M Pharmaceuticals, Inc.	Container Closure Extractables	1	Adequate	6/2/02 by Rogers	
	III	_____	_____	1	Inadequate	3/31/03 by Rogers	Supports DMF
	III	_____	_____	1	Inadequate	3/28/03 by Rogers	Supports DMF
	III	Bespak	Actuator/Spacer	1	Adequate	5/28/02 by Rogers	

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 Supporting Documents:

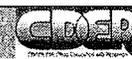
Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N/A					

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	51,456	Forest Laboratories	Aerobid (flunisolide hemihydrate in HFA-134a)
IND	_____	_____	_____
NDA	18-340	Forest Laboratories	Aerobid (flunisolide hemihydrate inhalation aerosol)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. CONSULTS/ CMC RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics			To be submitted	
EES		FUR 2/13/03	Incomplete	All sites are acceptable except 3M Pharmaceuticals in _____, which has OC recommendation pending.
Pharm/Tox	Unresolved for acceptable levels of flunisolide related impurities. Consult for acceptable leachables level will be submitted once extractables method has been approved.	10/27/00		
Biopharm			N/A	
LNC			Completed 5/8/03	DMETS has no objections to the use of the proprietary name. DDMAC finds the proprietary name acceptable from a promotional perspective.
Methods Validation			To be submitted	Methods validation will be accomplished in FDA laboratories once the analytical methods have been finalized.
OPDRA			Acceptable Hyc-Joo Kim 2/13/02	Update may be needed once application is approvable from a CMC perspective
EA			N/A	Applicant has applied for a categorical exclusion.
Microbiology				No Microbiological consult will be issued owing to having previously accepted specs

Appears This Way
On Original



The Chemistry Review for NDA 21-247

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application as submitted is not approvable from the standpoint of chemistry, manufacturing and controls. Deficiencies are detailed in the accompanying review notes and summarized in the attached draft letter to the applicant, chemistry portion.

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

Several commitments and agreements are listed in the Remarks/Comments section that need to be included in the final letter.

II. Summary of Chemistry Assessments

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

Drug Substance Description

All information pertaining to the flunisolide hemihydrate drug substance is referenced to the content of _____ DMF _____. DMF _____ includes _____ for manufacture of the drug substance, the _____. The _____ was not inspected and found unacceptable since it has been shut down and will no longer produce drug substance. The _____ is currently being used as drug substance release tester.

DMF _____ for drug substance manufacture has been reviewed and is adequate to support this application. The holder has been requested to provide complete results of drug substance release testing to DMF _____.

A Follow-Up Request was issued 2/13/03 for all sites. All sites are acceptable except 3M Pharmaceuticals _____ which has inspection pending. In the 12/7/01 amendment, the applicant has withdrawn both the _____ from the application as drug substance manufacturing sites. The drug substance stored in _____ was manufactured by _____ and will be used for the commercial batches once satisfactory identity, quality, and purity are shown. They have also been informed that we expect them to submit a separate and complete DMF for the _____ site. The applicant has agreed to submit a prior-approval supplement, after approval of this application, to support the manufacture of flunisolide hemihydrate at _____.

Drug substance used in all the toxicological, clinical and stability lots has been manufactured at the _____ using the same _____ process.

Forest Laboratories will provide the results of extensive drug substance characterization studies on each container of flunisolide hemihydrate stored in _____.

The PSD is not controlled as a profile since the drug product is _____.

Drug Product Description – Drug product is a pressurized metered-dose inhaler



CHEMISTRY REVIEW



Flunisolide hemihydrate HFA contains a solution of 0.24% flunisolide hemihydrate in Dehydrated Alcohol, USP and a hydrofluorocarbon propellant (HFA-134a) in a aluminum can fitted with a valve. The device includes a mouthpiece/actuator/spacer.

Pack Sizes proposed are 120-actuation and 60-actuation sizes using identical canister and valve. Both of these presentations deliver 139 µg flunisolide hemihydrate from the valve and 80 µg flunisolide hemihydrate (equivalent to 78 µg of flunisolide) from the spacer at a flow rate of 30 L/min for 4 sec. These correspond to a shot weight of approximately 58 mg.

The excipient Dehydrated Alcohol USP is used for drug substance. The formulation has valve mechanism.

COMPONENTS / COMPOSITION (p. 4: 31)

Raw Material	60-Act. g/Unit*	120-Act. g/Unit*	% w/w
Flunisolide hemihydrate, USP			
Dehydrated alcohol, USP			
Propellant HFA-134a			

*The g/unit values are based on target fill weight ().

The formulation density is at

Target fill weights are for 60 and 120 actuation units, respectively. The ranges of fill weight are during filling, respectively. The net fill-weights post-fill (acceptance criteria for stability and release testing) are 5.1 g, and 8.9 respectively.

Fill weight necessary to deliver 60 and 120 actuations based on shot weight (taking into account the mean leak rate over 2 years). These calculate to overfills of respectively at the label claim, and at the current minimum fill weight.

Solubility of flunisolide in 10% ethanol in HFA-134a was found to be The solubility of flunisolide in the formulation at is equal to its concentration in the drug product. The labeling shows the recommended storage temperature range is 15 - 30°C. All labeling should show the recommended storage temperature as 25°C since the real-world storage conditions will exceed the recommendations by a wide margin. The narrowest possible range should be specified on the labels to alert shippers and patients to the need for careful storage.

Batch formulae (as manufactured at) are provided on page 4: 56 and are listed in the following table:

G29 Ingredients	60 Actuations per Unit (Unit Batch)	120 Actuations per Batch (Unit Batch)
Flunisolide hemihydrate, USP		
Dehydrated Alcohol, USP		
1,1,1,2-Tetrafluoroethane		
Total		

Early development lots contained in order to be similar to the current Aerobid and Aerobid M CFC products. Tox studies and initial PK clinical study used solution formulations containing

The are probably not an issue taken alone. There is a potential change in flunisolide bioavailability and absorption rate brought about by inclusion of the when the tox formulation is compared with the to-be-marketed formulation. There may or may not be a change in absorption attributable to this addition.

The solubility of the drug substance in the formulation is adequate to prevent precipitation of the drug substance under the recommended storage conditions. Interpolation of the solubility data show the expected solubility of the drug substance in 10% alcohol/HFA-134a is _____ at 15°C, the lowest allowed storage temp. This allows a _____ deficiency of solvent or overcharge of drug substance before the solubility limit is reached. Although some propellant is apt to leak from the container, it is likely the solubility of the drug substance in the remaining formulation is increased by this change. It is likely that storage conditions under real-world shipping will cause precipitation of the drug substance from the formulation. For this reason, it is necessary to keep the shippers and patients advised that the recommended storage conditions are to be _____ 25°C.

Container/Closure Development History

- Three actuators were tested during the PK study program (see pages 3: 102-105).

_____ (1st PK study)

3 M _____ actuator (PK study ANC-PK1-97-004-000)

Bespak actuator/spacer (to be marketed configuration, PK study ANC-PK1-97-004-000 and all subsequent clinical trials and stability studies)

- Three _____ modifications were incorporated

The original _____ was only used in tox and PK studies

The first modification included _____

_____ (see Table 8 on page 4: 42). This modification was incorporated into all _____ lots used in NDA stability batches and Phase III clinical studies batches.

The second modification incorporated an _____

_____. The applicant reports that _____ with the above modification were used in the Phase III clinical trials.

Third modification to the _____

_____. The applicant states that no changes were made in the material or manufacturing process for the _____ . The change was reportedly made to _____

_____. The _____ ; evaluated (see Table 9 on page 4: 43) before and after the change in the _____ . This study showed the change caused a _____

_____ and almost doubled _____

- Three canisters were used in developmental work, differing in modifications to _____

First canister was not used in the critical clinical trials.

The first two modifications were reportedly implemented to _____

The first modification was to change the _____

The second modification _____

The results of _____ studies were provided on page 4:44 in Table 10. It is obvious from the data that the change in _____ from the canister. The modification _____



The third modification was to _____ : The canisters used in the Phase III clinical trials contained all above modifications.



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

According to the applicant, the drug product delivers 139 µg flunisolide hemihydrate per actuation from the valve and 80 µg flunisolide hemihydrate from the spacer (using 30 L/min for 4 sec). Valve delivery is 58 mg _____. Maximum daily dose is ____ µg. The dose per actuation from the spacer needs to be reevaluated once the Medication Delivery is clarified by further investigation.

The formulation density is _____ at _____.

Target fill weights are _____; for 60 and 120 actuation units, respectively. The ranges of fill weights are _____ during filling, respectively. The net fill-weights post-fill (acceptance criteria for stability and release testing) are 5.1 _____g, and 8.9 _____g, respectively.

Fill weight necessary to deliver 60 and 120 actuations based on shot weight are _____ (taking into account the mean leak rate over 2 years). This calculates to overfills of _____, respectively at the label claim, and _____, at the current minimum fill weight.

Solubility of flunisolide in 10% ethanol in HFA-134a was found to be _____. The solubility of flunisolide in the formulation at _____ is equal to its concentration in the drug product. The labeling shows the recommended storage temperature range is 15 - 30°C. All labeling should show the recommended storage temperature as _____ 25°C since the real-world storage conditions will exceed the recommendations by a wide margin. The narrowest possible range should be specified on the labels to alert shippers and patients to the need for careful storage.

Route of Administration is Oral Inhalation; minimum dose is 1 actuation bid; maximum dose _____.

Proposed expiration dating period is 24 months for both presentations.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has not provided adequate information pertaining to drug substance testing and specifications. Also deficient are information pertaining to drug product specifications, manufacturing, testing, and labeling.

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**D. Remarks/Comments:****Drug Substance**

1. All information pertaining to the flunisolide hemihydrate drug substance is referenced to DMF [redacted]. The sites supported by this DMF are [redacted]. The [redacted] site has been removed from DMF [redacted] and a separate DMF will be submitted for this site.
2. Drug substance used in all the toxicological, clinical and stability lots has been manufactured at [redacted] using the same [redacted] process.
3. The [redacted] was not inspected since it has been shut down and will no longer produce drug substance. A Follow-Up Request was issued 2/13/03 for all sites.
4. In the 12/7/01 amendment, the applicant has withdrawn [redacted] sites from the application. The drug substance stored in [redacted] was manufactured by [redacted] and will be used for the commercial batches once satisfactory identity, quality, and purity are shown. They have also been informed that we expect them to submit a separate and complete DMF for [redacted]. The applicant has agreed to submit a prior-approval supplement, after approval of this application, to support the manufacture of flunisolide hemihydrate [redacted].
5. We have not received data from drug product manufactured from flunisolide hemihydrate made at the proposed site for flunisolide hemihydrate manufacture [redacted].
6. The applicant must submit to the NDA the test results for all flunisolide hemihydrate containers stored in the facility in [redacted]. They commit to perform acceptance testing of drug substance batches no more than 90 days prior to formulation.
7. The applicant should reevaluate the [redacted] acceptance criterion once the applicant manufactures additional drug substance batches at [redacted]. Forest has committed to reevaluate the [redacted] levels and revise the acceptance criteria based upon the results obtained from analysis of the first three production-scale batches.
8. Agreement on the acceptance criteria for Related Substances is still pending and is dependent on satisfactory resolution of studies evaluating the genotoxicity of the [redacted]. If not resolved, the Related Substances' acceptance criteria will be resolved post-approval and the need for resolution must be communicated to the applicant in the AP letter.
9. The proposed acceptance criteria for related substances in the drug substance are on an interim basis until Forest submits the [redacted] to the application for approval. The drug substance acceptance criteria will be specific to and distinguished by the manufacturing site for the drug substance. For the flunisolide hemihydrate from [redacted], the applicant must amend the NDA to include revised acceptance specifications wherein the applicant commits to adopt the [redacted] specifications. After the applicant has manufactured three full-scale batches at the [redacted] Forest must submit test results for review and reevaluation of the acceptance criteria. This agreement must be communicated to the applicant in the AP letter.

Drug Product

1. Flunisolide hemihydrate HFA contains a solution of 0.24% flunisolide hemihydrate in Dehydrated Alcohol, USP and a [redacted] fluorohydrocarbon propellant (HFA-134a) in a [redacted] aluminum [redacted] can fitted with a [redacted] valve. The device includes a [redacted] mouthpiece/actuator/spacer.
2. Pack Sizes proposed are 120-actuation and 60-actuation sizes using identical canister and valve. Both of these presentations deliver 139 µg of flunisolide hemihydrate from the valve and 80 µg from the spacer at a flow rate of 30 L/min for 4 sec (2 L volume). The emitted dose per actuation must be reevaluated once the Medication Delivery method has been examined and new data submitted. These correspond to a shot weight c [redacted] mg when the concentration of drug substance in the formulation is used for calculations. The formulation density is [redacted] at



CHEMISTRY REVIEW

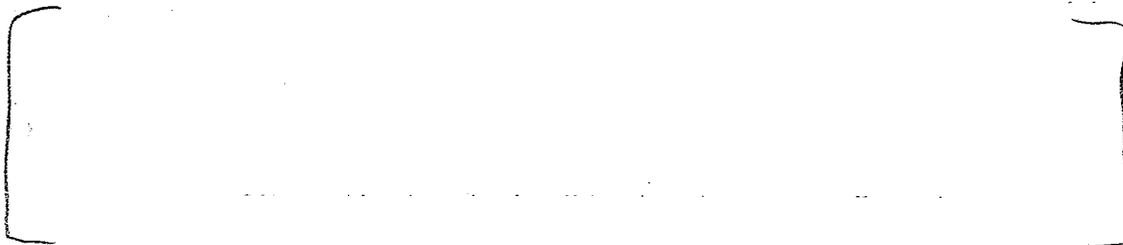


- The density, when combined with the nominal valve metering chamber volume of _____, indicates the valve delivery should be 58 mg per actuation.
3. The labeling should indicate _____
 4. The dependency of drug delivery on the flow should be reflected in the labeling. The amount of drug delivered at the mouthpiece and the fine particle mass are directly dependent on the flow rate. For example, the dose delivered per
[_____]
 5. Fill weight necessary to deliver 60 and 120 actuations based on shot weight are _____ (taking into account the mean leak rate over 2 years). This calculates to overfills of _____ respectively at the label claim, and _____ at the current minimum fill weight. The canister has a nominal volume of _____. The formulation density is _____ at _____.
 6. The Bepak actuator/spacer is a two-piece assembly with an orifice diameter of _____. The spacer has an internal capacity of 50 mL.
 7. _____
 8. An FUR was issued 2/13/03 for all sites. All sites are acceptable except the 3M Pharmaceuticals _____ site is pending inspection.
 9. The applicant has withdrawn the Forest Pharmaceuticals Inc. _____ site from the application in the 11/9/00 amendment.
 10. Forest has submitted the following two testing facilities for periodic testing of container-closure components to evaluate the results from 3M COA:

- Both of the above sites were issued ACCEPTABLE EERs on 2/14/03 by the OC.
11. The applicant has instituted a _____ period, as well as required testing, into their Master Batch Record. The Leakage Rate and thus Valve Delivery appear to stabilize after a sufficient period.
 12. Data from the plume-geometry characterization need to be submitted:
 13. Forest committed in the November 20, 2002 meeting to institute changes in their manufacturing process to minimize oxidation of flunisolide drug substance. They must be reminded of this agreement in the AP letter once it is issued.
 14. Forest has committed to repeat the tests given by _____ on the Certificate of Compliance for the first three lots intended for commercialization. Thereafter, Forest commits to test every _____ lot manufactured by _____ annually. In addition, Forest commits to testing the first three commercial lots for extractables using Forest test procedure _____ and for product performance measured by _____, and medication delivery/through life (test methods I _____). Forest must be reminded of these agreements in the AP letter.
 15. [_____]



16. Forest commits to review the fill weight data with 3M after one year of production and revise these specifications if appropriate. The applicant must be reminded of this agreement in the AP letter.
17. Forest has made a commitment in the November 20, 2002 meeting, to institute changes in their manufacturing process to minimize oxidation of flunisolide drug substance. This agreement must be reflected in the AP letter once issued.
18. Forest states that they commit to perform acceptance testing of flunisolide hemihydrate no more than 90 days prior to its use in the formulation. This agreement must be captured in the AP letter once issued.
19. Forest has agreed that the proposed acceptance criteria for related substances in the drug substance are on an interim basis until the _____ site is submitted to the application for approval. They have stated that _____ will file a new DMF for the drug substance and Forest will file a post-approval supplement to support the use of the drug substance from the _____ site prior to its use in the manufacturing of the drug product. This agreement needs to be reflected in the AP letter once issued.
20. We have not yet evaluated the limited and incongruous data to evaluate the proposed expiration dating period. The



21. A microbiology consult is not needed since the proposed acceptance criteria have been previously allowed in other applications.
22. A description of the investigational and stability batches is provided in the 6/13/00 amendment. No other formulations were used in IND studies.
23. The applicant has applied for a categorical exclusion under 21 CFR 25.31(b) and is justified in doing so.
24. Methods validation will be accomplished in FDA laboratories once the drug product specifications have been agreed to.
25. Forest must be made responsible for extractables and leachables testing and drug product specifications.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Brian Rogers/7/23/03
Guirag Poochikian
Ladan Jafari

C. CC Block

38 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

/s/

Brian Rogers
7/24/03 10:05:00 AM
CHEMIST

Craig Bertha
7/24/03 10:24:48 AM
CHEMIST

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CHEMISTRY REVIEW

**NDA 21-247
Review 3**

Aerospan (flunisolide HFA) Inhalation Aerosol

Forest Laboratories, Inc.

**Brian Rogers
Division of Pulmonary and Allergy Drug Products**



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Chemistry Review Data Sheet

1. NDA 21-247
2. REVIEW #3
3. REVIEW DATE: 5/5/03
4. REVIEWER: Brian Rogers
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
ORIGINAL	27-APR-2000
Amendment	02-JUN-2000
Amendment	13-JUN-2000
Amendment	21-SEP-2000
Amendment	22-SEP-2000
Amendment	02-OCT-2000
Amendment	09-NOV-2000
Amendment	26-DEC-2000
Review #1	03-MAY-2001
Action Letter (AE)	07-MAY-2001
Amendment	07-MAR-2001
Amendment	28-AUG-2001
Amendment	24-OCT-2001
Amendment	07-DEC-2001
Review #2	05-JUN-2002
Action Letter (AE)	11-JUN-2002



CHEMISTRY REVIEW



Chemistry Review Data Sheet

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	5-FEB-2003
Amendment	5-FEB-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Forest Laboratories
Harborside Financial Center
Address: Plaza Three, Suite 602
Jersey City, NJ 07311
Representative: David A. Lust
Associate Director, Regulatory Affairs
Telephone: 201-386-2024

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Aerospan (Flunisolide HFA) Inhaler System
- b) Non-Proprietary Name (USAN): flunisolide hemihydrate inhalation aerosol
- c) Code Name/#:
- d) Chem. Type/Submission Priority:
 - Chem. Type: 6
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

505(b)(1)

10. PHARMACOL. CATEGORY: Treatment of asthma as prophylactic therapy in adult/pediatric patients four years of age and older/for patients requiring oral corticosteroid therapy for asthma.

11. DOSAGE FORM: Inhalation Aerosol

12. STRENGTH/POTENCY: Claimed by the applicant to deliver 139 µg flunisolide hemihydrate per actuation from the valve, and 80 µg flunisolide hemihydrate (equivalent to 78 µg of flunisolide) from the spacer (using 30 L/min for 4 sec). Valve delivery is 58 mg/

Chemistry Review Data Sheet

13. ROUTE OF ADMINISTRATION: Oral Inhalation; 1 act. bid; max. _____

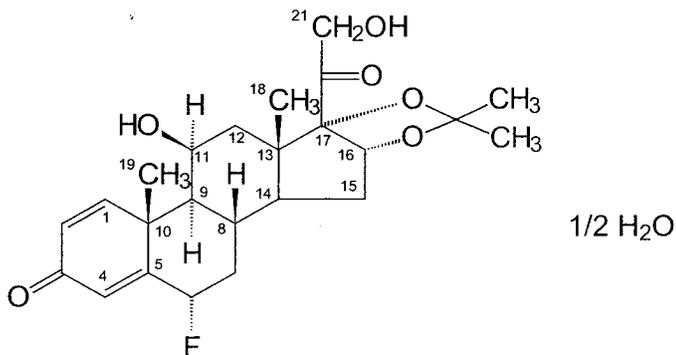
14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____ SPOTS product – Form Completed

Not a SPOTS product

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



Flunisolide hemihydrate
 $C_{24}H_{31}O_6F \cdot 1/2 H_2O$
 MW 443.51

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Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting Documents:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II	_____	_____	7	Adequate	4/17/03	Holder has withdrawn sites from application.
	V	_____	_____	3	Adequate	10/15/99 by KSwiss	
	V	_____	_____	3	Adequate	2/27/97 by MChun	
	III	3M Pharmaceuticals, Inc.	Valve	1	Inadequate	4/15/03 by Rogers	Inadequate for extractable method
	III	3M Pharmaceuticals, Inc.	Container Closure Extractables	1	Adequate	6/2/02 by Rogers	
	III	_____	_____	1	Inadequate	3/31/03 by Rogers	Supports DMF
	III	_____	_____	1	Inadequate	3/28/03 by Rogers	Supports DMF
	III	Bespak	Actuator/Spacer	1	Adequate	5/28/02 by Rogers	

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 Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N/A					

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	51,456	Forest Laboratories	Aerobid (flunisolide hemihydrate in HFA-134a)
IND	_____	_____	_____
NDA	18-340	Forest Laboratories	Aerobid (flunisolide hemihydrate inhalation aerosol)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. CONSULTS/ CMC RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics			To be submitted	
EES		FUR 2/13/03	Incomplete	All sites are acceptable except 3M Pharmaceuticals in which has inspection pending.
Pharm/Tox	Unresolved for acceptable levels of flunisolide related impurities. Consult for acceptable leachables level will be submitted once extractables method has been approved.	10/27/00		
Biopharm			N/A	
LNC			N/A	
Methods Validation			To be submitted	Methods validation will be accomplished in FDA laboratories once the analytical methods have been finalized.
OPDRA			Acceptable Hye-Joo Kim 2/13/02	Update may be needed once application is approvable from a CMC perspective
EA			N/A	Applicant has applied for a categorical exclusion.
Microbiology				No Microbiological consult will be issued owing to having previously accepted specs

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The Chemistry Review for NDA 21-247

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application as submitted is not approvable from the standpoint of chemistry, manufacturing and controls. Deficiencies are detailed in the accompanying review notes and summarized in the attached draft letter to the applicant, chemistry portion.

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

Several commitments and agreements are listed in the Remarks/Comments section that need to be included in the final letter.

II. Summary of Chemistry Assessments

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

Drug Substance Description

All information pertaining to the flunisolide hemihydrate drug substance is referenced to the content of _____ DMF _____. DMF _____ includes two sites for manufacture of the drug substance, _____. The _____ was not inspected and found unacceptable since it has been shut down and will no longer produce drug substance. The _____ is currently being used as drug substance release tester.

DMF _____ for drug substance manufacture has been reviewed and is adequate to support this application. The holder has been requested to provide complete results of drug substance release testing to DMF _____.

A Follow-Up Request was issued 2/13/03 for all sites. All sites are acceptable except 3M Pharmaceuticals in _____ which has inspection pending. In the 12/7/01 amendment, the applicant has withdrawn both the _____ from the application as drug substance manufacturing sites. The drug substance stored in _____ was manufactured by _____ and will be used for the commercial batches once satisfactory identity, quality, and purity are shown. They have also been informed that we expect them to submit a separate and complete DMF for the _____. The applicant has agreed to submit a prior-approval supplement, after approval of this application, to support the manufacture of flunisolide hemihydrate _____.

Drug substance used in all the toxicological, clinical and stability lots has been manufactured at _____ using the same _____ process.

Forest Laboratories will provide the results of extensive drug substance characterization studies on each container of flunisolide hemihydrate stored in _____.

The PSD is not controlled as a profile since the drug product _____.

Drug Product Description – Drug product is a pressurized metered-dose inhaler



CHEMISTRY REVIEW



Flunisolide hemihydrate HFA contains a solution of 0.24% flunisolide hemihydrate in Dehydrated Alcohol, USP and a _____ hydrofluorocarbon propellant (HFA-134a) in a _____ aluminum _____ can _____ valve. The device includes a _____ mouthpiece/actuator/spacer.

Pack Sizes proposed are 120-actuation and 60-actuation sizes using identical canister and valve. Both of these presentations deliver 139 µg flunisolide hemihydrate from the valve and 80 µg flunisolide hemihydrate (equivalent to 78 µg of flunisolide) from the spacer at a flow rate of 30 L/min for 4 sec. These correspond to a shot weight of approximately 58 mg.

The excipient Dehydrated Alcohol USP is used for _____ drug substance. No : _____ mechanism.

COMPONENTS / COMPOSITION (p. 4: 31)

Raw Material	60-Act. g/Unit*	120-Act. g/Unit*	% w/w
Flunisolide hemihydrate, USP	_____	_____	_____
Dehydrated alcohol, USP	_____	_____	_____
Propellant HFA-134a	_____	_____	_____

*The g/unit values are based on target fill weight (_____ g).

The formulation density is _____ at _____.

Target fill weights are _____, for 60 and 120 actuation units, respectively. The ranges of fill weight are _____, during filling, respectively. The net fill-weights post-fill (acceptance criteria for stability and release testing) are 5.1 _____ g, and 8.9 _____ g, respectively.

Fill weight necessary to deliver 60 and 120 actuations based on shot weight are _____, (taking into account the mean leak rate over 2 years). These calculate to overfills of _____, respectively at the label claim, and _____ at the current minimum fill weight.

Solubility of flunisolide in 10% ethanol in HFA-134a was found to be _____. The solubility of flunisolide in the formulation at _____ is equal to its concentration in the drug product. The labeling shows the recommended storage temperature range is 15 - 30°C.

Batch formulae (as manufactured at _____) are provided on page 4: 56 and are listed in the following table:

G29 Ingredients	60 Actuations per Unit (_____ Unit Batch)	120 Actuations per Batch (_____ Unit Batch)
Flunisolide hemihydrate, USP	_____	_____
Dehydrated Alcohol, USP	_____	_____
1,1,1,2-Tetrafluoroethane	_____	_____
Total	_____	_____

Early development lots contained _____ in order to be similar to the current Aerobid and Aerobid M CFC products. Tox studies and initial PK clinical study used solution formulations containing ' _____ and _____.

The _____ are probably not an issue taken alone. There is a potential change in flunisolide bioavailability and absorption rate brought about by inclusion of the _____ when the tox formulation is _____.

compared with the to be marketed formulation. There may or may not be a change in absorption attributable to this addition.

The solubility of the drug substance in the formulation is adequate to prevent precipitation of the drug substance under the recommended storage conditions. Interpolation of the solubility data show the expected solubility of the drug substance in 10% alcohol/HFA-134a is _____ at 15°C, the lowest allowed storage temp. This allows a deficiency of solvent or overcharge of drug substance before the solubility limit is reached. Although some propellant is apt to leak from the container, it is likely the solubility of the drug substance in the remaining formulation is increased by this change.

Container/Closure Development History

- Three actuators were tested during the PK study program (see pages 3: 102-105).
_____ (1st PK study)
3 M _____ actuator (PK study ANC-PK1-97-004-000)
Bespak actuator/spacer (to be marketed configuration, PK study ANC-PK1-97-004-000 and all subsequent clinical trials and stability studies)

- Three valve modifications were incorporated
The original _____ was only used in tox and PK studies

The first modification included _____

_____ The
_____ mg (see Table 8 on page 4: 42). This modification was incorporated into
a _____ lots used in NDA stability batches and Phase III clinical studies batches.

The second modification incorporated an _____

_____ The applicant reports that _____ with the above modification were
used in the Phase III clinical trials.

Third modification to the _____
_____ The applicant states that no changes were made in the material or manufacturing
process for _____. The change was reportedly made to ease assembly of _____
_____. The _____ was evaluated (see Table 9 on page 4: 43) before and
after the change in _____. This study showed the change _____

- Three canisters were used in developmental work, differing in modifications to _____

First canister was not used in the critical clinical trials.

The first two modifications were reportedly implemented to _____

The first modification was to change the _____

The second modification altered the _____

The results of _____ studies were provided on page 4:44 in Table 10. It is obvious from the data that the change in _____ from the canister. The modification _____ from _____).

The third modification was to _____ The canisters used in the Phase III clinical trials contained all above modifications.



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

According to the applicant, the drug product delivers 139 µg flunisolide hemihydrate per actuation from the valve and 80 µg flunisolide hemihydrate from the spacer (using 30 L/min for 4 sec). Valve delivery is 58 mg _____ Maximum daily dose is _____

The formulation density is _____ at _____

Target fill weights are _____; for 60 and 120 actuation units, respectively. The ranges of fill weights are _____ during filling, respectively. The net fill-weights post-fill (acceptance criteria for stability and release testing) are 5.1 _____ g, and 8.9 _____ respectively.

Fill weight necessary to deliver 60 and 120 actuations based on shot weight are _____ (taking into account the mean leak rate over 2 years). This calculates to overfills of _____, respectively at the label claim, and _____, at the current minimum fill weight.

Solubility of flunisolide in 10% ethanol in HFA-134a was found to be _____. The solubility of flunisolide in the formulation at _____ is equal to its concentration in the drug product. The labeling shows the recommended storage temperature range is 15 - 30°C.

Route of Administration is Oral Inhalation; minimum dose is 1 actuation bid; maximum dose _____

Proposed expiration dating period is 24 months for both presentations.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has not provided adequate information pertaining to drug substance testing and specifications. Also deficient are information pertaining to drug product specifications, manufacturing, testing, and labeling.

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On Original

**D. Remarks/Comments:****Drug Substance**

1. All information pertaining to the flunisolide hemihydrate drug substance is referenced to DMF [redacted]. The sites supported by this DMF are [redacted]. The [redacted] site has been removed from DMF [redacted] and a separate DMF will be submitted for this site.
2. Drug substance used in all the toxicological, clinical and stability lots has been manufactured at the Bahamas site using the same [redacted] process.
3. The [redacted] was not inspected since it has been shut down and will no longer produce drug substance. A Follow-Up Request was issued 2/13/03 for all sites.
4. In the 12/7/01 amendment, the applicant has withdrawn [redacted] sites from the application. The drug substance stored in [redacted] was manufactured by [redacted] and will be used for the commercial batches once satisfactory identity, quality, and purity are shown. They have also been informed that we expect them to submit a separate and complete DMF for the [redacted]. The applicant has agreed to submit a prior-approval supplement, after approval of this application, to support the manufacture of flunisolide hemihydrate at [redacted].
5. No data has been received from drug product manufactured from flunisolide hemihydrate made at the proposed site for flunisolide hemihydrate manufacture ([redacted]).
6. The applicant must submit to the NDA the test results for all flunisolide hemihydrate containers stored in the [redacted] facility in [redacted].
7. The [redacted] acceptance criterion should be reevaluated once additional drug substance batches are manufactured at [redacted] facility. Forest has committed to reevaluate the [redacted] levels and revise the acceptance criteria based upon the results obtained from analysis of the first three production-scale batches.
8. Agreement on the acceptance criteria for Related Substances is still pending and is dependent on satisfactory resolution of studies evaluating the genotoxicity of [redacted]. If not resolved, the Related Substances' acceptance criteria will be resolved post-approval and the need for resolution must be communicated to the applicant in the AP letter.
9. The proposed acceptance criteria for related substances in the drug substance are on an interim basis until the [redacted] site is submitted to the application for approval. The drug substance acceptance criteria will be specific to and be distinguished by the site where the drug substance is manufactured. For the drug substance from [redacted] the NDA will be amended to include revised acceptance specifications wherein the applicant commits to adopt the [redacted] specifications. After three full-scale batches are manufactured at the [redacted] site, test results from [redacted] Forest will be submitted for review and reevaluation of the acceptance criteria. This agreement must be communicated to the applicant in the AP letter.

Drug Product

1. Flunisolide hemihydrate HFA contains a solution of 0.24% flunisolide hemihydrate in Dehydrated Alcohol, USP and a [redacted] fluorohydrocarbon propellant (HFA-134a) in a [redacted] aluminum [redacted] can fitted with [redacted] valve. The device includes a [redacted] mouthpiece/actuator/spacer.
2. Pack Sizes proposed are 120-actuation and 60-actuation sizes using identical canister and valve. Both of these presentations deliver 139 µg of flunisolide hemihydrate from the valve and 80 µg from the spacer at a flow rate



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of 30 L/min for 4 sec (2 L volume). These correspond to a shot weight of _____ when the concentration of drug substance in the formulation is used for calculations. The formulation density is _____ at _____. The density, when combined with the nominal valve metering chamber volume of _____ indicate the valve delivery should be 58 mg per actuation.

3. The labeling should indicate _____

4. The dependency of drug delivery on the flow should be reflected in the labeling. The amount of drug delivered at the mouthpiece and the fine particle mass are directly dependent on the flow rate. For example, the dose

[_____]

5. Fill weight necessary to deliver 60 and 120 actuations based on shot weight are _____; (taking into account the mean leak rate over 2 years). This calculates to overfills of _____, respectively at the label claim, and _____ at the current minimum fill weight. The canister has a nominal volume of _____. The formulation density is _____ at _____.

6. The Bepak actuator/spacer is a two-piece assembly with an orifice diameter of _____. The spacer has an internal capacity of 50 mL.

7. _____

8. An FUR was issued 2/13/03 for all sites. All sites are acceptable except the 3M Pharmaceuticals _____ site is pending inspection.

9. The applicant has withdrawn the Forest Pharmaceuticals Inc. _____ from the application in the 11/9/00 amendment.

10. Forest has submitted the following two testing facilities for periodic testing of container-closure components to evaluate the results from 3M COA:

Both of the above sites were issued ACCEPTABLE EERs on 2/14/03 by the OC.

11. The applicant has been requested to institute a _____ period, as well as required testing, into their Master Batch Record. The applicant may not need to provide controls for a maximum _____ period, since this requirement is less critical for a solution MDI. The Leakage Rate and thus Valve Delivery appear to stabilize after a sufficient period.

12. Data from the following studies need to be submitted:

a. [_____]

b. [_____]

13. Forest committed in the November 20, 2002 meeting to institute changes in their manufacturing process to minimize oxidation of flunisolide drug substance. They must be reminded of this agreement in the AP letter



CHEMISTRY REVIEW



once it is issued.

14. Forest has committed to limiting the level of flunisolide _____ in the drug product to _____ unless there is FDA agreement that it has been shown not to be genotoxic. They must be reminded of this agreement in the AP letter.
15. Forest has committed to repeat the tests given by _____ Certificate of Compliance for the first three lots intended for commercialization. Thereafter, Forest commits to test every _____ at manufactured by _____ annually. In addition, Forest commits to testing the first three commercial lots for extractables using Forest test procedure _____ for product performance measured by _____ and medication delivery/through life (test methods _____). Forest must be reminded of these agreements in the AP letter.
16. A proposal has been submitted to utilize _____

17. Forest commits to review the fill weight data with 3M after one year of production and revise these specifications if appropriate. The applicant must be reminded of this agreement in the AP letter.
18. We have not yet evaluated the limited and incongruous data to evaluate the proposed expiration dating period. The stability data provided are inadequate owing to:
19. A microbiology consult is not needed since the proposed acceptance criteria have been previously allowed in other applications.
20. A description of the investigational and stability batches is provided in the 6/13/00 amendment. No other formulations were used in IND studies.
21. The applicant has applied for a categorical exclusion under 21 CFR 25.31(b) and is justified in doing so.
22. Methods validation will be accomplished in FDA laboratories once the drug product specifications have been agreed to.
23. Forest must be made responsible for extractables and leachables testing and drug product specifications.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block



Brian Rogers/5/5/03
Guirag Poochikian
Ladan Jafari

C. CC Block

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 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Brian Rogers
5/6/03 09:17:29 AM
CHEMIST

Guiragos Poochikian
5/6/03 11:07:26 AM
CHEMIST

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NDA 21-247

Aerospan (flunisolide HFA) Inhaler System

Forest Laboratories, Inc.

Brian Rogers
Division of Pulmonary and Allergy Drug Products



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Chemistry Review Data Sheet

1. NDA 21-247
2. REVIEW #2
3. REVIEW DATE: 6/05/02
4. REVIEWER: Brian Rogers

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
ORIGINAL	27-APR-2000
Amendment	02-JUN-2000
Amendment	13-JUN-2000
Amendment	21-SEP-2000
Amendment	22-SEP-2000
Amendment	02-OCT-2000
Amendment	09-NOV-2000
Amendment	26-DEC-2000
Review #1	03-MAY-2001
Action Letter (AE)	07-MAY-2001

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	07-MAR-2001
Amendment	28-AUG-2001
Amendment	24-OCT-2001
Amendment	07-DEC-2001



CHEMISTRY REVIEW



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Forest Laboratories
Harborside Financial Center
Address: Plaza Three, Suite 602
Jersey City, NJ 07311
Representative: Robert Ashworth, Ph.D.
Senior Director, Regulatory Affairs
Telephone: 201-386-2009

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Aerospan (Flunisolide HFA) Inhaler System
- b) Non-Proprietary Name (USAN): flunisolide hemihydrate inhalation aerosol
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 6
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: Treatment of asthma as prophylactic therapy in adult/pediatric patients four years of age and older/for patients requiring oral corticosteroid therapy for asthma.

11. DOSAGE FORM: Inhalation Aerosol

12. STRENGTH/POTENCY: Claimed by the applicant to deliver 139 µg flunisolide hemihydrate per actuation from the valve, and 85 µg flunisolide hemihydrate from the spacer (using 30 L/min for 5 sec). Valve delivery is 58 mg ~~_____~~. These dose delivered data will be updated upon receiving requested data.

13. ROUTE OF ADMINISTRATION: Oral Inhalation; 1 act. bid; ~~_____~~

14. Rx/OTC DISPENSED: Rx OTC



CHEMISTRY REVIEW



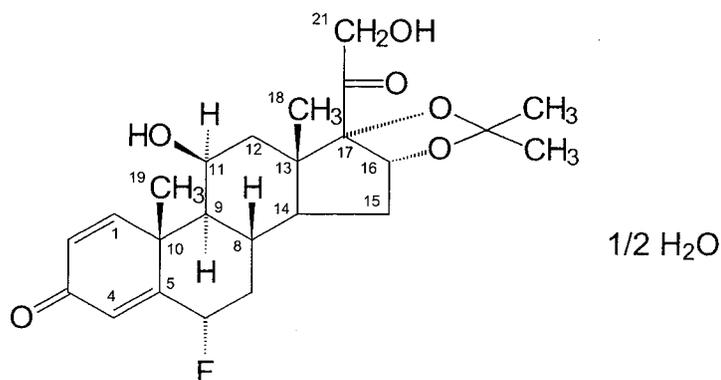
Chemistry Review Data Sheet

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____ SPOTS product – Form Completed

X Not a SPOTS product

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



Flunisolide hemihydrate
 $C_{24}H_{31}O_6F \cdot 1/2 H_2O$
 MW 443.51

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting Documents:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II	_____	_____	7	Inadequate	10/2/00 by CHKim	Holder has withdrawn sites from application.
	V	_____	_____	3	Adequate	10/15/99 by KSwiss	
	V	_____	_____	3	Adequate	2/27/97 by MChun	
	III	3M Pharmaceuticals, Inc.	Valve	1	Inadequate	6/5/02 by Rogers	Inadequate for extractable method
	III	3M Pharmaceuticals, Inc.	Container Closure Extractables	1	Adequate	6/2/02 by Rogers	
	III	_____	_____	1	Inadequate	5/31/02 by Rogers	
	III	Bespak	Actuator/Spacer	1	Adequate	5/28/02 by Rogers	



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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 Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	51,456	Forest Laboratories	Aerobid (flunisolide hemihydrate in HFA-134a)
IND			
NDA	18-340	Forest Laboratories	Aerobid (flunisolide hemihydrate inhalation aerosol)

18. CONSULTS/ CMC RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics			To be submitted	
EES		FUR 3/21/02	Withhold	WITHHOLD status report was received 6/5/02 for application. All sites are acceptable except WITHHOLD recommendations issued 6/5/02, 5/13/02, and 4/8/02, for 3M Pharmaceuticals and Forest Laboratories, respectively.
Pharm/Tox	Unresolved for acceptable levels of flunisolide related impurities. Consult for acceptable leachables level will be submitted once extractables method has been approved.	10/27/00		
Biopharm			N/A	
LNC			N/A	
Methods Validation			To be submitted	Methods validation will be accomplished in FDA laboratories once the analytical methods have been finalized.
OPDRA			Acceptable Hye-Joo Kim 2/13/02	Update may be needed once application is approvable from a CMC perspective
EA			N/A	Applicant has applied for a categorical exclusion.
Microbiology				No Microbiological consult will be issued owing to having previously accepted specs

The Chemistry Review for NDA 21-247

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application as submitted is not approvable from the standpoint of chemistry, manufacturing and controls. Deficiencies are detailed in the accompanying review notes and summarized in the attached draft letter to the applicant, chemistry portion.

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

Any noted will be summarized in the next review

II. Summary of Chemistry Assessments

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

Drug Substance Description

All information pertaining to the flunisolide hemihydrate drug substance is referenced to the content of _____ DMF _____. DMF _____ includes two sites for manufacture of the drug substance, _____. The _____ was not inspected and found unacceptable since it has been shut down and will no longer product drug substance.

DMF _____ for drug substance manufacture has been reviewed and found inadequate to support this application. A letter was sent to the holder dated 11/7/00.

A Follow-Up Request was issued 3/21/02 for all sites. WITHHOLD status report was received from OC 6/5/02 for application. All sites are acceptable except WITHHOLD recommendations issued 6/5/02, 5/13/02, and 4/8/02, for 3M Pharmaceuticals _____ and Forest _____ Laboratories, respectively. In the 12/7/01 amendment, the applicant has withdrawn both the _____ sites from the application. The drug substance stored in _____ was manufactured by _____ and will be used for the commercial batches once satisfactory identity, quality, and purity are shown. They have also been informed that we expect them to submit a separate and complete DMF for the _____. The applicant has agreed to submit a prior-approval supplement, after approval of this application, to support the manufacture of flunisolide hemihydrate _____.

Drug substance used in all the toxicological, clinical and stability lots has been manufactured at _____ using the same _____ process.

The PSD is not controlled as a profile since the drug product _____.

Drug Product Description – Drug product is a pressurized metered-dose inhaler

Flunisolide hemihydrate HFA contains a solution of 0.24% flunisolide hemihydrate in Dehydrated Alcohol, USP and _____ hydrofluorocarbon propellant (HFA-134a) in a _____ aluminum _____ can



_____ valve. The device includes a _____ mouthpiece/actuator/spacer.

Pack Sizes proposed are 120-actuation and 60-actuation sizes using identical canister and valve. Both of these presentations deliver 139 µg flunisolide hemihydrate from the valve and 85 µg from the spacer at a flow rate of 30 L/min for 5 sec. These correspond to a shot weight of approximately 58 mg.

The excipient Dehydrated Alcohol USP is used for _____ the drug substance. No _____ mechanism.

COMPONENTS / COMPOSITION (p. 4: 31)

Raw Material	60-Act. g/Unit*	120-Act. g/Unit*	% w/w
Flunisolide hemihydrate, USP	_____	_____	_____
Dehydrated alcohol, USP	_____	_____	_____
Propellant HFA-134a	_____	_____	_____

*The g/unit values are based on target fill weight (_____).

The formulation density is _____ at _____.

Target fill weights are _____ for 60 and 120 actuation units, respectively. The ranges of fill weight are _____ during filling, respectively. The net fill weights post-fill (acceptance criteria for stability and release testing) are 5.1 _____, and 8.9 _____, respectively. The applicant has been requested to tighten these acceptance criteria.

Fill weight necessary to deliver 60 and 120 actuations based on shot weight are _____ (taking into account the mean leak rate over 2 years). This calculates to overfills of: _____ respectively at the label claim, and _____, at the current minimum fill weight.

Solubility of flunisolide in 10% ethanol in HFA-134a was found to be _____. The solubility of flunisolide in the formulation at _____ is equal to its concentration in the drug product. The labeling shows the recommended storage temperature range is 15 - 30°C.

Batch formulae (as manufactured at the _____) are provided on page 4: 56 and are listed in the following table:

G29 Ingredients	60 Actuations per Unit (_____ Unit Batch)	120 Actuations per Batch (_____ Unit Batch)
Flunisolide hemihydrate, USP	_____	_____
Dehydrated Alcohol, USP	_____	_____
1,1,1,2-Tetrafluoroethane	_____	_____
Total	_____	_____

Early development lots contained ' _____' in order to be similar to the current Aerobid and Aerobid M CFC products. Tox studies and initial PK clinical study used solution formulations containing ' _____ and _____'.

The _____ are probably not an issue taken alone. There is a potential change in flunisolide bioavailability and absorption rate brought about by inclusion of the _____ when the tox formulation is compared with the to be marketed formulation. There may or may not be a change in absorption attributable to this addition.

The solubility of the drug substance in the formulation is adequate to prevent precipitation of the drug substance under the recommended storage conditions. Interpolation of the solubility data show the expected solubility of the drug substance in 10% alcohol/HFA-134a is _____ at 15°C, the lowest allowed storage temp. This allows a _____ deficiency of solvent or overcharge of drug substance before the solubility limit is reached. Although some propellant is apt to leak from the container, it is likely the solubility of the drug substance in the remaining formulation is increased by this change.

Container/Closure Development History

- Three actuators were tested during the PK study program (see pages 3: 102-105).
_____ (1st PK study)
3 M _____ actuator (PK study ANC-PK1-97-004-000)
Bespak actuator/spacer (to be marketed configuration, PK study ANC-PK1-97-004-000 and all subsequent clinical trials and stability studies)

- Three _____ ifications were incorporated
The original _____ ifiguration was only used in tox and PK studies

The first modification included _____
_____ The
path of formulation flow is unchanged by these modifications. _____

_____ This modification was incorporated into
all _____ lots used in NDA stability batches and Phase III clinical studies batches.

The second modification incorporated an _____
_____ The applicant reports that valves with the above modification were
used in the Phase III clinical trials.

Third modification to the _____
_____ The applicant states that no changes were made in the material or manufacturing
process for _____ The change was reportedly made to ease assembly of _____
_____ The _____ was evaluated (see Table 9 on page 4: 43) before and
after the change in _____ This study showed the change caused a _____

- Three canisters were used in developmental work, differing in modifications to _____

First canister was not used in the critical clinical trials.

The first two modifications were reportedly implemented to _____

The first modification was to change _____

The second modification altered the _____

The results of _____ dies were provided on page 4:44 in Table 10. It is obvious from the data that
the change in _____ : from the canister. The modification _____



The third modification was to _____ The canisters used in the Phase III clinical trials contained all above modifications.

[

]

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

According to the applicant, the drug product delivers 139 µg flunisolide hemihydrate per actuation from the valve and 85 µg flunisolide hemihydrate from the spacer (using 30 L/min for 5 sec). Valve delivery is 58 mg _____. Maximum daily dose _____. These drug delivery values will be modified to reflect the data from the requested studies.

The formulation density is _____ at _____

Target fill weights are _____, for 60 and 120 actuation units, respectively. The ranges of fill weights are _____ during filling, respectively. The net fill-weights post-fill (acceptance criteria for stability and release testing) are 5.1 _____ and 8.9 _____ respectively. The applicant has been requested to tighten the acceptance criteria for release and stability testing.

Fill weight necessary to deliver 60 and 120 actuations based on shot weight are _____ (taking into account the mean leak rate over 2 years). This calculates to overfills of _____, respectively at the label claim, and _____ at the current minimum fill weight.

Solubility of flunisolide in 10% ethanol in HFA-134a was found to be _____. The solubility of flunisolide in the formulation at _____ is equal to its concentration in the drug product. The labeling shows the recommended storage temperature range is 15 - 30°C.

Route of Administration is Oral Inhalation; minimum dose is 1 actuation bid; maximum dose _____

Proposed expiration dating period is 24 months for both presentations.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has not provided adequate information pertaining to drug substance testing and specifications. Also deficient are information pertaining to excipient acceptance criteria, drug product specifications, manufacturing, labeling, and stability.

Appears This Way
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**D. Remarks/Comments:****Drug Substance**

1. All information pertaining to the flunisolide hemihydrate drug substance is referenced to DMF [redacted] the sites supported by this DMF are [redacted].
2. Drug substance used in all the toxicological, clinical and stability lots has been manufactured [redacted] site using the same [redacted] process.
3. The [redacted] was not inspected since it has been shut down and will no longer product drug substance. A Follow-Up Request was issued 3/21/02 for all sites. Status in EES shows inspection for 3M [redacted] [redacted] is still pending inspection as of the date of this review.
4. In the 12/7/01 amendment, the applicant has withdrawn [redacted] sites from the application. The drug substance stored in [redacted] was manufactured by [redacted] and will be used for the commercial batches once satisfactory identity, quality, and purity are shown. They have also been informed that we expect them to submit a separate and complete DMF for [redacted] site. The applicant has agreed to submit a prior-approval supplement, after approval of this application, to support the manufacture of flunisolide hemihydrate at [redacted].
5. The applicant should provide a commitment to adopt [redacted] specifications for batches manufactured at the [redacted] site.
6. No data has been received from drug product manufactured from flunisolide hemihydrate made at the proposed site for flunisolide hemihydrate manufacture ([redacted]). According to the 3/19/01 amendment in DMF [redacted], no production-scale batches of flunisolide hemihydrate have yet been manufactured at the [redacted] facility. The holder has just submitted accelerated stability data from registration batches. No long-term stability data are available.
7. The applicant must provide to the NDA a copy of the drug substance specifications and testing protocol for acceptance testing the flunisolide hemihydrate manufactured [redacted] and stored in [redacted]. They must also submit to the NDA the test results for all flunisolide hemihydrate containers stored in the [redacted] facility in [redacted].
8. The [redacted] acceptance criterion should be reevaluated once additional drug substance batches are manufactured [redacted] facility.
9. Agreement on the acceptance criteria for Related Substances is still pending. These acceptance criteria are dependent on the results obtained from the genotoxicity study.
10. The use of only median diameters to limit particle size distribution of the drug substance is inadequate to control the critical larger particle sizes. The applicant must implement an upper limit to allowed particle size.

Drug Product

1. Flunisolide hemihydrate HFA contains a solution of 0.24% flunisolide hemihydrate in Dehydrated Alcohol, USP and [redacted] hydrofluorocarbon propellant (HFA-134a) in a [redacted] aluminum [redacted] can fitted with [redacted] valve. The device includes a [redacted] mouthpiece/actuator/spacer.
2. Pack Sizes proposed are 120-actuation and 60-actuation sizes using identical canister and valve. Both of these presentations deliver 139 µg of flunisolide hemihydrate from the valve and 85 µg from the spacer at a flow rate of 30 L/min for 5 sec (2.5 L volume). These correspond to a shot weight of [redacted], when the concentration of



active in the formulation is used for calculations. The formulation density is _____, at _____ The density, when combined with the nominal valve metering chamber volume of _____ indicate the valve delivery should be 58 mg per actuation. The label claim drug delivered per actuation must be re-evaluated and revised when data is received from CU under conditions of 30 L/min for 4 sec (2.0 L per determination).

3. The labeling should indicate _____
4. The dependency of drug delivery on the flow should be reflected in the labeling. The amount of drug delivered at the mouthpiece and the fine particle mass are directly dependent on the flow rate. For example, the dose
[_____]
5. Target fill weights are _____ for 60 and 120 actuation units, respectively. The minimum fill weights (p. 4: 46) are 5.1 g and 8.9 g, respectively. The applicant has been requested to decrease the range of allowable fill weights.
6. Fill weight necessary to deliver 60 and 120 actuations based on shot weight are _____ (taking into account the mean leak rate over 2 years). This calculates to overfills of _____, respectively at the label claim, and _____ at the current minimum fill weight. The canister has a nominal volume of _____. The formulation density is _____ at _____.
7. The Bepak actuator/spacer is a two-piece assembly with an orifice diameter of _____.
8. The spacer has an internal capacity of 50 mL.
9. An FUR was issued 3/21/02 for all sites. WITHHOLD status report was received from OC 6/5/02 for application. All sites are acceptable except WITHHOLD recommendations issued 6/5/02, 5/13/02, and 4/8/02, for 3M Pharmaceuticals _____ and Forest _____ Laboratories, respectively.
10. 3M _____ The following comment from the Director LADO is inserted in EES under the DO WH recommendation for the _____ TWO PRE APPROVAL INSPECTIONS HAVE BEEN CONDUCTED FOR THIS PRODUCT. THE FIRST PAI RESULTED IN A RECOMMENDATION TO WITHHOLD APPROVAL, DUE TO THE FIRM CONTINUING DEVELOPMENT OF THE _____ MANUFACTURING METHOD AFTER THE CLINICAL BATCHES WERE MANUFACTURED (SEE DO RECOMMENDATION OF 19-DEC-2000). THE SECOND PAI WAS CONDUCTED IN RESPONSE TO A FOR CAUSE ASSIGNMENT FROM HFD-324, AND RESULTED IN A WITHHOLD RECOMMENDATION DUE TO THE FIRM CHANGING THE FILLING TECHNOLOGY FROM WHAT WAS FILED IN THE NDA. THE FIRM STATED IN THEIR RESPONSE THAT THE FILLING PROCESS WOULD NOT BE CHANGED. A TELECON WAS HELD WITH _____ PLANT QUALITY ASSURANCE MANAGER OF 3M PHARMACEUTICAL ON 4/15/02 AND 4/16/02 TO DISCUSS THE STATUS OF NDA 21-247 FLUNISOLIDE HFA. MR. _____/STATED THAT NO CHANGES HAD OCCURRED WITH RESPECT TO THE PRODUCT SINCE THE LAST INSPECTION. THE FIRM HAD STATED IN THEIR MARCH 7, 2001 RESPONSE TO THE FDA 483 THAT THE APPLICANT (FOREST) WAS TO NOTIFY CDER THAT _____ EQUIPMENT WILL BE USED TO MANUFACTURE FLUNISOLIDE HFA IN ACCORDANCE WITH THE PROCESS FILED IN THE NDA. MR. _____ CONFIRMED THIS AGAIN VERBALLY ON THE TELEPHONE. LOS-DO KNOWS OF NO REASON WHY ANOTHER INSPECTION SHOULD BE CONDUCTED AT THIS FIRM. THE DISTRICT CONTINUES TO RECOMMEND WITHHOLDING APPROVAL BASED ON THE REASONS PREVIOUSLY STATED IN THE 19-DEC-2000 DO RECOMMENDATION MILESTONE. This issue must be clarified with the OC or LADO. The applicant has stated that only _____ filling will be used.
11. Forest _____ Laboratories site: The stability testing site at Forest/ _____ Laboratories _____ has been issued a WH recommendation because it is not performing the function indicated in the application. The



OC has made the following comment in EES: FIRM DOES NOT CONDUCT ANY TESTING AT THE _____ SITE. THIS FACILITY IS USED EXCLUSIVELY FOR PACKAGING OF FINISHED PRODUCT AND STORAGE OF STABILITY SAMPLES. The applicant states that this site is responsible for release and stability testing on page 4: 59 of the original application. The applicant needs to address this discrepancy. They also need to specify a site for stability testing. There are no sites designated with this responsibility in the application.

- 12. The _____ facility in _____ was issued a WH recommendation. The inspector entered the following comment into the EES system: THIS INSPECTION OF A CONTROL-TESTING LABORATORY WAS CONDUCTED IN RESPONSE TO A PRE-APPROVAL ASSIGNMENT FOR FLUNISOLIDE HFA INHALER NDA 21-247. THE APPLICANT WAS FOREST LABS LOCATED _____. THE APPLICATION SPECIFIED THAT _____ WOULD PERFORM TESTING OF THE DRUG SUBSTANCE. THE PRE-APPROVAL ASSIGNMENT ALSO REQUESTED GMP COVERAGE AT THE FACILITY. (FACTS ASSIGNMENT ID 1158943 AND OPERATION ID 961454). THE PREVIOUS INSPECTION AT THE FACILITY WAS CONDUCTED IN 4/2000 AND WAS CLASSIFIED "NAI". THE CURRENT INSPECTION FOUND THAT THE _____ FACILITY IN _____ HAD SUFFERED DAMAGE DUE TO A FIRE IN FEBRUARY 2002 AND WAS NOT OPERATIONAL. THE FIRM IS NOW IN THE PROCESS OF SETTING UP NEW LABORATORY OPERATIONS AT A FACILITY IN _____. THE _____ FACILITY WAS NOT OPERATIONAL AT THE TIME OF THIS INSPECTION; THEREFORE, NO INSPECTION COULD BE PERFORMED.
- 13. The applicant has withdrawn the Forest Pharmaceuticals Inc. _____ site from the application in the 11/9/00 amendment.
- 14. The applicant has been requested to institute a _____ period, as well as required testing, into their Master Batch Record. The applicant may not need to provide controls for a maximum: _____ period, since this requirement is less critical for a solution MDI. The Leakage Rate and thus Valve Delivery appear to stabilize after a sufficient period.
- 15. Data from the following studies need to be submitted:

a.

b.

c.

d.

e.

f.

g.



16. The labeling must be revised to indicate the need to prime the device after storage for two weeks.

17.

[

]

18.

[

]

19. The labeling must be revised to include a warning that failing to inhale strongly prior to actuation causes inadequate drug delivery from the spacer. A supplemental statement must be included to indicate that only 25% or less of the label claim of drug is delivered if the inhalation is delayed by as much as one second.

20. Forest has committed to repeat the tests given by [redacted] the Certificate of Compliance for the first three lots intended for commercialization. Thereafter, Forest commits to test every [redacted] lot manufactured by [redacted] annually. In addition, Forest commits to testing the first three commercial lots for extractables using Forest test procedure [redacted] and for product performance measured by [redacted]), and medication delivery/through life (test methods [redacted]).

21.

[

]

22. We have not yet evaluated the limited and incongruous data to evaluate the proposed expiration dating period. The stability data provided are inadequate owing to

[

]

23. A microbiology consult is not needed since the proposed acceptance criteria have been previously allowed in other applications.

24. A description of the investigational and stability batches is provided in the 6/13/00 amendment. No other formulations were used in IND studies.

25. The applicant has applied for a categorical exclusion (p. 4: 388) under 21 CFR 25.31(b) and is justified in doing so.

26. Methods validation will be accomplished in FDA laboratories once the drug product specifications have been agreed to.

27. Forest must be made responsible for extractables and leachables testing and drug product specifications.



III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Brian Rogers/6/5/02
Guirag Poochikian/6/5/02
Ladan Jafari/6/5/02

C. CC Block

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Deliberative Process (b5)

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this page is the manifestation of the electronic signature.**

/s/

Brian Rogers
6/5/02 05:34:58 PM
CHEMIST

Guiragos Poochikian
6/5/02 06:23:01 PM
CHEMIST

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

NDA #: 21-247 **CHEM. REVIEW #:** 1 **REVIEW DATE:** 4/27/00

RECOMMEND ACTION: NOT APPROVABLE

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	4/27/00	4/27/00	5/11/00
Amendment	6/2/00	6/5/00	6/9/00
Amendment	6/13/00	6/14/00	6/16/00
Amendment	9/21/00	9/22/00	9/22/00
Amendment	9/22/00	9/25/00	10/13/00
Amendment	10/2/00	10/3/00	10/13/00
Amendment	11/9/00	11/15/00	11/26/00
Amendment	12/26/00	12/27/00	12/28/00

NAME & ADDRESS OF APPLICANT: Forest Laboratories, Inc.

DRUG PRODUCT NAME:

Proprietary:

None

Nonproprietary/USAN:

flunisolide HFA-134A inhalation aerosol

Code Name/#:

Chem. Type/Ther. Class:

6S

PHARMACOL.

Treatment of asthma as prophylactic therapy in adult/pediatric patients four years of age and older/for patients requiring oral corticosteroid therapy for asthma. inhalation aerosol

CATEGORY/INDICATION:

DOSAGE FORM:

STRENGTHS:

Delivers 139 µg flunisolide hemihydrate per actuation from the valve, and 85 µg flunisolide hemihydrate from the spacer (using 30 L/min for 5 sec). Valve delivery is 58 mg

ROUTE OF ADMINISTRATION:

Oral Inhalation; 1 act. bid; max. _____

DISPENSED:

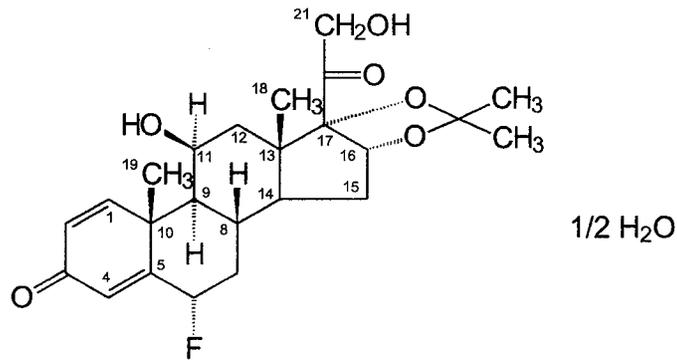
Rx OTC

SPECIAL PRODUCTS:

YES NO

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

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

Flunisolide hemihydrate
 $C_{24}H_{31}O_6F \cdot 1/2 H_2O$
 MW 443.51

SUPPORTING DOCUMENTS:**DMFs**

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in Reviews
_____	_____	_____	Inadequate	10/2/00 by CHKim	p. 5 of CR 1
_____	_____	_____	Adequate	10/15/99 by KSwiss	p. 76 of CR 1
_____	_____	_____	Adequate	2/27/97 by MChun	None
_____	3M Pharmaceuticals, Inc.	Valve Type III	Inadequate	4/27/01 by Rogers	p. 76 of CR 1
_____	3M Pharmaceuticals, Inc.	Container Closure Extractables	Inadequate	4/27/01 by Rogers	p. 76 of CR 1
_____	_____	_____	Inadequate	4/27/01 by Rogers	p. 76 of CR 1
_____	Bespak	Actuator/Spacer	Inadequate	4/17/01	p. 76 of CR 1

RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject
IND	51,456	Forest Laboratories	Aerobid (flunisolide hemihydrate in HFA-134a)
IND	_____	_____	_____
NDA	18-340	Forest Laboratories	Aerobid (flunisolide hemihydrate inhalation aerosol)

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	Submitted	Withhold	ACCEPTABLE EER status report was received 3/8/01 for all sites except WITHHOLD recommendation issued 2/23/01 for 3M Pharmaceuticals
Microbiology, HFD-160	No Microbiological consult will be issued owing to having previously accepted specifications		
Biometrics, HFD-710	To be requested once specification are finalized and additional stability data are submitted/reviewed	Deferred	
Environmental Assessment	Not applicable		Applicant has applied for a categorical exclusion.
Labeling & Nomenclature Committee	To be requested once a trade name is proposed.	Deferred	Action incomplete

CONCLUSIONS AND RECOMMENDATIONS:

The application as submitted is not approvable from the standpoint of chemistry, manufacturing and controls. Deficiencies are detailed in the accompanying review notes and summarized in the attached draft letter to the applicant, chemistry portion.

cc:

Orig. NDA 21-247

HFD-570/Division File

HFD-570/BRogers/4/27/00

HFD-570/SBarnes

HFD-570/GPoochikian

HFD-570/DBirenbaum

HFD-800/CHoiberg

R/D Init. by: _____

filename: 21247.001.doc

 Brian D. Rogers, Ph.D. Review Chemist

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REMARKS/COMMENTS:**Drug Substance**

- 1 All information pertaining to the drug substance is referenced to the content of _____
_____ DMF _____. DMF _____ includes two sites for manufacture of the drug
substance. The other is _____ was inspected and found unacceptable.
- 2 DMF _____ for drug substance manufacture has been reviewed and found inadequate to support
this application. A letter was sent to the holder dated 11/7/00.
- 3 An EES request was sent 9/1/00 for these sites. An ACCEPTABLE EER status report has been
received for _____ dated _____. A WITHHOLD recommendation was received for
_____. A note in EES from OC stated "PER 1/23/01
LETTER FROM _____ WILL CEASE PRODUCTION IN 2 MONTHS. REQUEST
SHOULD BE CANCELLED WHEN OFFICIALLY WITHDRAWN." We have recommended that the
applicant provide a statement withdrawing this site from consideration.
- 4 The PSD is not controlled as a profile since the drug product _____

- 5 No data has been received from drug product manufactured from flunisolide hemihydrate made at
the proposed site for flunisolide hemihydrate manufacture. According to the latest amendment in
DMS _____, no production-scale batches of flunisolide hemihydrate have yet been
manufactured at _____ facility. The holder has just submitted accelerated stability data from
registration batches. No long-term stability data are available

Drug Product

1. Flunisolide hemihydrate HFA contains a solution of 0.24% flunisolide hemihydrate in Dehydrated
Alcohol, USP and a _____ hydrofluorocarbon propellant (HFA-134a) in a _____
_____ aluminum _____ can fitted with _____ valve. The device
includes a _____ mouthpiece/actuator/spacer.
2. Pack Sizes proposed are 120-actuation and 60-actuation sizes using identical canister and valve.
Both of these presentations deliver 139 µg flunisolide hemihydrate from the valve and 85 µg from
the spacer at a flow rate of 30 L/min for 5 sec. These correspond to a shot weight of approximately
58 mg.
3. The labeling should indicate that the product must be primed with two actuations after _____
when two actuations per dose are used.
4. The dependency of drug delivery on the flow should be reflected in the labeling. The amount of
drug delivered at the mouthpiece and the fine particle mass are directly dependent on the flow rate.
For example, the dose delivered per actuation

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5. Target fill weights are _____ for 60 and 120 actuation units, respectively. The minimum fill weights (p. 4: 46) are 5.1 g and 8.9 g, respectively. The applicant has been requested to increase the minimum fill weights.
6. Fill weight necessary to deliver 60 and 120 actuations based on shot weight are _____. This calculates to overfills of _____, respectively at the label claim, and _____ at the minimum fill weight.
7. The Bepak actuator/spacer is a two-piece assembly with an orifice diameter _____
8. The spacer has an internal capacity of _____
9. ACCEPTABLE EER status report was received 3/8/01 for all sites with the following exceptions:

WITHHOLD recommendation issued 2/23/01 for 3M Pharmaceuticals _____
WITHHOLD recommendation issued 11/14/00 for Forest Laboratories _____
10. The applicant has subsequently withdrawn the _____ site from the application in the 11/9/00 amendment. The _____ Forest Laboratories site is the correct site for performing drug product release and stability testing.
11. The Master Batch Record has no description of a lagging period or testing to be accomplished after this storage. The applicant has been requested to institute both a minimum and maximum lagging period, as well as required testing, into their Master Batch Record.
12. Data from the following studies need to be submitted:
 - a. The mass of drug deposited in the actuator and spacer under defined *in vitro* conditions.
 - b. Plume geometry characterization
13. Forest commits (p. 4: 532) to retest, on an annual basis, one lot of actuator/spacers according to the specifications provided by Bepak on their COC and for extractables and product performance. This commitment may not be adequate. The form of this commitment will depend on the results from testing of the first three commercial batches of actuator/spacers. The number of batches tested annually need to be specified as a fraction of total production. There also needs to be specified a minimum set of acceptance specifications.
14. [_____]
15. The applicant has been asked to modify the actuator/spacer pivot and/or interference ridges to increase the reliability and reproducibility of the angle between the actuator and the spacer when positioned for releasing an actuation for patient dosing. We feel that this angle may vary widely in the hands of patients and needs to be more precisely fixed in-use.
16. The applicant has been asked to modify the Patient Package Insert to reflect both a correct and incorrect finger placement for using the device to aid in the reliability of dosing. The correct finger

placement must have the spacer supported by some portion of the thumb to hold the spacer firmly against the actuator. The incorrect finger placement is as shown currently in the Patient Package Insert, with the thumb held against the side of the actuator.

17. Another design change requested is to

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18. The applicant was requested to institute a control on

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19. The actuator and spacer are extremely easy to separate by light pressure on the top and bottom of the spacer, deforming this portion of the device. The effect of this pressure is to expand the sides of the spacer and thus withdraw the spacer pins from the slots on the sides of the actuator. The applicant was asked to providing any information in their possession on the effect of this structural weak point on the use of this product.

20. Forest commits (p. 4: 532) to testing the first three commercial lots of actuator/spacers manufactured by Bepak according to the methods and specifications provided by Bepak on their Certificate of Compliance (COC). In addition, Forest commits to testing the first three commercial lots for extractables using Forest test procedure PRD-641 and for product performance measured by PSD (test method PRD-633P), and medication delivery/through life (test methods PRD-637 or PRD-567).

21. Forest commits (p. 4: 532) to retest, on an annual basis, one lot of actuator/spacers according to the specifications provided by Bepak on their COC and for extractables and product performance. This commitment may not be adequate (see deficiencies).

22. We are unable to evaluate the limited and incongruous data to evaluate the proposed expiration dating period. The stability data provided are inadequate owing to

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23. A microbiology consult is not needed since the proposed acceptance criteria have been previously allowed in other applications.

24. A description of the investigational and stability batches is provided in the 6/13/00 amendment. No other formulations were used in IND studies.

25. The applicant has applied for a categorical exclusion (p. 4: 388) under 21 CFR 25.31(b) and is justified in doing so.
26. Methods validation will be accomplished in FDA laboratories once the analytical methods have been finalized.

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 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

/s/

Brian Rogers
5/3/01 04:44:45 PM
CHEMIST

Guiragos Poochikian
5/3/01 05:04:23 PM
CHEMIST

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 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)