

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-247

APPROVABLE LETTER



NDA 21-247

Forest Laboratories, Inc.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

Attention: David A. Lust,
Associate Director, Regulatory Affairs

Dear Mr. Lust:

Please refer to your new drug application (NDA) dated April 27, 2000, received, April 27, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aerospan (flunisolide HFA) Inhalation Aerosol.

We acknowledge receipt of your submissions dated February 5, and 21, May 1, June 5, and 10, July 1, and 16, 2003.

The February 5, 2003, submission constituted a complete response to our January 10, 2002, action letter.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies. (Note that parenthesis following our comments refer to the comments listed in the May 8, 2003, Discipline Review Letter.)

1. Provide an agreement to submit data from flunisolide hemihydrate analysis, as requested in Comment 2 of our letter dated May 8, 2003, for drug substance used in all batches of drug product (Comment 2).
2. Provide updated specification sheets for both presentations of the drug product once we have agreed to all specifications (Comment 6).
3. As stated in our letters dated May 8, 2003 and June 11, 2002, the method provided for Plume Geometry evaluation is inadequate. Evaluate the characteristics of the plume geometry for this product with a method capable of determining the 3-dimensional geometry of the plume, as a function of time after actuation, from two directions orthogonal both to each other and the generated plume. Provide actual photographs of the plume at the various time points (Comment 10).

4. As stated in our letter dated May 8, 2003, the proposed levels of _____ in the drug product are not reflective of the data provided. Tighten the acceptance criteria for _____ to NMT — % at release and NMT — % over the shelf life (Comment 11).
5. The data on pages 241 and 242 in Appendix 7 are both attributed to analysis of Lot P02390 at the 24-month time point, inverted, at the beginning-of-can. Clarify the identity of these data (Comment 14).
6. The mass deposited in the actuator/spacer, the Mass Balance as measured in the particle size distribution method (Attachments 7 and 8), and the Dose Delivery from the Valve data (Attachment 10) are all consistent in that they all show an expected level of variability from beginning- to end-of-canister. Provide data from an investigation to improve the unacceptable variability seen from the beginning- to the end-of-canister in the method *Through-Life/Medication Delivery Assay for HFA 134a Flunisolide Hemihydrate MDI, 0.24% w/w, — μ L Valve* (Comments 14 and 16).
7. We are withholding comments on delivered dose per actuation pending receipt of the results of the investigation into the analytical method *Through-Life/Medication Delivery Assay for HFA 134a Flunisolide Hemihydrate MDI, 0.24% w/w — μ L Valve* (Comments 14 and 16).
8. The change requested pertaining to the drug delivery per actuation in the Physician's Package Insert is incompletely implemented. Modify the statement in the Physician's Package Insert to accurately reflect the request as shown in Comment 15 in our letter dated May, 5, 2003 (Comment 15).
9. DMF _____ is inadequate to support your application. A letter was sent to the DMF holder (Comment 19).
10. As stated in our letter dated June 11, 2002, comments on the expiration dating period are deferred pending agreement on acceptance criteria for _____, and satisfactory completion of the investigation of the _____ (Comment 20).
11. List the acceptance criteria for leachables as requested in Comment 29 of our letter dated June 11, 2002. The acceptance criteria are not listed, but instead there is a statement that the leachables are controlled as extractables at the component level. This footnote should be referenced by the parameter and not take the place of the acceptance criteria. As commented on previously, this statement is premature and still depends on establishing an acceptable extractables/leachables correlation (Comment 21.a.).
12. Submit to the application an updated stability protocol containing all changes adopted in response to Comments 21.b-e in our letter dated May 8, 2003. Please note that the change requested in Comment 21.e. was not included in your commitment letter in Attachment 12. This statement must also be included in the updated stability protocol (Comment 21.b-e.).

13. Since there are numerous unclear issues pertaining to the performance characteristics of your drug product, the number of batches proposed to be placed annually in your stability testing program is inadequate. Provide a proposal to increase this number until such time as the performance characteristics of your drug product are more completely characterized over time (Comment 21.b.).

14. The following information pertaining to extractables and leachables testing is requested as indicated in our previous letter (Comment 22).

a. The footnote in the specification sheet and the Stability Protocol pertaining to the establishment of a relationship between extractables and leachables in the listing of leachables acceptance criteria is premature and has not yet been agreed to. In order to establish a correlation between extractables and leachables, there must be: 1) data on extractables from appropriately validated method(s) with adequate Limits of Detection and Limits of Quantitation; 2) data on leachables, from appropriately validated method(s) with adequate Limits of Detection and Limits of Quantitation, from at least three batches of drug product or placebo formulation throughout the shelf life, and preferably from batches of drug product manufactured with the gasket batches tested for extractables; 3) asymptotic behavior of both the extractables and leachables' levels over time in their respective determinations; and 4) the levels of extractables must in all cases be equal to or greater than the levels of leachables on a per-valve basis.

b. The specification sheet and stability protocol shows "N/A" in the method and "# of samples/interval" for leachables instead of a method number. Method numbers, sampling frequencies, and testing intervals must be specified since periodic leachables testing is required.

c. Modify the specification sheet and stability protocol to include appropriate limits for *any unspecified*: _____

_____s; where the acceptance criteria for "any unspecified" and "total" leachables of each category are derived from the appropriate LOQ or the sum of the LOQs for each individual, respectively.

15. Provide samples of the modified drug product with canisters to assist in our evaluation of your proposed changes in the actuator/spacer design (Comments 25.a-e.).

16. Label both the spacer and actuator since the label on the actuator is not visible when the unit is closed (Comment 26.c.).

Provide draft and mockup labeling incorporating the following preliminary labeling comments.

17. The following are preliminary CMC comments. Apply these to all labeling where appropriate (Comment 26.d.).

a. Modify all labeling to indicate that the recommended storage conditions are — 25°C.

- b. Since the name *Aerospan* is associated with the delivery system, change the established name in all instances to *Aerospan (flunisolide HFA inhalation aerosol)*.
- c. Increase the **prominence** of the established name to be equal to that of the proprietary name and increase its size so that it is at least half as large as the letters comprising the proprietary name in accordance with 21CFR201.10(g)(2).
- d. Modify the net contents of the canisters to 5.1 g and 8.9 g for the 60- and 120-actuation presentations, respectively, and label the values as the "net weight".
- e. The usual dosage stated on the container label and carton labeling differs from the package insert labeling. The container label and carton labeling state that the usual dose is _____ However, the specifics of the _____ are not stated under the *Dosage and Administration* for either adults (lines 528-530) or children (lines 532-534). The usual dose including any specifics _____ should be the same throughout the product's labels and labeling.
- f. Insert the NDC code on the professional sample labeling where applicable.
- g. Change the term *Metered Inhalations* to read *Metered Actuations* for consistency with actuation content statement.
- h. The drug delivered per actuation is not yet determined. This value may be changed once additional data is submitted.
18. The following are preliminary CMC comments on the canister labels.
- a. To increase readability, remove statements pertaining to _____
 _____ Increase the font size of the remaining lettering on that portion of the canister label and that within the black box.
- b. Decrease the prominence of the net quantity statement and increase the prominence of the number of total metered actuations.
- c. Modify the statement: _____
 _____ Increase the prominence of this statement to give better visibility.
- This statement may need to be further modified once all changes have been instituted and the labeling reevaluated.
- d. Modify the statement: *Usual Dose:* _____
 _____ See package insert for dosage information to: **Important:** Do not take more inhalations or use more often than prescribed. See package insert for dosing and storage information.

e. Use the largest possible label for the canisters to assist in readability.

19. The following are preliminary CMC comments on the drug product carton:

a.

b.

c.

d. Modify the statement: *Usual Dose:* _____
SEE ACCOMPANYING PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION to: *Dosage:* Use only as directed by your doctor. **Important:** Read accompanying Patient's Instructions for Use leaflet carefully for further information.

e. Decrease the prominence of the net quantity statement and increase the prominence of the number of total metered actuations.

f. Insert the following statements.

- (1) Keep out of reach of children
- (2) Protect from freezing temperatures and direct sunlight
- (3) For best results, the canister should be at room temperature before use
- (4) Do not use this product with any external spacer devices.

20. The following are preliminary labeling CMC comments on the Package Insert:

a. *DESCRIPTION* section

- (1) Insert a description of the available presentations, including in each the number of actuations per container.

- (2) Insert both initial and used priming information into the paragraph that describes the emitted dose.
- (3) In addition to other attributes, include "pressurized" in the description of Aerospan.
- (4) Delete the paragraphs on lines 41-45 and lines 47-51.
- (5) Modify the sentence (lines 32-33) pertaining to include the solubilities of flunisolide hemihydrate in ethyl alcohol and HFA-134a, and delete references to the _____
- (6) Change all instances of the word "activation" to "actuation".
- (7) The statement: *Each activation delivers approximately _____* must be modified to: *Using an in-vitro method at a fixed volume of 2 L, each actuation at the beginning of canister content delivers 76 mcg (95% of the label claim) at a flow rate of 30 L/min, 61 mcg (76% of the label claim) at 20 L/min, 85 mcg (106% of the label claim) at 40 L/min, and 96 mcg (120% of the label claim) at 60 L/min.*

b. *HOW SUPPLIED* section:

- (1)  
- (2) The warning _____ must be substituted for the one on lines 578-580.
- (3) The warning *Do not use this product with any external spacer devices* must be added into the paragraph on lines 582-587.
- (4) Insert the statement *For best results, the canister should be at room temperature before use* into the paragraph on lines 582-587.

21. The following are preliminary CMC comments on the Patient Instructions for Use Pamphlet:

- a. Both the 120-and 60-actuation presentations must have individualized check-off matrices to allow patients to keep track of the number of actuations remaining in the canister. These matrices may be deleted ~~_____~~
The instructions for counting actuations must specify the number of actuations available in the package in the patient's possession.
- b. Insert instructions in the *How to Check the Contents of Your Canister* for the patient to use the check-off matrix to keep track of remaining actuations. Also insert a warning stating that the correct amount of medication in each inhalation cannot be ensured after the labeled number of actuations even though the canister may not be completely empty.
- c. Insert instructions in *Step Two, item 5* to instruct the patient to shake the inhaler prior to priming. Also, in this item, highlight the priming instructions.
- d. Bold line 729 which states "Shake the inhaler immediately before each use.
- e. Delete the section between lines 617 and 630.
- f. Insert instructions to:
 - (1) Not use the Aerospan device with any external spacer.
 - (2) Not use the Aerospan canister with other actuators or the device with other canisters.
 - (3) Not use after the date shown as "EXP" on the label or box.
 - (4) _____
- g. Insert the following instructions:
 - (1) REMEMBER: This medicine has been prescribed for you by your doctor. DO NOT give this medicine to anyone else.
 - (2) []
 - (3) Use your inhaler as directed by your doctor. _____
[]
- h. []

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described under 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file (an) amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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NDA 21-247

Forest Laboratories, Inc.
Harborside Financial center
Plaza 3, Suite 602
Jersey City, NJ 07311

Attention: Robert Ashworth, Ph.D.
Sr. Director, Regulatory Affairs

Dear Dr. Ashworth:

Please refer to your new drug application (NDA) dated April 27, 2000, received April 27, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aerospan (flunisolide HFA) Inhaler System.

We acknowledge receipt of your submissions dated January 3, February 14, March 7, and 29, June 29, August 28, October 11, and 24, and December 7, 2001. Your submission of December 7, 2001, constituted a complete response to our May 7, 2001, action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following. (Note that parenthesis following comments refer to comments in the May 7, 2001, approvable letter).

1. The following comments pertain to the drug substance specifications:
 - a. The specification sheet for the *Flunisolide Hemihydrate (for HFA Products) Pharmaceutical Grade* _____ must be complete, with all parameters and acceptance criteria (comment 1.e.).
 - b. We remind you of your commitment, as agreed to in our November 2, 2001, telecon, to reevaluate the _____ acceptance criterion once additional drug substance batches are manufactured at the _____ facility (comment 1.e.).
 - c. We remind you that the drug substance specifications have not yet been agreed to. Acceptance criteria for Related Substances are still dependent on satisfactory resolution of the issue outlined in comment 7.o. of the May 7, 2001, approvable letter and contained in comment 17 below (comment 1.e.).

- d. Revise your specification sheet for flunisolide hemihydrate to include your commitment to adopt _____ specifications for batches manufactured at the _____ site (comment 1.g.).
- e. As described in your submission dated August 28, 2001, and commented in our communication dated October 1, 2001, provide to the NDA a copy of the drug substance specifications and testing protocol for acceptance testing the flunisolide hemihydrate manufactured at _____ in the _____ and stored in _____ (comment 1.h.).
- f. The requirements for testing of flunisolide hemihydrate containers from _____ were proposed initially in your submission dated August 28, 2001, and commented on in our FAX response dated October 1, 2001. Submit to the NDA the test results for all flunisolide hemihydrate containers stored in the _____ facility (comment 3.b.).

2. The following comments pertain to the acceptance criteria for _____ USP:

- a. The alcohol assay must be obtained by direct measurement. Institute acceptance criteria and a test method for _____ Content (comment 3.c.).
- b. Tighten the following parameters in the acceptance criteria for _____ USP to the indicated levels to reflect the supportive data:

Water	NMT — % (w/w)
	NMT ppm

c. Alternatively, provide all available data from batches of _____ USP to justify your proposed acceptance criteria for the above impurities (comment 3.d.).

3. Currently, three of your proposed sites, the 3M site in _____ the Forest _____ Laboratories site in _____ and the _____ have unsatisfactory cGMP status. Satisfactory inspections will be required for all these facilities before this application may be approved (comment 4).

4. According to our records, the Forest _____ Laboratories site in _____ is not conducting any testing. The District Office reported that this facility is used exclusively for packaging of finished product and storage of stability samples. Clarify the actual function of your _____ facility. If no stability testing is to be performed at this site, provide to your application a site that will be responsible for drug product stability testing. Under these circumstances, also identify the site at which the stability testing is currently being and has historically been accomplished (comment 4).

5. []

6. []

7. []

8. []

[]

9. The following comments pertain to the method and acceptance criteria for *Particulate Matter in HFA-134a Flunisolide Hemihydrate MDI* (comment 7.d).

- a. _____
- b. []
- c. []
- d. _____
- e. _____
- f. []
- g. []
- h. _____

10. Provide complete analytical test results from all parameters in the batch whose particle size distribution data are provided on page 17 of your December 7, 2001, submission. Historical data, including batch identity and age, must be also provided for comparative purposes (comment 7.e).

- 11. []
- []

12.

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13.

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14.

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15.

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NMT	%
NMT	%
LT 0.	
NMT	%
LT 0.	
NMT	%
NMT	%

Total

Please note that at least two significant figures are to be adopted in the acceptance criteria for related impurities (comment 7.n.). Also note that we have no record of having agreed to your proposed acceptance criteria for _____ and _____, in the Telecon dated September 13, 2001.

16.

As stated in our letter dated May 7, 2001, the above comments on the related impurity levels are tentative pending evaluation of the impurity levels in drug product batches made from flunisolide hemihydrate from the _____ manufacturing facility. The permissible levels of

- 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 (comment 9.k.).
24. In order to perform periodic testing of the container-closure components to assure confidence in the values presented in the Certificates of Analysis from 3M, they must provide you or a laboratory acceptable to you with appropriate acceptance specifications (test methods and acceptance criteria) used for the actuator, container, valve, and each of its components. These may include extractables profile and performance characteristics (comment 10.a.).
 25. DMF — is inadequate to support your application. A letter was sent to the holder (comment 10.c.).
 26. Provide a final revised specification sheet for the actuator/spacer assembly once we have agreed to acceptance criteria for *Particle Size Distribution* via ~~—————~~ *Cascade Impactor* (comment 10.e.i.).
 27. Comments on the expiration dating period are deferred pending satisfactory resolution of various core issues (comment 10.i.i.).
 28. As stated in our letter dated May 7, 2001, include the quality, purity, and source of the drug substance and excipients in the stability protocol. This is desired for ease of future reference. Provide an updated stability protocol to the application (comment 10.i.ii).
 29. Include the test methods and appropriate acceptance criteria for leachables in both the drug product specification sheet and the stability protocol. If and only if you establish an adequately defined relationship between extractables and leachables, the parameter in both of the above documents may be modified by a footnote stating to the effect that leachables are normally controlled through extraction of the individual valve components (comment 10.i.iv.).
 30. The following comments pertain to your proposed post-approval stability protocol (comment 10.i.v.):
 - a. As stated in our letter dated May 7, 2001, provide an updated Stability Protocol containing commitments to place the first three production batches in the stability program, to place batches into the stability testing program annually based upon the number of production batches, and to require a prior-approval supplement containing real-time data to extend the expiration dating period (owing to limited stability data from the drug product manufacturing method and container and closure configuration intended for marketing). In addition, you must provide a commitment in the stability protocol to withdraw from the market any lot failing to meet the approved specifications for the drug product. If evidence exists that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, you will immediately discuss the out-of-specification result with FDA and provide justification for continued distribution of the lot.
 - b. Revise the stability protocol to include information on the packaging components (e.g., see the descriptions and table on page 4: 936 of the original submission).

31. As requested in our letter dated May 7, 2001, monitor and report peaks greater than or equal to _____ . The use of two significant figures is necessary to better define the boundary concentration and clarify the applicable rounding principle (comment 10.j.).
32. As requested in our letter dated May 7, 2001, provide data (or its location within the application) cross-referencing all manufactured drug product batches and the type of O-ring used (_____) and whether or not inline stress testing had been performed on the batches. The amendment you cited dated November 9, 2000 does not contain all the requested data (comment 11).
33. The following are comments pertaining to the design and manufacture of the actuator/spacer assembly (comment 10.h.v.).
 - a. The actuator and spacer are extremely easy to separate. Modify the spacer or actuator to make separation more difficult. If the spacer is stiffened, it may be advisable to indicate the points on the spacer to press to separate the two pieces.
 - b. Modify the actuator/spacer assembly to make it very difficult for a patient to insert the actuator into the spacer with the actuator rotated 180° along its longitudinal axis from its intended orientation (i.e., where it would spray backwards).
34. The following are preliminary comments pertaining to labeling of the actuator/spacer assembly.
 - a. The words *Inhaler* _____ should be deleted from all labeling.
 - b. As required in 21CFR201.10(g)(2), the established name shall in all cases be printed with a prominence commensurate with the prominence with which the proprietary name or designation appears. This requirement applies equally to the printing on the spacer and actuator as on the other portions of the labeling.
 - c. The actuator must be suitably labeled.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

We recommend that a meeting be held to discuss and help resolve the above issues.

When you respond to the above deficiencies, include a safety update as described under 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.

Director

Division of Pulmonary and Allergy Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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Food and Drug Administration
Rockville MD 20857

NDA 21-247

Forest Laboratories, Inc.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

5/7/01

Attention: Lester S. Gibbs, Ph.D.
Manager, Regulatory Affairs

Dear Dr. Gibbs:

Please refer to your new drug application (NDA) dated April 27, 2000, received April 27, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for flunisolide HFA inhalation aerosol.

We acknowledge receipt of your submissions dated May 31, June 2, 13, 16, August 28, September 21, 22, 27, October 2, 19, November 9, and December 26, 2000, February 14 and March 29, 2001.

We also refer to your submissions dated December 4, 2000 and January 3, and March 7, 2001. These submissions have not been reviewed in the current review cycle. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following deficiencies.

1. The following comments pertain to the drug substance.
 - a. DMF — was reviewed and found inadequate to support this application. A letter was sent to the holder dated November 7, 2000.
 - b. We have been informed in a letter dated January 23, 2001, from — that — will not be manufacturing flunisolide hemihydrate in two months from the date of the letter. Provide a statement withdrawing this site from consideration for approval of this application.
 - c. Provide Certificates of Analysis from three production-scale batches of flunisolide hemihydrate manufactured at the proposed — facility. The Certificates of Analysis must specify the production batch size and contain complete analytical results.
 - d. To support the use of the — facility to manufacture flunisolide hemihydrate, provide all available drug product stability data from drug product batches manufactured with drug substance manufactured at the — facility.

- e. The acceptance criteria (e.g., _____, etc.) for the drug substance are inadequate. Tighten these acceptance criteria significantly to reflect the available data.
 - f. The use of _____ of the drug substance is inadequate to control the _____. Implement an upper limit to allowed _____.
 - g. Provide a commitment to adopt specifications for the drug substance once they are agreed to between the Agency and Syntex.
 - h. Once finalized, provide updated specifications and test methods (including sampling plan) for acceptance testing of the drug substance. Also, provide data obtained from various batches using the above methods to confirm the ability to verify your results on the certificate of analysis.
2. Provide the headspace volume for both drug product presentations when filled to the target volume with the valve in place.
3. The following comments pertain to acceptance testing of the drug product components.
- a. Perform Identity testing on every received lot of flunisolide hemihydrate drug substance.
 - b. Submit all analytical test methods for acceptance of the drug substance as well as all available results to the application.

c. []

d. []

Water []

NMT _____
NMT | ppm
NMT | ppm

period must be justified by appropriate stability data.

- d. Include 100% check weighing and spray testing as test parameters after the lagging period.
- e. Provide data on the rejection rate of canisters on a per-batch basis after lagging. Propose acceptance criteria for check weighing and spray testing after lagging.
- f. The allowed variability for drug substance particle size is quite large. Provide the results of studies on the following variables to achieve an adequate understanding of the ramifications of this allowed variability on manufacturing:
 - (i) Study the effect of drug substance particle size (in particular on the upper part of the allowed range of particle sizes) on its dissolution rate in the formulation under the conditions encountered during manufacture.
 - (ii) Study the effect of drug substance particle size on bulk formulation uniformity over the time required for filling, and thus beginning- to end-of-batch content uniformity
- g. 

h. Provide assurance that no filling procedure other than the _____ will be used for drug product manufacturing. If a different filling procedure is to be adopted for manufacture of marketed product, submit appropriate supportive data and revised Master Batch Records. 

- 6. The following comments pertain to the Master Batch Records for both presentations of the drug product.
 - a. Specify the intervals (e.g., every 1000 units) between subsequent checks for drug build-up on the fill valve nozzle surface and for cleaning (if required).
 - b. Include periodic checking of the flow _____, and specify the period between checks for this parameter.
 - c. Specify the minimum duration after which filling down time must be recorded. The use of the word _____ in describing unallowable downtime is unsatisfactory. The allowable downtime should be validated as not affecting the performance of the subsequently manufactured drug product.
 - d. Submit an updated Master Batch Record that includes all modifications. Please provide an index to locations of all changes to the Master Batch Record.

7. The following comments pertain to the acceptance criteria for the drug product.
- a. For *Identification*, institute a second, non-spectrometric test for Identity of the drug product.
 - b. The wording of the acceptance criteria for *Identification* needs to be changed to "The intensity and frequency of maxima in the infrared absorbance spectrum of the sample are identical to that of the standard spectrum."
 - c. Reference for inspection, in the acceptance criteria for *Appearance*, the appearance of all container and closure components including the valve, actuator, spacer, and canister. These components must conform to their respective descriptions as an indication of the drug product integrity. In addition, state in the acceptance criteria for the canister that the interior of the canister must be free from corrosion and any other visible defects.
 - d. Include a separate test method and acceptance criteria for *Particulate Matter*. This test must control particulates of any size and description other than those indigenous to the sprayed and captured formulation. Data must be provided which allow acceptance criteria to be created limiting the identity, size and quantity of all particles that are not flunisolide hemihydrate. In this regard, we suggest evaluating and identifying all foreign particles in an ethanol solution of formulation. The solution may be either from actuations or from evaporation residue directly from canisters. Once foreign particulate matter is quantitated and identified from representative batches of drug product, apply appropriate acceptance criteria reflecting the data obtained (e.g., number of particles less than 10 μm , greater than or equal to 10 μm , and greater than 25 μm).
 - e. Comments on the acceptance criteria for *Water Content* are withheld pending evaluation of the effect of water content on the formulation through stability testing and subsequent analysis.
 - f. The proposed acceptance criteria for *Ethanol Content* are inadequate to insure a solution formulation at _____ and must be tightened to _____.
 - g. Modify the acceptance criteria for *Leakage Rate* to be reflective of the data as follows:

The average leakage rate of 12 canisters is not more than _____ per year, and none of the canisters leaks more than _____ g per year. If 1 container leaks more than _____ mg per year, and if none of the canisters leaks more than _____ per year, determine the leakage rate of an additional 24 containers.

Not more than _____ of the 36 canisters leak more than _____ per year, and none of the 36 canisters leak more than _____ per year.
 - h. The stability data provided do not support the *Fill Weight* acceptance criteria. Tighten the acceptance criteria to _____ for the 60-actuation presentation, and _____ the 120-actuation presentation. Include the target fill weight in the statement of the acceptance criteria.

- i. The following comments pertain to acceptance criteria for Fine Particle Fraction.
- (i) Rename the parameter *Fine Particle Fraction* to *Particle Size Distribution via _____ Cascade Impactor*.
 - (ii) Your proposed acceptance criteria for *Fine Particle Fraction* do not provide an acceptable level of control over the particle size distribution. Provide a proposal for acceptance criteria for *Particle Size Distribution via _____ Cascade Impactor* that both reflect the provided data and group stages in a way that controls width, height, and position of the distribution. All groupings must have controls on both mean and individual determinations. Comments on groupings and acceptance criteria are withheld pending receipt of updated stability data.
 - (iii) Evaluate the particle size distribution data at 40°C/75% RH up to 6 months. If a significant change is observed, a study must be conducted at 25°C/75% RH for at least one third of the proposed expiration dating period and stability studies at 30°C/60% RH for 12 months must be conducted. If significant particle size changes are still seen in the 25°C/75% RH study, then appropriate steps should be taken to reduce this change (e.g., storage temperature change, overwrap, etc.).
 - (iv) For ease of review and data analysis, provide an update of both mean and individual cascade impactor data in Excel spreadsheet format.
- j. Adopt the following acceptance criteria in *Content Uniformity/Medication Delivery*.
- Tier 1 - The mean medication delivery of flunisolide hemihydrate of the 10 canisters is within 72-98 µg or 85-115% of Label Claim. Not more than 1 of the 10 canisters delivers outside of 68-102 µg or 80% to 120% of Label Claim, and none of the 10 canisters are outside of 64-106 µg or 75-125% Label Claim.
- Tier 2 - If 2 or 3 canisters are outside of 68-102 µg or 80-120% Label Claim, none of the canisters are outside of 64-106 µg or 75-125% Label Claim, and the mean is not outside 72-98 µg or 85-115% Label Claim, test 20 additional canisters. The mean of the 30 canisters is within 72-98 µg or 85-115% Label Claim. Not more than 3 of 30 canisters are outside of 68-102 µg or 80-120% Label Claim, and none of the 30 canisters are outside of 64-106 µg or 75-125%.
- k. Adopt the following acceptance criteria in *Through-Life/Medication Delivery*.
- Specifications apply to Beginning, Middle and End
- Tier 1 - Assay 3 canisters at the beginning, middle and end of the canister contents. The mean medication delivery of flunisolide hemihydrate for each of the beginning, middle, and end determinations is within 72-98 µg or 85-115% of Label Claim. Not more than 1 of the 9 determinations delivers outside of 68-102 µg or 80% to 120% of Label Claim, and none of the 9 determinations are outside of 64-106 µg or 75-125% Label Claim.

Tier 2 - If 2 or 3 of the 9 determinations are outside of 68-102 µg or 80-120% Label Claim, and none of the individual means are outside 72-98 µg or 85-115% Label Claim, test 7 additional canisters. The mean for each of the beginning, middle, and end determinations is within 72-98 µg or 85-115% Label Claim. Not more than 3 of the 30 determinations are outside of 68-102 µg or 80-120% Label Claim, and none of the 30 determinations are outside of 64-106 µg or 75-125%.

- l. Regarding the acceptance criterion for *Assay*, revise the limits for flunisolide hemihydrate content in each canister to be 0.216% - 0.264% w/w (0.240 w/w ±10%). No second-tier testing is permitted.
- m. The *Spray Pattern* and *Plume Geometry* from the actuator (minus the spacer component) needs to be controlled. Implement appropriate test methods and acceptance criteria.
- n. The acceptance criteria for *Impurities* should be modified to the following (see Comment 7.0. below):

	┌	NMT: _____
		NMT: _____
		LT: _____
		NMT: _____
	└	LT: _____
Total		NMT: _____

Insert a parameter into the acceptance criteria for *Impurities* to provide control over total unspecified related impurities. Submit a proposal with supportive data for the corresponding acceptance criterion.

The above comments on the related impurity levels are tentative pending evaluation of impurity levels in drug product batches made from flunisolide hemihydrate from the _____ manufacturing facility.

- o. The following comments pertain to toxicological evaluation and qualification of _____ and _____ levels in the drug product.
 - (i) Provide any available data on whether these compounds are metabolites in animals or humans.
 - (ii) Provide data on levels of _____ and _____ in the batches of flunisolide hemihydrate used in the multi-dose pre-clinical studies longer than 3 months duration. Provide data on the levels of flunisolide _____ present in the flunisolide hemihydrate batches used in the carcinogenicity studies.
 - (iii) If the above data are not available, conduct a 3-month inhalation study in the most appropriate species for both _____ and _____

— In addition, for the —, conduct *in vitro* genotoxicity tests for point mutation and chromosomal aberration.

8. The following comments pertain to the test methods used for release and stability testing of the drug product.
- a. The following comments pertain to *Fine Particle Fraction: Cascade Impactor Assay for HFA-134a Flunisolide Hemihydrate MDI, 0.24% w/w, 50 µL Valve (60 and 120 Inhalations)*.
- (i) The use of — priming actuations is unacceptable. The number of priming actuations used in the analytical method should be the same as that recommended in the labeling.
 - (ii) The use of the phrase “—” in describing suitable columns for HPLC is inappropriate. Only validated columns may be listed and used in the method.
 - (iii) The resolution between flunisolide hemihydrate and 11-keto flunisolide for system suitability is inadequate. This criterion for system suitability needs to be increased to 1.5.
 - (iv) Provide data from a modified PSD test method using a fixed volume of air (e.g., 2 L) through the cascade impactor.
- b. The following comments pertain to *Content Uniformity/Medication Delivery Assay for HFA 134a Flunisolide Hemihydrate MDI, 0.24% w/w, 50 µL Valve (60 and 120 Inhalations)(PRD-639-02) and Through-Life/Medication Delivery Assay for HFA 134a Flunisolide Hemihydrate MDI, 0.24% w/w, 50 µL Valve (PRD-567-04 and PRD-637-02)*.
- (i) The use of — priming actuations is unacceptable. Use the same number of priming actuations in the analytical methods as that recommended in the labeling.
 - (ii) The use of — actuations per determination is unacceptable. Each determination must be one actuation to reflect the minimum number of actuations per dose in the labeling.
 - (iii) Modify the test methods to use a fixed volume (e.g., 2 L) of air pulled through the mouthpiece.
 - (iv) The use of the phrase “—” in describing suitable columns for HPLC is inappropriate. Only validated columns may be listed and used in the methods.
 - (v) Only the validated Unit Spray Content Apparatus (USCA) may be used in the methods. The listing of the USCA under “EQUIPMENT (as listed or equivalent)” is inappropriate. List the USCA separately as it is the only validated

collection device.

- (vi) The resolution between flunisolide hemihydrate and 11-keto flunisolide for system suitability is inadequate and needs to be increased to 1.5.
- c. The following comments pertain to *Assay and Degradation Products for HFA-134a Flunisolide Hemihydrate MDI, 0.24% w/w, 50 µL (60 and 120 Inhalations)*.
- (i) The use of the phrase "_____ " in describing suitable columns for HPLC is inappropriate. List and use only validated columns in the method. In this regard, the statement in the System Suitability section pertaining to column replacement must be modified to indicate that any replacement column must be one that is listed in the method as validated.
 - (ii) The resolution between flunisolide hemihydrate and 11-keto flunisolide in the Resolution Solution is inadequate and needs to be increased to at least 1.5 to decrease variability owing to peak overlap.
 - (iii) The Limits of Quantitation (LOQ) demonstrated in the method validation (0.15% and 0.22% LC of flunisolide hemihydrate for the 120- and 60-actuation products, respectively) are inadequate to reliably quantitate impurities at or around 0.1%. Increase the sensitivity of the method to decrease the LOQ appropriately.
9. The following comments pertain to drug product characterization studies.
- a. Provide appearance data from the Temperature Cycling Study which describe any changes in the appearance of the valve exterior and interior, gaskets, and canister interior of the units in the study.
 - b. The conditions of the temperature cycling study you have provided are inadequate to assess the robustness of the container and closure components, as well as the formulation physical stability. Provide the results of a study where the drug product has been cycled between subfreezing (e.g., -10°C) and 40°C for 6-hour periods over 4-6 weeks.
 - c. Provide complete priming studies and data from single actuation doses instead of means of two actuations. These data are necessary to establish priming requirements for the minimum dose permitted by the labeling.
 - d. Provide data from a priming study addressing the length of time canisters can be stored without priming when they are 80-90% of canister life and the number of actuations necessary to prime these canisters. As stated above, a single actuation dose must be used.
 - e. The Patient In-Use Study submitted was inadequate to determine if device cleaning by the patient was necessary under the range of product use scenarios (one actuation twice

daily to four actuations twice a day). Provide a Patient In-Use Study utilizing the above range of schedules to simulate the range of dosing schedules recommended in the labeling. This study must include instances of substantial canister use (e.g., 80% of label claim doses) followed by a period of non-use and then Dose Content Uniformity and particle size distribution (PSD) testing. The schedule and testing for this study must be suitable for evaluating possible orifice clogging. Beginning- and end-of-canister Dose Content Uniformity and PSD data from the above study must be submitted. Data from both the beginning and end of canister must be obtained with both a clean spacer/mouthpiece and one used and uncleaned. The uncleaned spacer/mouthpieces to be used should have deposits that are reflective of the number of actuations wasted to achieve the desired point in the life of the canister.

- f. Provide evidence that the cleaning procedure used and the interval between cleanings were effective in removing residual formulation deposits from the container and closure components.
- g. Provide detailed data from the in-use study on the amount of drug substance deposited on each component of the container and closure components for mass balance purposes.
- h. Provide the results of a study determining the profiles of drug delivered and aerodynamic particle size distribution versus individual actuation number from the point at which the labeled number of actuations have been dispensed until no more actuations are possible. The study provided in the application, *Profiling of the Actuations near Canister Exhaustion*, is inadequate to establish the drug's performance in this regard.
- i. Supply the results of a study on the effect of different flow rates at constant volume (e.g. 2 L) through the flunisolide device on both the Unit Spray Content Mean Dose Delivery and variability of individual measurements. The dose delivery study must be conducted using one actuation per determination, to simulate the lowest allowable number of actuations per dose permitted in the labeling. Revise the method for Unit Spray Content to adopt the constant volume condition used in this study.
- j. For the purpose of additional drug product characterization, detailed characterization of the plume geometry from the actuator (minus spacer) is necessary to establish a baseline from which any changes to the product may be evaluated (in terms of the results obtained from the clinical batches).
- k. Provide data from Particle Size Distribution and one-actuation Dose Uniformity testing showing the effect of varying the time between actuation of the device and inhalation. The times tested should be at intervals of 0, 1, 2, 4, 8, and 16 seconds. Data should include both new and used/uncleaned actuators.
- l. In addition to the single-actuation-per-dose study outlined above, perform a similar study for doses of two and four actuations for at least one of the waiting periods, with no cleaning of the actuator between actuations. The measurements should be obtained as described in the Patient Package Insert, one actuation per measurement. Additional measurements are obtained from separate actuation/inhalation cycles immediately

following the previous one.

- m. Provide the results of a study to determine the time necessary to achieve a solution formulation at room temperature after cooling canisters of the drug product to -20°C .

10. The following comments pertain to the container and closure system.

- a. Provide in the application appropriate acceptance specifications (test methods and acceptance criteria) for the actuator, container, valve, and each of its components. These may include dimensional measurements, extractable profile, and performance characteristics.
- b. Provide a Letter of Authorization for the Bespak DMF containing information about the actuator and spacer. The letter dated March 30, 2000, does not contain the DMF number.
- c. DMFs _____ were reviewed and found inadequate to support your application. Letters were sent to the holders.
- d. Provide accurate technical drawings of the actuator/spacer assembly with all dimensions and tolerances for reference.
- e. The specifications for the actuator/spacer assembly are inadequate in the following ways.

(i)



(ii)



(iii)



- f. Provide the test results, as obtained from the Forest Laboratories testing facility, from all lots of actuator/spacers used in clinical and stability batches of drug product. Test results should include those on the _____ *ertificate of Compliance*, as well as extractables profile and performance characteristics.
- g. Your commitment to _____ may not be adequate. The form (e.g., attributes and frequency of testing) of this commitment will depend on the available data from several batches of actuator/spacers intended for commercialization.
- h. The following comments pertain to the design and manufacture of the actuator/spacer

assembly.

(i) 



(ii) 





(iii) 





(iv) 



(v) 









- i. Provide an updated Stability Protocol containing the following changes.
 - (i) Include all test parameters and acceptance criteria. Although the provided protocol refers to Appendix I for the specifications of the drug product, these should be included in the stability protocol. Extensive acceptance criteria may be footnoted.
 - (ii) Include the quality, purity and source of drug substance and excipients.
 - (iii) Include the sampling plan.
 - (iv) Include the tests for particulates and leachables in the protocol for the inverted configuration.
 - (v) Include commitments to place the first three production batches in the stability

program, to place batches into the stability testing program annually based upon the number of production batches, and to require a prior-approval supplement containing real-time data to extend the expiration dating period (owing to limited stability data from the drug product manufacturing method and container and closure configuration intended for marketing). In addition, you must provide a commitment to withdraw from the market any lot failing to meet the approved specifications for the drug product. If evidence exists that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, you will immediately discuss the out-of-specification result with FDA and provide justification for continued distribution of the lot.

- (vi) Include microbial limits testing at the 6-month testing interval for under accelerated conditions, and at the 12-month time under 30°C/60% RH conditions.
 - (vii) Include testing for water content and leakage in the upright storage orientation.
 - (viii) Include a protocol for 25°C/75% RH testing.
 - (ix) Accomplish appearance testing as modified in drug product release testing (see above comment under drug product acceptance criteria)
- j. Monitor and report peaks equal to or greater than $\frac{1}{10}$ (reference page 4: 00940)
11. Provide data for (or its location within the application) a cross-reference to all manufactured drug product batches and the type of O-ring used (_____) and whether or not inline stress testing had been performed on the batches.
 12. The stability data provided are inadequate owing to: 1) insufficient comparative batches between presence and absence of in-line 100% stress testing (since no validation has been performed to justify the use of the conditions employed, as well as the paucity of comparative data); 2) Inadequate comparative data for evaluation of the effect of O-ring extraction and identity (_____) numerous changes in the preparation procedure of the formulation concentrate (_____); 4) changes in the canister fill method (_____); and 5) exclusive use of flunisolide hemihydrate manufactured and micronized by _____ in the clinical trials and stability batches, instead of the drug substance source to be used in the marketed product (Sýntex SA). Provide adequate stability data [accelerated, intermediate (if applicable), and long term] to assess the effect of these variables.
 13. We remind you of your commitment to identify peak 2 (reference page 4-00941).
 14. Approval is not adequately supported in children 4 –5 years of age. A study that demonstrates efficacy over placebo and adequate safety in this age group would be required.
 15. Submit 90% confidence intervals for the point estimates (ratio of geometric means) for dose

activity when tested in the *in vitro* chromosomal aberration assay using Chinese Hamster CHL cells and in the *in vivo* mouse bone marrow chromosomal aberration assay.

Studies on the effects of flunisolide hemihydrate on fertility in female rats showed that flunisolide hemihydrate, at an oral dose of 200 mcg/kg/day (approximately _____ times the maximum recommended daily inhalation dose on a mg/m² basis) _____ impaired fertility, but was devoid of such effects at doses up to _____ 40 mcg/kg/day (less than _____ the maximum recommended daily inhalation dose on a mg/m² basis).

Pregnancy: Teratogenic Effects: Pregnancy Category C. As with other corticosteroids, flunisolide hemihydrate has been shown to be teratogenic and fetotoxic in rabbits and rats at doses of 40 and 200 mcg/kg/day, respectively (_____ times, respectively, the maximum recommended daily inhalation dose on a mg/m² basis). There are no adequate and well-controlled studies of flunisolide hemihydrate in pregnant women. Flunisolide hemihydrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiological, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

- e. Revise the OVERDOSAGE section as follows.

Flunisolide hemihydrate infused intravenously at doses up to 4000 mcg/kg in mice, rats and dogs (approximately _____ 25, 50 and 170 times the maximum recommended daily inhalation dose on a mg/m² basis, respectively) produced no mortality.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

You are advised to contact the division regarding the extent and format of your safety update prior to responding to this letter.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

We recommend that you request an informal meeting with this division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the

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application is approved.

If you have any questions, call Sandy Barnes , Chief, Project Management Staff, at (301) 827-1055.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.

Director

Division of Pulmonary and Allergy Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and
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/s/

Robert Meyer

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