

MEMORANDUM OF MEETING MINUTES

MEETING DATE / TIME: September 24, 2003

NDA 21-247: Aerospan (flunisolide hemihydrate in HFA-134a Inhalation Aerosol)

SPONSOR: Forest Laboratories, Inc.

TYPE OF MEETING: Telephone Conference

FDA ATTENDEES:

Division of Pulmonary & Allergy Drug Products (DPADP, HFD-570):

Sandy Barnes	Chief, Project Management Staff
Badrul A. Chowdhury, MD, Ph.D.	Division Director
Guirag Poochikian, Ph.D.	Chemistry Team Leader
Brian Rogers, Ph.D.	Review Chemist
Peter Starke, M.D.	Medical Officer
Eugene Sullivan, M.D.	Acting Clinical Team Leader

Forest Laboratories, Inc.

Sebastian Assenza, Ph.D.	Vice President, Analytical Research and Development
David Lust	Acting Director, Regulatory Affairs
Shashank Mahashabe, Ph.D.	Vice President, Formulation Development

BACKGROUND

Forest requested this telephone conference on August 20, 2003, to obtain clarification on several of the comments from the approvable letter dated July 30, 2003.

MEETING NOTES

The questions from the August 20, 2003 background package are listed in italics followed by the agencies response in plain text.

Comment 13: The Forest proposal of — of all post-marketing batches to be placed on stability in response to Comment 21b in our June 5, 2003 submission is deemed unacceptable. In the May 8, 2003 Discipline Review Letter, the number of batches to be placed on stability was to be related to the production rate (e.g. 10%). What is the minimum percentage of yearly stability that would be deemed acceptable?

Based on Forest's estimate of _____ batches per year, the Agency stated that 10% of the batches should be placed on stability. These samples should be distributed throughout the year. Forest could submit a supplement to revise the number of batches to be placed on stability per year once they have sufficient experience in manufacturing and if the data indicate the product is sufficiently stable.

Comment 15: Will the Division be able to comment on the modification to the design of the actuator/spacers at this meeting in the event that new prototypes would need to be prepared? Two assemblies have been sent to Ms. Jafari under separate cover.

No, the Division has no further comment on the actuator/spacer.

Comment 16: Based on the design modifications to the actuator/spacer assembly made thus far, does the Division agree that additional _____ is not required?

It is acceptable not to _____ the actuator.

Comment 21b: Is a matrix similar to the one presented in Asmacort Patient Instructions satisfactory for Aerospan? A copy of the Asmacort Patients Instructions matrix and the proposed Aerospan matrices (60 and 120) are presented in Attachment 1 and 2, respectively.

The matrix is acceptable. The instructions for use of the matrix should be detailed in the Patient Instructions for Use Pamphlet. We expect that the use of the matrix is a temporary measure and a supplement for the proposed actuation counter will be submitted for approval soon.

Forest pointed out that questions 20.b.(1) and 20.a.(7) were duplicate comments. The Division stated that the duplication was intentional to emphasize the comment.

In response to a question from the Division, Forest stated that they are planning to request a meeting to discuss the actuation counter. Studies are ongoing to determine the force to count vs the force to the actuate the valve.

Forest plans to respond to the July 30, 2003, approvable letter within the next two weeks.

[This discussion concluded the telephone conference]

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Sandra Barnes
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: June 5, 2003

To: David Lust	From: Ladan Jafari
Company: Forest	Division of Pulmonary and Allergy Drug Products
Fax number: 201-524-9711	Fax number: 301-827-1271
Phone number: 201-386-2024	Phone number: 301-827-1084
Subject: NDA 21-247	

Total no. of pages including cover: 2

Comments:

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NDA 21-247

Dear Mr. Lust:

In addition to the comments sent in our letter dated May 8, 2003, we have the following additional comments:

1. Provide a commitment to perform acceptance testing of flunisolide hemihydrate immediately before formulation for drug product manufacturing.
2. Provide all available stability data on drug product batches that incorporate the ~~_____~~ O-ring. If no data are available, generate and submit these data as soon as possible.

If you have any questions, I may be reached at 301-827-1084.

Ladan Jafari, Regulatory Project Manager

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Page 2

Initialed by: Barnes/6-5-03
Rogers/6-5-03
Poochikian/6-5-03

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NDA 21-247

DISCIPLINE REVIEW LETTER

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

Attention: David Lust
Associate Director, Regulatory Affairs

Dear Mr. Lust:

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

We also refer to your submission dated February 5, 2003.

Our review of the Chemistry, Manufacturing and controls section of your submission is complete, and we have identified the following deficiencies. Please note that the alphanumeric designations appearing in parentheses following the comments below refer to the comments of the June 11, 2002, agency letter.

1. In the specification sheet in Attachment 1, the name of the test *Clarity of Solution* has been changed to *Color of Solution* with no corresponding change in the acceptance criterion. Reverse this name change to cause *Clarity of Solution* to remain in force and institute a test for *Color of Solution* with an appropriate quantitative acceptance criterion (Comment 1.e.).
2. Provide all available data from flunisolide hemihydrate analysis as conducted in accordance with your proposed testing protocol as provided in Attachment 1, and modified as directed in Comment 1 above. Subsequent data must be submitted when obtained as amendments to the application. Provide an agreement to submit these data as requested. Submitting these data in Annual Reports is unacceptable (Comment 1.f.).
3. Provide Master Batch Records for the two presentations that indicate clearly that each individual canister in a batch must be ~~including operator instructions to this effect~~ including operator instructions to this effect (Comment 7.a.).

4. Provide Master Batch Records for the two presentations that:
 - a. Clearly indicate the procedure for weight checking of each unit after lagering.
 - b. Clearly indicate the procedure for using the weight challenge units.
 - c. Utilize weight challenge units as positive controls for rejection. That is, units must be rejected by the check weighing system to be considered a positive challenge result (Comment 7.b.).
5. As clarified in our Telecon on November 20, 2002, provide identities of the found particulates, the general sizes of each type of particle, and relative abundance (Comment 9.a.).
6. Modify each individual acceptance criterion for *Foreign Particulates* to clarify the fraction of the canister of which each are representative. These must take into account the number of actuations counted as well as the fraction of the filter examined (Comments 9.g. and 9.h.).
7. The proposed acceptance criterion for *Water Content* is excessive from a manufacturing quality standpoint and must be lowered to NMT _____ to reflect the data in the primary stability batches (Comment 10).
8. The name of the test method *Spray Pattern/Plume Geometry/Spray Centrality* must be modified to *Spray Pattern/Spray Centrality* since it does not involve a measurement of Plume Geometry (Comment 13).
9. The proposed acceptance criterion for *Maximum Diameter in Spray Pattern/Spray Centrality* are not supported by the data in your December 7, 2001, amendment. The acceptance criterion must be modified to NMT _____ (Comment 13).
10. The method provided for Plume Geometry evaluation is inadequate. As stated in our letter dated June 11, 2002, 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 14).
11. 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. We remind you that the permissible levels of _____ are dependent on the results of the relevant toxicity studies, and that you have committed to limiting the level of _____ to LT _____ % unless there is FDA agreement that it has been shown to not be genotoxic. (Comment 15).]

12. We remind you of your commitment, made in the November 20, 2002 meeting, to institute changes in your manufacturing process to minimize oxidation of flunisolide drug substance (Comment 16).
13. We remind you 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 (Comment 16).
14. The *Through Life Medication Delivery* data in Attachment 20 show a significant trend in beginning to end of canister dose delivery. Provide an adequate explanation of this trend (Comment 18.b.).
15. The statement concerning dependency of the emitted dose upon flow rate does not reflect the data provided. Revise the statement in the Physician's Package Insert to be formatted as follows, assuming an 80- μ g drug delivery per actuation (see Comment 26.b. below) as the label claim (Comment 18.d.):

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.
16. Provide individual and mean drug delivery from the valve (DDV) data from all available drug product batches at the beginning-, middle-, and end-of-canister. These data must be obtained from canisters stored under various conditions. (Comment 21.a.).
17. Similarly, provide *Particle Size Distribution via _____ Cascade Impactor* data from all available drug product batches at the beginning-, middle-, and end-of-canister. These data must be obtained from canisters stored under various conditions, and preferably obtained from the same canisters as the above DDV data (Comment 21.a.).
18. In the method and calculation results for *Particle Size Distribution via _____*, include a sum of the mass deposited on the valve stem, throat, Stage 0, Plates 0-7, and filter for *Mass Balance*. The acceptance criterion for *Mass Balance* must be _____ % of the label claim drug delivery from the valve per actuation. Update the data in the stability tables to include these results (Comment 21.c.).
19. DMF _____ is inadequate to support your application. A letter was sent to the holder (Comment 25).
20. As stated in our letter dated June 11, 2002, comments on the expiration dating period are deferred pending agreement on acceptance criteria for _____ (Comment 27).

21. The following comments pertain to the post-approval stability protocol (Comment 28):
- a. No acceptance criteria for leachables are listed 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 at the component level. This footnote should be referenced by the parameter and not take the place of the acceptance criteria. As commented on above, this statement is premature and still depends on establishing an acceptable extractables/leachables correlation.
 - b. Provide a commitment in the Stability Protocol specifying the number of batches per year to be placed in the stability-testing program. The number of production batches placed in the stability-testing program annually after the first three production batches should be related to the production rate (e.g., 10%). The percentage of batches tested on stability should be clearly stated in the protocol.
 - c. Provide a commitment to periodically submit the results of the stability-testing program in Annual Reports.
 - d. Provide a commitment to withdraw from the market any lots found to fall outside the approved specifications for the drug product. Also state that if there is evidence that the deviation is a single occurrence and does not affect the safety and efficacy of the drug product, the result will be immediately discussed with the reviewing division with provided justification for the continued distribution of that batch.
 - e. Indicate that any extension of the expiration dating period will only be based on statistical analysis of actual data generated.
22. The following comments pertain to extractables and leachables testing (Comment 29).
- a. The footnote in the specification sheet and the Stability Protocol pertaining to the establishment of: _____ 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
~~_____~~
~~_____~~ 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.
23. Provide both complete manufacturing information and stability data from all drug product batches manufactured since 1999. Provide updated stability and release data from all batches (Comment 32).
 24. Clarify why batch P01938 was manufactured on November 3, 1998, and not placed in the stability-testing program until April 9, 1999 (Comment 32).
 25. The following comments pertain to modifications to the actuator/spacer assembly (Comments 33.a. and b.).
 - a. Increase the height of the ridge on the actuator near the top of the canister to permit easier removal of the actuator from within the spacer.
 - b. Decrease the height of the rear of the actuator opposite the ridge to further expose the canister and permit easier actuation by patients with smaller hands. When used as depicted in the Patient's Instruction for Use pamphlet, the product is difficult to actuate for small hands owing to the small height difference between the rear edge of the actuator and the bottom of the canister. The large overall height of the device also adds to this problem.
 - c. Increase the height of the debossing on both the actuator and spacer to provide additional sight and touch feedback to the correct orientation for actuation.
 - d. If _____ is added, further modifications in addition to those proposed above in this comment will be necessary to protect the _____ from both accidental activation and physical damage.
 - e. Submit final drug product devices with canisters to permit evaluation of the modifications made.

26. The following are preliminary comments pertaining to labeling (Comment 34):
- a. In all instances, the name of the drug product must be changed to Aerospan (flunisolide HFA) Inhalation Aerosol.
 - b. We withhold comments on delivered dose per actuation pending submission of data requested above.
 - c. Since the actuator may still be detached from the spacer, both the spacer and actuator must be suitably labeled.
 - d. In addition to _____ Aerospan actuator/spacer assemblies as requested in the previous comments, provide mock-ups of cartons, Physician Package Insert, and Patient Instructions for Use Pamphlet for our evaluation.
 - e. In the Patient Instructions for Use Pamphlet, Step 2, Items 9 and 10 show a patient inhaling the medication with his or her mouth around the spacer at the point it has a circular cross-section. This is incorrect for this device. Modify all such drawings to show a patient with their mouth on the flattened portion of the spacer.
 - f. Step 2, Item 5 shows at first a left hand holding the Aerospan device and then a right hand actuating it. Step 6 subsequently shows a left hand shaking the Aerospan device. Step 7 then shows a right hand holding the device in preparation to actuate. Reconcile these drawings to show the same hand performing all these functions to prevent confusion on the part of the user.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

Guirag Poochikian, Ph.D.
Chemistry Team Leader
Division of Pulmonary and Allergy Drug Products, HFD-570
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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FACSIMILE TRANSMITTAL SHEET

DATE: April 9, 2003

To: David Lust	From: Ladan Jafari
Company: Forest	Division of Pulmonary and Allergy Drug Products
Fax number: 201-524-9711	Fax number: 301-827-1271
Phone number: 201-386-2024	Phone number: 301-827-1084
Subject: Aerospan	
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NDA 21-247
Drug: Aerospan
Applicant: Forest
Telecon date: March 31, 2003

Forest Representatives:

Robert Ashworth, Ph.D., Senior Director, Regulatory Affairs
Robert Jackson, Senior Director, Corporate Project Management
David Lust, Associate Director, Regulatory Affairs
Michael Olchaskey, Associate Director, Regulatory Affairs
Sebastian Assenza, Ph.D., Vice President, Research & Development
Shashank Mahashabde, Ph.D., Senior Director, Formulation Development
_____, Ph.D., Toxicology Consultant
Kenneth Newman, Senior Medical Director

Division of Pulmonary & Allergy Drug Products (DPADP):

Brian Rogers, Ph.D., CMC Reviewer
Guirag Poochikian, Ph.D., CMC Team Leader
Lawrence Sancilio, Ph.D., Preclinical Reviewer
Joe Sun, Ph.D., Supervisory Pharmacologist
Peter Starke, M.D., Medical Reviewer
Eugene Sullivan, M.D., Acting Medical Team Leader
Marianne Mann, M.D., Deputy Director
Badrul Chowdhury, M.D., Ph.D., Director
Ladan Jafari, Regulatory Health Project Manager

Office of New Drug Chemistry:

Eric Duffy, Ph.D., Director

Background: The Division had a telecon with Forest on November 20, 2002, and discussed issues related to _____ in the drug substance and the drug product of Forest's Aerospan NDA (21-247). In that meeting the Division recommended changes in manufacturing procedures and container/closure to minimize the oxidation of the flunisolide drug substance. The Division advised Forest that as a post-approval commitment, Forest must either provide additional preclinical data such as a SHE cell assay to show that the _____ is not potentially carcinogenic, or a P53 assay to show no evidence of carcinogenicity, or provide a 2-year traditional carcinogenicity study involving appropriate exposure to _____ to show no evidence of carcinogenicity. The Division requested this telecon to inquire as to what steps Forest has taken so far toward reducing the _____ content in the drug product. The Division asked that Forest submit a telephone facsimile prior to this telecon and include a summary of any efforts taken toward this end. Forest submitted a telephone facsimile on March 20, 2003, and indicated that they have indeed evaluated _____ in the SHE cell transformation assay, and their unaudited reports indicate that _____ was negative in the SHE cell transformation assay.

NDA 21-247

Drug: Aerospan

Applicant: Forest

Telecon date: March 31, 2003

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- The Division initiated the meeting by asking Forest about the details of the SHE cell assay.
- Forest indicated that they used the impurity _____) alone to perform the SHE cell transformation assay. This test was done at _____ where the highest concentrations tested were cytotoxic to more than 50% of the cells. The unaudited report indicate that _____ is not positive in this assay. Forest stated that they would submit the full audited report to the Division in May 2003.
- The Division indicated that we are pleased about the outcome of this test and would have to review the data before we can confirm with Forest's assessments. The Division asked that Forest submit the report to the Division as soon as possible so that it can be reviewed during this review cycle (PDUFA date: August 6, 2003).
- Forest asked for the clarification of the need to submit the report of the SHE cell assay during this review cycle. Forest thought that the requirement of the SHE cell assay was a post-approval commitment.
- The Division explained that we had asked Forest to minimize the oxidation of the drug substance and it does not seem that any steps have been taken to correct this deficiency, therefore, the review of the SHE cell assay is critical.
- Forest indicated that they believe it would take them about: _____ do any reformulation to minimize the oxidation processes, therefore, they decided to perform the SHE cell transformation assay instead.
- The Division stated that, at this time, we do not expect any attempt at reformulation but that we expect manufacturing processes to be optimized to minimize the oxidation of the drug substance. The Division asked about the availability of the _____ facility.
- Forest indicated that the _____ site has prepared three demonstration batches that they plan to put on stability. Forest also indicated that the commercial batches would have 3 months and 6 months stability data, which they plan to submit in a supplement post-approval.
- Forest asked if the Division was planning on providing any labeling comments during this review cycle.

NDA 21-247
Drug: Aerospan
Applicant: Forest
Telecon date: March 31, 2003
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- The Division indicated that unless there are substantial deficiencies that might lead to an Approvable action, we would plan to provide labeling comments during this review cycle.
- Forest asked if the Division would give any feedback on the spacer by the end of April 2003.
- The Division agreed to provide feedback on the spacer by the end of April 2003.

Action: Forest will submit the report of the SHE cell assay to the Division in May 2003, and the Division will give feedback on the spacer by the end of April, 2003.

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NDA 21-247
Drug: Aerospan
Applicant: Forest
Telecon date: March 31, 2003
Page 4

Drafted by: LJ/4-2-03

Initialed by: Sancilio/4-2-03
Sun/4-2-03
Starke/4-7-03
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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Robert W. Ashworth, PhD
Senior Director, Regulatory Affairs
Forest Laboratories, INC.
Harborside Financial Center
Plaza Three, Suite 602
New Jersey, NJ 07311

Friday, January 17, 2003

Dear Dr. Ashworth,

This letter is a formal response to your request for a Dispute Resolution, submitted on December the 19, 2002, regarding NDA 21-247 for Aerospan (flunisolide hemihydrate in HFA-134a). The resolution that you sought was for FDA to provide Forest with the minutes/review of the Genotoxicity Assessment Committee regarding the determination of genotoxicity for the _____ impurity of flunisolide. You further requested that the available genotoxicity data be reviewed by a mutually agreed upon (between FDA and Forest) outside, independent expert panel.

Let me address the points sequentially:

1. The minutes documenting the review and determination of the Genotoxicity Assessment Committee cannot be released to Forest prior to product approval. These minutes represent pre-decisional materials of a deliberative nature and it is FDA policy NOT to release such pre-decisional materials. The minutes would be subject to a Freedom of Information request *after* approval, but are not at this time, since Aerospan has not received approval. In arriving at this answer to your Dispute Resolution answer, I consulted both the Acting Associate Director for Pharmacology and Toxicology (Dr. Osterberg) and reviewed a recommendation to him on an identical request from the Office of Regulatory Policy here in CDER.
2. From my discussions with Dr. Osterberg, with the division, and from my full review of their materials and yours, I further believe that the finding of genotoxicity for the _____ was without substantive internal dispute, including amongst FDA's own reviewers, who have considerable expertise and experience on matters of genotoxicity determinations. Therefore, I do not believe that enlisting an outside panel of consultants, even if mutually agreed upon, would be productive. The opinion of the CDER reviewers would not be swayed by additional arguments in this regard.

I do want to assure you that the division is treating this circumstance entirely consistently with how other similar situations have been treated. Further, due to your particular situation with your current supply of drug substance, I believe the division has shown, and I will help assure that they continue to show, flexibility in data-driven specifications for the _____ impurity until such time that either further data become available to clarify the genotoxicity signal (e.g., a SHE-cell assay) or until a new source of drug substance is available and qualified that can achieve the expected _____ limit.

We look forward to working with Forest to resolve all the remaining issues necessary for the approval of this product.

Respectfully yours,

Robert J. Meyer, MD
Director,
Office of Drug Evaluation II
Room 13B-28, HFD-102
Center for Drug Evaluation and Research,
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FACSIMILE TRANSMITTAL SHEET

DATE: December 10, 2002

To: David A. Lust	Ladan Jafari
Company: Forest	From: Division of Pulmonary and Allergy Drug Products
Fax number: 201-524-9711	Fax number: 301-827-1271
Phone number: 201-386-2024	Phone number: 301-827-1084

Subject: Aerospan November Telecon Minutes

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NDA 21-247

Date of Telecon: November 20, 2002

Drug: Aerospan

Sponsor: Forest

IMTS: 9572

Forest Representatives:

Robert Ashworth, Ph.D., Senior Director, Regulatory Affairs

David Lust, Associate Director, Regulatory Affairs

Sebastian Assenza, Ph.D., Vice President, Forest Research Institute

Shashank Mahashabde, Ph.D., Senior Director, Formulations Development

Charles Lindamood, Ph.D., Senior Director, Pharmacology/Toxicology

_____, Ph.D., Consultant

Robert Jackson, Senior Director, Corporate Project Management

Division of Pulmonary & Allergy Drug Products (DPADP):

Brian Rogers, Ph.D., CMC Reviewer

Guirag Poochikian, Ph.D., CMC Team Leader

Lawrence Sancilio, Ph.D., Pharmacology/Toxicology Reviewer

Joe Sun, Ph.D., Pharmacology/Toxicology Supervisor

Marianne Mann, M.D., Deputy Director

Ladan Jafari, Regulatory Project Manager

Background: Forest met with the Division on September 19, 2002, and discussed several deficiencies cited in the approvable letter dated June 11, 2002. Forest requested this meeting to further discuss and clarify some of the CMC and preclinical deficiencies.

- The Division initiated the telecon by indicating that the _____ contains a structural alert, and is genotoxic. The mouse carcinogenicity study that was performed was negative, but the study's age and design does not leave us fully confident of its rigor and therefore its resultant information. Thus, the acceptance criterion for the impurity should be less than _____% for both the drug substance and the drug product.

For the current submission, we are aware of the limitations posed by the currently available drug substance. In light of this, we will not require the acceptance criterion of less than _____% for both the drug substance and drug product to be met, but we will require the proposed acceptance criteria to be as tight as possible, given your manufacturing capabilities. Processes to minimize oxidation of the flunisolide drug substance, both in the formulation over the shelf life and during manufacturing are recommended, including the use of appropriate manufacturing procedures/conditions, reformulation, all available protection from air during compounding, a non-permeable container/closure system protective packaging, and storage at refrigerated temperature. We will also expect as a post-approval commitment by you to either:

- a. Provide additional preclinical data, such as a SHE cell assay to show that the _____ is not potentially carcinogenic, or a P53 assay to show no evidence of carcinogenicity, or
 - b. A 2-year traditional carcinogenicity study involving appropriate exposure to _____ will need to show no evidence of carcinogenicity.
- ❖ The Division clarified that in the genotoxicity assay, i.e., SHE Assay, the pure _____ should be tested in contrast to the 2-year carcinogenicity assay, whereby the test article may be _____ alone or flunisolide spiked with an adequate amount of _____.

In the future, all new drug applications or supplements that involve a new drug source/site, new method for drug substance manufacturing, or change in formulation will be required to:

- a. Meet the qualification of $< \text{---} \%$ for _____ in both the drug substance and drug product, or
- b. Provide additional preclinical data, such as a SHE cell assay to show that _____ is not potentially carcinogenic or a P53 assay to show no evidence of carcinogenicity, or
- c. Provide results from a 2-year traditional carcinogenicity study involving appropriate exposure to _____ that shows no evidence of carcinogenicity.

In addition to the above comments, the Division stated that the _____ site is considered a new site. If the drug product were made using flunisolide from this site, we would require that this drug substance and drug product meet the qualification criterion of less than _____ % or alternatively preclinical data must be provided that shows no evidence of carcinogenicity.

- Forest inquired if a negative mouse micronucleus assay would provide adequate assurance. The Division replied that this is not a sensitive assay and that a negative SHE cell is more appropriate to assess potential carcinogenicity.

- Forest asked if the Division have presented Forest's argument (summary report and the two published articles) to the Center's Genotoxicity Committee for their evaluation. The Division replied positively and indicated that the committee is also in agreement with the Division's conclusions. Forest asked if they could see the comments made by the Genotoxicity committee or if they could bring an outside panel to review the genotoxicity studies. The Division stated that we could check on this issue and let Forest know of the outcome.

Post-meeting notes: The Division discussed the issue of sharing the Genotoxicity Committee's review with Forest as well as bringing in an outside panel to review the genotoxicity studies. Minutes from the Genotoxicity Committee cannot be shared because these are predecisional and deliberative comments. We could only share these minutes with you after your product is approved. The Division does not have outside panel meetings to review findings from genotoxicity studies, but has been advised to encourage Forest to go through the dispute resolution pathway (addressing their concerns with the Office of Drug Evaluation 2, if they still have different views on this issue.

CMC:

- Forest asked if the Division agreed that they use _____ of particles from known components (i.e., scrapings from the canister, O-rings, and coating) for the identification of unknown particles in a test sample.
- The Division replied that Forest may use any method of identification, however, it is likely that the _____ of manufactured particles will not help Forest to identify micron-size particles. The Division suggested that Forest apply other additional identification methods as well.
 - Forest asked if the Division agreed that they exclude the extraneous metal filings that result from opening the canister or should these particles be included in the size/number of foreign particles observed.
- The Division responded that Forest should not include the extraneous metal filings, and should avoid procedure(s) that contribute to such extraneous matter. We expect the analytical method to look for and be able to count foreign particulates in the opened unused canister and the foreign particulates in sprays from the valve near the end of the canister. The latter method should be able to both quantitatively and qualitatively analyze particulates that result from actuation of the valve.
 - Forest asked if the Division agreed if the label claim of drug delivered per actuation can be set to 80 mcg, instead of _____ per actuation.

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Sponsor: Forest

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- The Division stated that we have to review the full extent of the data before we can agree on the label claim.

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Sponsor: Forest
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Drafted by: LJ/11-26-02

Initialed by: Sancilio/12-3-02
Sun/12-3-02
Rogers/11-29-02
Poochikian/11-29-02
Mann/12-5-02, 12-9-02

Filename: Forest Nov tcon.doc

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: October 4, 2002

To: David Lust	From: Ladan Jafari
Company: Forest	Division of Pulmonary and Allergy Drug Products
Fax number: 201-524-9711	Fax number: 301-827-1271
Phone number: 201-386-2024	Phone number: 301-827-1084
Subject: September 19 meeting minutes	

Total no. of pages including cover: 13

Comments:

Document to be mailed: YES NO

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NDA 21-247

Drug: Aerospan (flunisolide HFA)

Applicant: Forest Laboratories, Inc.

Meeting Date: September 19, 2002

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Dr. Duffy initiated the meeting by reminding both 3M and Forest that although 3M representatives are only attending part of the meeting, there would be an open discussion format and if there are any proprietary information that either group does not wish to discuss in the presence of the other, that should be brought to the Agency's attention immediately. Both Forest and 3M agreed to the terms of the meeting. Forest and 3M were also informed that the meeting minutes would be shared with Forest only and it is up to the discretion of Forest to share any portions of the minutes with 3M.

1. *Comment 5. Your supplied Average Valve Delivery data do not adequately support a 30 day lagging period. Provide a Master Batch Record that contains a requirement for at least 30 days of lagging storage after manufacture and before release testing (comment 5.c).*

Response

3M believe that the valve delivery data reaches target levels beginning at the 30 day post-spray testing and remains stable throughout the 30 day test period. All data points are within the specification limits and day - data is within 5% of the target valve delivery.

Given our interpretation of this data, we would request clarification of your interpretation of the valve delivery data, which you believe, supports a 30 day lagging period.

The Division noted the following points in response to question 1 above.

- ? It is unclear at what point the valve delivery stabilizes during the storage testing. It appears that the limited data supplied for Valve lots 1 and 2 reach minimum values at the 30 day data point in both cases. The data thus support a 30 day lagging period if equilibration of the seals, as measured by the valve delivery, is the determining factor. The Division believes that a 30 day lagging period, however, may be sufficient.
- ? It is clear that the valve delivery begins higher than the target valve delivery (1.5 mg) and ends, after equilibration of the seals, lower than that of the target valve delivery. The proximity of the valve delivery to the target is irrelevant to this discussion for this reason.

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- ? Neither leak rate or valve delivery is a direct measure of gasket swelling. Both of these dependent variables may be insensitive to further gasket swelling after an unknown point of formulation absorption. One of the tests most sensitive to gasket swelling may be valve stem binding after actuation. This variable is both a non-linear and sudden-onset measurement and thus must be tested under conservative conditions. No data have been provided showing changes in percentage valve failures as a function of storage time, where failures can be continuous firing, lack of firing, or valve-stem binding.
- ? Once you have significantly more experience with manufacture of commercial-scale batches, you may submit a prior-approval supplemental application after NDA approval to support a change in lagging period.
- ? Provide data in the above supplement showing the rejection rate (percent canisters rejected) for both the various function tests and fill weight from both your proposed and the approved lagging periods.
2. *Comment 6. Your statement for meeting minimum release fill weight specifications after the hold period is incomplete and unclear as to what units are to be tested. Modify this statement to explicitly state that spray testing and fill weight checking of every production unit must be accomplished after the lagging period (see previous comment). Institute 100% spray testing and fill weight checking after the lagging period to evaluate the valve performance at equilibrium seal condition. Provide a revised Master Batch Record with these modifications (comment 5.d).*

Response

3M spray tests each unit of every batch. This is accomplished at least 24 hours after filling for temperature-equilibration purposes. The purpose of spray testing is to assess gross valve performance and cull those units that do not fire and those that fire continuously. 3M believes that the provided data show spray testing is independent of the lag period.

The Division noted the following points in response to question 2 above.

- ? We notice that you are not addressing 100% fill weight checking after a lagging period. We therefore assume that you intend to institute this test and this will be entered into the Master Batch Record.

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- ? An important purpose of 100% spray testing is to cull those units that do not have the valve stem completely return to the relaxed position, in addition to the defects that you mention. It may be that inability to return to the relaxed position is the failure mode most sensitive to the state of the gasket after reaching its largest size owing to formulation absorption.
- ? As stated in the previous comment, and for the above reason, spray testing must be accomplished after the gasket has reached equilibration with the formulation. Also, neither leak rate or valve delivery is a direct measure of gasket swelling.
- ? Valve failure, as measured by the inability of the valve stem to return to the relaxed position after firing, will occur with differing frequency with different lots of gaskets and valve stems, etc. For this reason, we feel that a conservative approach is most appropriate.
- ? Since 100% spray testing must be accomplished after the lagging period, then the time at which valve delivery testing is accomplished, relative to spray testing, is irrelevant.
- 3. *Comment 8. The start-up data in Figure 5 show the initial cans filled for lot 990561 are much different in canister drug content than those filled later down the filling timeline. Specify in the Master Batch Record the minimum duration after which filling down time must be recorded. Also, specify in the Master Batch Record how many initial canisters must be discarded, either after the filling line has been restarted, or alternatively, after the fill weight has come within specifications. Justify your choice of parameters and instructions with data provided to the application. Also, provide to the application an updated copy of the Master Batch Record with all changes made (comment 6.c).*

Response

According to the data, 3M believes that the data from lot 990561 are within the acceptable variability after the fill weight has reached target ? — g. They feel that discarding those units that fail to meet fill weight criteria during packaging assures that all finished product will be within specification for drug content.

The Division responded that the significant downward trend in drug content signifies that the process is not yet at a steady state for filling

- ? Filling of marketed product should not proceed until reasonably consistent filling at both the drug content and fill weight targets are achieved.

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- ? The Division inquired as to what caused this batch to behave differently than the other batches displayed. Forest responded that they did not investigate since the fill weights were within specifications.
- ? The Division inquired as to what point in the filling did the drug content level out to a semblance of a steady-state process. Forest responded that they have not investigated that.
4. *Comment 11. As stated in our letter dated May 7, 2001, the stability data provided do not support your proposed Fill Weight acceptance criteria. Tighten the acceptance criteria to _____ for the 60-actuation presentation, and _____ for the 120-actuation presentation. The two batches that do not conform to these acceptance criteria, P01170 (manufactured November 8, 1997) and P01502 (manufactured May 28, 1998), are not considered to be representative of the filling capability of the manufacturing process, nor that of current manufacturing capabilities. It is expected that the latter batches will have lower Fill Weight variability as shown in the most recently manufactured batch P01938 (manufactured November 3, 1998) and P01593 (manufactured May 28, 1998) (comment 7.h.).*

Response

P01502 and P01593 are sub-lots of the same master batch produced on the same day under identical conditions.

All batches referenced in FDA Comment 11 were produced at a scale considered representative of the routine manufacturing process and the normal process capability.

Additional data from three more recently manufactured lots are provided to help facilitate clarification.

Note that the three most recently manufactured lots of drug product had yield losses between _____ due to incorrect fill weights. These yield losses were obtained using the target weight limit of target ? —g. They feel that additional losses are unacceptable.

Given the clarification provided above and your consideration of the data collected for the last three batches, please provide an explanation of your comment.

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The Division responded that with the exception of one batch (990230), the failure rate of the more modern batches is quite low ~~—————~~ We wish to emphasize that failure rate is a function of manufacturing quality. Thus, an inadequate level of quality in one batch can not justify widening of acceptance criteria. In general, process control limits must reflect the normal ability to manufacture and not the worst-case scenario where a filling problem went unnoticed or uncorrected. Both low target fill weight (as seen in at least two of the batches shown in Figure 1 on the previous page of your meeting package) and poor manufacturing QC will cause additional failures that are not representative of manufacturing capability, and thus should not be used to justify acceptance criteria or process controls.

3M made the point that the reviewer's method of using the stability data to evaluate failure rate in filling is unwise since the all the OOS canisters have been removed from the data base before this point, and thus only canisters that initially pass the fill weight acceptance criteria are present.

The Division responded by assuring 3M that this point is well taken and we will discuss this issue internally. We further clarified that the rejection rates seen for these acceptance criteria were higher than those seen in our experience. The Division stated that we expect 3M to minimize rejection rates through improvement of manufacturing quality, not through implementation of wide acceptance criteria.

Further discussion within the Division resulted in our agreement that the data set used for evaluation of failure rates was inaccurate and we will reevaluate data pertaining to this issue. It should be noted that no data have been submitted by the applicant, in amendments to the NDA, specifically to justify the current acceptance criteria for fill weight. For this purpose, we request the applicant submit to the application all available data to support the proposed in-process fill weight controls and propose acceptance criteria that reflect the data provided.

5. *Comment 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.).*

Response

Forest understands that since 3M purchases them, 3M is required to test and release these components.

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Individual component testing for the container/closure components is performed independent of Forest Laboratories. Given their understanding as stated above, please provide clarification on the need for 3M to share the container closure component test methods and acceptance criteria with Forest.

The Division responded that periodic testing of 3M's results is necessary to provide duplicate results as required for maintaining container closure batch-to-batch quality standards and thus reproducible drug product quality. Any purposeful or inadvertent changes in 3M testing must be detected by periodic testing if the change results in passing of a bad batch of components. Extractables testing is the most critical issue in this regard.

For this purpose, Forest may develop their own test methods and acceptance criteria. Container and closure components that currently undergo redundant testing owing to their being tested by both 3M and their supplier, need not be retested by Forest.

It was at this point in the meeting that the 3M representatives left the meeting and only Forest representatives were present from this point in the meeting onward.

6. *Comment 1.f. The following comments pertain to the drug substance specifications:*

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.).

Response

The drug substance stored at _____ was tested using method and specifications approved for Aerobid CFC. The specifications for the HFA product have not yet been finalized between _____ and FDA. Therefore, they are not sure what are the appropriate data that needs to be submitted to the NDA. Every canister will be tested in accordance with the finalized specifications by both _____ and Forest.

Does the agency agree with this plan?

The Division agreed with the proposal and indicated that in addition, each canister of drug substance must be evaluated separately for its impurity profile. Very tight controls need to be in place for the batches in ' _____, particularly the levels of _____ . Possibly others may need to be monitored.

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7. *Comment 9. The following comments pertain to the method and acceptance criteria for Particulate Matter in HFA-134a Flunisolide Hemihydrate MDI (comment 7.d).*
- a. *Validate the method for precision, sensitivity, and accuracy of particle dimensions.*
 - b. *Identify the reticule(s) validated for use in particle sizing. The use of the phrase "or equivalent" is inappropriate in this context. Only validated reticules are to be used and listed.*
 - c. *The method should provide for sample agitation before opening to suspend as many foreign particles as possible.*
 - d. *The method should dilute the formulation as little as possible to maximize sensitivity.*
 - e. *Specify the coolant for both the glass vials and the canisters.*
 - f. *Clarify the procedure used for _____ including _____ volumes.*
 - g. *Using the validated method, propose acceptance criteria based on the data from multiple samples from each NDA stability batch of drug product. The proposed acceptance criteria must institute individual controls on particles less than 10 μ m, greater than or equal to 10 μ m, and greater than 25 μ m.*
 - h. *Specify the number of fields-of-view examined.*

Response

The applicant agrees to modify the method, but wishes to _____

Is the agency in agreement with this proposal?

The Division did not agree with the proposal and indicated that the test method must be able to detect and quantitate the particulate matter particle sizes as stated in the comment. They must provide a validated test method for this purpose, particularly with regard to sensitivity and sampling. Specifically, those particulates < 10 μ m, \geq 10 μ m, and > 25 μ m. The identity of these particulates need to be established also.

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8. *Comment 15. Based on the presence of impurity levels in batches used in clinical trial ANC-MD-04, having used drug product batches P01170, P01502, P01593, and P01938 at ages of 24 months, 18 months, 18 months, and 13 months, respectively, the acceptance criteria for Impurities should be modified to the following:*

_____	NMT — %
_____	NMT — %
_____	LT — %
_____	NMT — %
Individual unspecified	LT — %
Total unspecified	NMT — %
Total	NMT — %

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 _____ in the Telecon dated September 13, 2001.

Response

Has the report dated August 28, 2001 been reviewed? Does the agency still concur with Dr. Sancilio's assessment based on the data presented therein?

The Division responded that we have received and reviewed the report. The Division stated that _____ was genotoxic in the chromosomal aberration assay in the presence of metabolic activation (S9). Therefore, the levels of this impurity should be less than _____ % in the drug product. One of the members of the Genotoxicity Committee after being informed of the data also concluded that _____ was genotoxic. Dr. _____ disagreed with the Division's evaluation and stated that in the chromosomal aberration assay, _____ was negative without S9, and equivocal with S9. Dr. _____ also discussed the negative results in the E. coli reverse mutation assay, and stated that they do not believe _____ to be genotoxic. The Division will present Forest's argument to the Center's Genotoxic Committee for their evaluation. Their argument will include Forest's summary report and the two submitted articles. It should be noted that Dr. Sancilio's assessment was made in the context of qualification from a toxicological viewpoint. The acceptance criteria cited in the letter are based on a quality control evaluation and still hold.

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The Division stated that following the Center's Genotoxic Committee assessment, we will need to address the appropriate cutoffs for _____ in both drug substance, and drug product for this drug application. When asked, Forest replied that they would need cutoff levels of less than _____% for the drug substance and less than _____% for the drug product in order to have a marketable drug (well above FDA cutoffs for a genotoxic compound). Forest added that they had a 21-month mouse carcinogenicity study from 1976, which used oral (not inhaled) drug administration. Levels of _____ in the drug administered in that study were reportedly _____%. The Division concluded that Forest should put together a package that includes their interpretation of the genotoxicity studies, data from the mouse carcinogenicity study, data on the levels of _____ observed in the drug substance/product, and suggested levels for _____ that they feel are supported. The Division will review this package and meet with Forest to discuss this issue further, as it is a critical issue regarding the approvability of this product.

9. *Comment 19. Since you intend to _____*

Response

Forest states that they will submit the data as requested.

The Division accepted the proposal.

10. *Comment 21.c. We note that in the Particle Size Distribution data, the mean mass balance of all canisters of all lots at the initial time point is _____ of label claim from the actuator. The corresponding mean mass balance at the final time point from both clean and used and unclean actuators is _____ of label claim past the actuator. Provide an explanation with supportive data as to why a consistently _____ s balance is seen after the _____ storage period, under all conditions, and in all lots of drug product.*

Response

The data submitted by Forest was generated based on the comments from the agency. After the initial test, the actuator was not rinsed. Therefore, the mass balance is around _____ The mass balance at the end and past the end of canister is around _____ because it includes the rinse from both the valve and the actuator. The results show that the mass balance is more than _____ the dose delivered ex-valve.

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Does the agency interpret the data differently?

The Division stated that it was unclear the meaning of the values in the PSD tables under the rows titled "Final" and "Final Repeat" since both means were consistently high. Please explain the values seen, taking into account the consistently high values for both rows in all tables pertaining to PSD.

Forest clarified that the data was stated as ? g per actuation and not ? g or % of label claim as was the data in the previous tables for content uniformity.

11. *Comment 33.a. The following comments pertain to the design and manufacture of the actuator/spacer assembly (comment 10.h.v.).*

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.

Response

A modified actuator/spacer was previously submitted to the Agency to address the questions previously raised by the Agency. The applicant states that the spacer has been stiffened. In addition, ridges have been added to make separation of the two components more difficult. Finger pads were added to the sides of the spacer so that separation will not occur when the patient opens and operates the product in its intended fashion. They maintain that separation is difficult when the spacer is gripped properly.

Instructions to the patient will indicate where to hold the spacer during opening and operation, as well as where to apply pressure to disassemble for cleaning, and for reassembly. The instruction will also state that pressure should not be applied at the center of the spacer during opening and/or operation.

Based on these changes and adequate patient instructions, they feel that concerns regarding separation of the spacer and actuator have been addressed. They are interested in any feedback from the agency regarding appropriate wording in the Patient Package Insert to assure the proper grip is used to open and operate the product. Forest provided mock-ups of a new design that incorporated _____ that apparently made separation of the two components more difficult. Forest stated that they would provide samples of the product as soon as possible.

12. *Comment 33.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).*

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Response

Forest proposes to institute instructions in the labeling to assure the patient will point the orifice in the correct direction during assembly.

The feel that the concerns regarding the potential to misalign the actuator have been addressed.

The Division stated that the device could still be assembled in a reverse orientation. This needs to be corrected.

13. *Comment 34.b. The following preliminary comments pertain to labeling of the actuator/spacer assembly.*

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.

Response

The : _____ ; on the spacer prominently displays the established name. As shown on the samples sent to Dr. Rogers on June 5, 2002, the patient will clearly see the label on the spacer.

Is it necessary to have labeling on the actuator as well?

The Division stated that it is necessary to have labeling on the actuator as well. All visible and separable components of the container and closure must have labeling. This comment pertains to the previous version of the device. Forest provided a mock-up of a new drug product container closure that made it more difficult to separate the two components. The need for separate labeling of the spacer and actuator will be reevaluated once the Division receives actual samples of the device.

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Drafted by: LJ/9-25-02

Initialed by: Rogers/9-27-02
Poochikian/9-27-02
Sancilio/9-25-02
Sun/9-25-02
Mann/10-2-02

Filename: N21247Sept02mtgmin.doc

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/s/

Ladan Jafari
10/4/02 10:13:39 AM

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Date of Telecon: September 13, 2001

FDA Representatives:

Ladan Jafari, Regulatory Project Manager
Brian Rogers, CMC Reviewer
Larry Sancilio, Preclinical Reviewer

Forest Representatives:

Robert Ashworth, Sr. Director, Regulatory Affairs
Sebastian Assenza, Sr. Director, Analytical R7D
Kevin Halloran, Director, CMC Regulatory Affairs
Robert Kelly, Assistant Director, Regulatory CMC
Charles Lindamood, Sr. Director, Pharmacology & Toxicology
Shahsank Mahashabde, Director, Formulations & Clinical Development

Background: The Division requested this telecon to discuss the impurities present in the drug substance used in the carcinogenicity studies for Flunisolide HFA Inhalation System.

- The Division raised concerns about the specifications in the drug product that were beyond acceptable levels for two impurities (_____). The Division asked if the animals used in the carcinogenicity studies were exposed to these levels throughout the study. Forest indicated that they will try to obtain that information as soon as possible. They may have to search for historical data that may not be available any longer, but would try to obtain as much information as possible and get back to the Division.
- Forest asked about the use of the drug substance stored in the _____ facility in _____. The Division stated that they would have to review the data before they could respond to that question. The Division indicated however, that there are no GMP issues with the use of the material manufactured in _____ facility. The Division emphasized that we have to review the data to make sure that it has the correct identity, and sufficient strength, quality, and purity. Additional testing beyond that of release testing will be required since there is no way to establish the quality of the manufacturing facility.

Action: Forest will attempt to provide the information requested by the Division regarding the impurities in the drug substance.

Memo to file: NDA 21-247

In a telecon with Bob Ashworth of Forest Labs, they informed us that they are expecting to submit a complete response to our AE letter around the end of the month (November).

According to their representative, they will provide all the dose content uniformity data we requested in our AE letter (pertaining to one actuation dosing) by submission of data obtained on older product, specifically, the 24-month stability time point. Note that this proposal does not include any stability data obtained under accelerated storage conditions.

I explained that we expected to receive data from release and long-term and accelerated stability studies from new batches in the response to our AE letter.

He also said we did not explicitly request new stability studies and associated data using analytical methods modified to include one actuation dosing.

Although strictly true, we did issue the following general comment pertaining to deficiencies in their submitted stability studies:

12. We are unable to evaluate the limited and incongruous stability data for the purpose of evaluating your proposed expiration dating period. The stability data provided are inadequate owing to:

_____ of
_____ Provide adequate stability data [accelerated, intermediate (if applicable), and long term] to assess the effect of these variables.

They also said that they have agreed internally to adopt our recommendations for testing of the _____ drug substance stored in _____, and they are in the process of testing the _____ drug substance.

They have not manufactured any new batches of drug product from batches of _____ drug substance tested under the agreed-to protocol. They cited scheduling problems with 3M for the reason they have not yet produced any new batches of drug product.

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cc:

HFD-570/Divfiles

HFD-570/Sancilio

HFD-570/Rogers

HFD-570/Jafari

Initialed by: Sancilio/9-25-01
Rogers/9-25-01

Filename: Flunisolideimpurities

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/s/

Ladan Jafari
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IND 51,456

Date of Telecon: December 18, 2001

Forest Representatives:

Robert Ashworth, Regulatory Affairs
Sebastian Assenza, Pharmaceutical Research & Development
Shashank Mahashabde, Pharmaceutical Research & Development
Monica Senick, Project Manager

Division of Pulmonary & Allergy Drug Products (DPADP):

Craig Bertha, Chemistry Reviewer
Debra Birenbaum, Medical Reviewer
Ladan Jafari, Regulatory Project Manager
Marianne Mann, Deputy Director
Guirag Poochikian, Chemistry Team Leader
Brian Rogers, Chemistry Reviewer
Alan Schroeder, Chemistry Reviewer
Vibhakar Shah, Chemistry Reviewer

Background: Forest Labs submitted an amendment to their flunisolide HFA IND application and proposed a testing program for the _____ The Division arranged for a telecon with Forest to discuss this submission.

The Division identified several deficiencies with the proposal as outlined below.

1. ✓

2.

3.

4.

✓

2 Page(s) Withheld

 X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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Date of Telecon: December 18, 2001

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Initialed by: Birenbaum/1-3-02
Schroeder/1-3-02
Bertha/1-7-02
Poochikian/1-7-02
Mann/1-8-02
Rogers/1-14-02

Filename: Flunisolide ~~_____~~ tcon

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/s/

Ladan Jafari
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Memo to file: N 21-247

In a telecon dated December 5, 2001, the Division discussed the preclinical testing requirements for _____, _____, the impurity in flunisolide, possesses a structural alert, and needs to be qualified for a _____ specification in the drug product to be acceptable.

At our request, Forest indicated that the level of the _____ present in the flunisolide batch used in the carcinogenicity assay was _____.

The Division stated that based on the exposure of the _____ to rats in the carcinogenicity assay at the NOEL, the results do not support the proposed _____ specification for the impurity in the drug product. The Division recommended that _____ be tested for genotoxicity in the in vitro point mutation and chromosomal aberration assays. If positive, the specification should be lowered to not more than _____ in the drug product. If negative, the proposed specification is acceptable.

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Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: October 1, 2001

To: Dr. Lester Gibbs	From: Ladan Jafari
Company: Forest	Division of Pulmonary and Allergy Drug Products
Fax number: 201-524-9711	Fax number: 301-827-1271
Phone number: 201-386-2123	Phone number: 301-827-5584

Subject: CMC comments

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES NO

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We are reviewing your submission dated August 28, 2001. Your submission describes the strategy to assure the quality of the stored flunisolide hemihydrate drug substance. We do not agree with your strategy and have the following comments.

Once _____ has released each individual container of flunisolide hemihydrate (confirming that each individual container meets all current release acceptance criteria), comprehensive characterization of the physical and chemical properties of the drug substance should be accomplished by you prior to the use of the flunisolide hemihydrate in each individual container in manufacture of drug product.

In addition to the testing proposed in your submission, the following tests must be performed individually on each container: related impurities profile (instead of purity), particle size distribution (instead of particle size), hemihydrate percentage, XRD for particle morphology analysis, residual solvents levels, microbial quality, pH of solution, specific rotation, color of solution, residue on ignition, specific rotation, melting range, and heavy metals.

The sampling of the containers by 3M must include samples from both top and bottom of each separate container. The top-to-bottom uniformity of each container must be demonstrated for each of the following parameters: particle size distribution, particle morphology, hemihydrate percentage (uniformity of water content), XRD, residual solvents levels, microbial quality, pH of solution. All testing not listed above as being required for establishing top-to-bottom uniformity of the drug substance in each container must be accomplished on blended samples from the top and bottom of each container.

As a general concept, acceptance criteria and tests should be instituted to control those drug substance parameters considered key to ensuring reproducibility of the physicochemical properties of the drug substance. These controls must be instituted to ensure the identity, strength, quality, and purity of the contents of each individual container. In addition, before we can agree to release containers of drug substance for drug product manufacturing, agreement must be reached on all acceptance criteria.

Provide batch numbers, manufacturing dates, and assign individual container numbers for all containers stored at _____ so that all analytical results can be traced to a specific container/batch.

Since the _____ manufacturing site is closed and cannot be inspected for GMP compliance, it cannot be approved as a proposed drug substance manufacturing site and must be withdrawn. Submit a statement in an amendment to this effect.

NDA 21-247

Page 3

cc:

HFD-570/Divfiles

HFD-570/Rogers

HFD-570/Poochikian

HFD-570/Jafari

Initialed by: Barnes/9-26-01
Rogers/9-28-01
Poochikian/9-28-01

Filename:Forestcomments

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NDA 21-247

Date of Telecon: September 13, 2001

FDA Representatives:

Ladan Jafari, Regulatory Project Manager
Brian Rogers, CMC Reviewer
Larry Sancilio, Preclinical Reviewer

Forest Representatives:

Robert Ashworth, Sr. Director, Regulatory Affairs
Sebastian Assenza, Sr. Director, Analytical R7D
Kevin Halloran, Director, CMC Regulatory Affairs
Robert Kelly, Assistant Director, Regulatory CMC
Charles Lindamood, Sr. Director, Pharmacology & Toxicology
Shahsank Mahashabde, Director, Formulations & Clinical Development

Background: The Division requested this telecon to discuss the impurities present in the drug substance used in the carcinogenicity studies for Flunisolide HFA Inhalation System.

- The Division raised concerns about the specifications in the drug product that were beyond acceptable levels for two impurities (_____). The Division asked if the animals used in the carcinogenicity studies were exposed to these levels throughout the study. Forest indicated that they will try to obtain that information as soon as possible. They may have to search for historical data that may not be available any longer, but would try to obtain as much information as possible and get back to the Division.
- Forest asked about the use of the drug substance stored in the _____ facility in _____. The Division stated that they would have to review the data before they could respond to that question. The Division indicated however, that there are no GMP issues with the use of the material manufactured in _____ facility. The Division emphasized that we have to review the data to make sure that it has the correct identity, and sufficient strength, quality, and purity. Additional testing beyond that of release testing will be required since there is no way to establish the quality of the manufacturing facility.

Action: Forest will attempt to provide the information requested by the Division regarding the impurities in the drug substance.

NDA 21-247

cc:

HFD-570/Divfiles
HFD-570/Sancilio
HFD-570/Rogers
HFD-570/Jafari

Initialed by: Sancilio/9-25-01
Rogers/9-25-01

Filename: Flunisolideimpurities

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**Food and Drug Administration
Center for Drug Evaluation and
Research**

Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: August 17, 2001

To: Dr. Lester Gibbs	From: Ladan Jafari
Company: Forest	Division of Pulmonary and Allergy Drug Products
Fax number: 201-524-9711	Fax number: 301-827-1271
Phone number: 201-386-2123	Phone number: 301-827-5584
Subject: CMC meeting minutes	

Total no. of pages including cover: 14

Comments:

Document to be mailed: YES NO

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NDA 21-247

Sponsor: Forest Laboratories, Inc.

Date: July 18, 2001

Robert Ashworth	Senior Director, Regulatory Affairs, Forest
Sebastian Assenza	Senior Director, Analytical Research & Development, Forest
Lester Gibbs	Manager, Regulatory Affairs, Forest
Kevin Halloran	Director, CMC Regulatory Affairs, Forest
Shashank Mahashabde	Director, Formulations Development, Forest
Lawrence Olanoff	Executive Vice President, Scientific Affairs, Forest

Ladan Jafari	Regulatory Project Manager, DPADP
Robert Meyer	Director, DPADP
Guirag Poochikian	CMC Team Leader, DPADP
Brian Rogers	CMC Reviewer, DPADP
Larry Sancilio	Preclinical Reviewer, DPADP
Joe Sun	Supervisory Pharmacologist, DPADP

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Background: Forest Laboratories, Inc. submitted a meeting request to discuss the CMC issues raised in the Agency's approvable letter dated May 7, 2001. The deficiencies cited in the approvable letter are printed in *Italics* below followed by Forest's response and the Division's evaluations of the responses provided by Forest.

8.b.ii. The use of 2 actuations per determination is unacceptable. Each determination must be one actuation to reflect the minimum number of actuations per dose in the labeling.

- Forest indicated that they are in the process of revising the test method to use one puff per determination and plan to _____ and asked if the Division would agree with this proposal.
 - The Division did not agree with Forest's proposal and stated under current proposed labeling, we expect the Dose Content Uniformity method to be performed using the lowest labeled dose. _____ if a one puff dose is to be a recommended dose. This means that the method must be developed and submitted to the application prior to approval. The evaluation of the available DCU stability data is critical to evaluation of the performance of the drug product.
- Forest indicated that since 1 puff dosing is used for children 6-12 years of age, they are proposing to _____. Forest also indicated that they have some stability data that they have obtained from 1 puff HFA sample, however, they would like to obtain additional stability data and submit _____ for the 1 puff BID dosing.
 - The Division stated that they would get back to Forest regarding this request, however, stated that inclusion of the accelerated stability data is required.

1.b. We have been informed in a letter dated January 23, 2001, from _____ 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.

- Forest stated that they intend to use material from _____ stored in _____ until exhausted. Then the material from the _____ facility will be used. Forest asked if they could continue to use material manufactured at _____ and inventoried in _____, _____ if they withdraw the site from the application.”
 - The Division stated that the material from _____ can not be used in marketed drug

product unless that site is approved as part of the application. The Division stated that if Forest wants to use the material stored in _____, then Forest must not withdraw the _____ site from the application.

The Division stated that at the present time, we can not assess the GMP status of the _____ site since we understand that it is shut down and unavailable for inspection. The status of this site must be resolved internally.

The Division reminded Forest to submit a protocol for establishing the quality and purity of the flunisolide stored in _____. Each container of the drug substance must be qualified separately with analyses for each individual container that establish its suitability for use over time.

Until these issues are resolved, this application cannot be approved.

- Forest stated that they believe the drug product stored at _____ facility meets the specifications required by the Division.
- The Division stated that meeting the specifications is not the only factor and Forest must be concerned with impurities, contamination, storage conditions, condition of containers, as well as other physical properties.
 - Forest inquired if they could submit a proposal with data to address the Division's concerns.
- The Division indicated that they would discuss this further internally and with the Office of Compliance, but reminded Forest that the specifications must meet the new specifications independent of the site, with the exception of the _____.

1.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.

- Forest indicated that commercial scale manufacturing at _____ is not scheduled to begin until 2003. COAs for commercial scale batches will be available at that time. Forest will provide these COAs and stability data from the _____ site as part of a post-approval supplement to qualify this site and asked if the Division agrees that this stability program is acceptable.
- The Division stated that inadequate information was provided to evaluate the proposed stability protocol. To support the use of the _____ facility, data showing equivalence must be submitted. Also, adequate stability data from both drug substance and drug product batches manufactured with drug substance from

_____ must be submitted.

- Forest indicated that the _____ facility would be a future supplier, and asked if they could submit _____ accelerated stability data to show batch to batch consistency.
- The Division indicated that forest should withdraw the _____ facility and support its use with a prior approval supplement, post approval of this current application. The amount of stability data needed to show batch to batch consistency, would be a review issue. The Division reminded Forest that if the _____ material is found to be unacceptable, then Forest must submit 3 batches of data from both long-term and accelerated stability testing. The Division asked about the status of the _____ and the _____ site. Forest responded that the _____ site is currently shut down, and the opening of the _____ facility is up to _____

10.h. The following comments pertain to the design and manufacture of the actuator/spacer assembly.

(i) 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.

- Forest stated that they intend to keep the design as proposed and increase the clarity of the instructions for patient use and inquired if the Division agreed that this is an appropriate way to address this issue. Forest showed a diagram of what was acceptable way of holding the device and how they could better educate the patients on the use of this device. Included in their presentation was a proposed drawing from the Patient Package Insert.
- The Division stated that this is a quality control problem more than one of patient compliance. The flexibility in the joint must be reduced when in the in-use position. This flexibility varies greatly from unit to unit and can only become more variable once in production. The Division also mentioned that a couple of the samples which were provided to the Division, failed to perform, and that we need to have assurance that this is a reliable device, as the variability in manufacturing will undoubtedly worsen as the manufacturing process goes into production scale.

In addition, the Division provided comments on how the proposed drawing for illustration of use of the inhaler could be improved. It was noted that the drawing was confusing since the patient in the drawing was shown holding the inhaler with first one hand and then the other. Also, the proposed technique for using the device, as

shown in the drawing, inadequately supported the bottom of the spacer with the patient's thumb. This actuating position also caused the finger actuating the canister to sit outside of the depressions made to accommodate it. The Division recommended that the drawing be modified to correct all of these weak points.

The Division stated that it is an important factor in labeling to be able to identify the correct position of handling the device.

(v). 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. Provide any information in your possession on the effect of this structural weak point on the use of this product. Stiffen this portion of the spacer against vertical compressive forces.

- Forest indicated that the patient instructions for use will be modified and asked if the Division agree with this proposal for addressing the issue of the spacer/actuator separation.
 - The Division stated that the proposal is incomplete since there was no actual labeling changes provided for evaluation. We would like to make it clear that we recommend modifying the spacer by either increasing the wall thickness or incorporating external stiffeners.
- Forest stated that they designed it so the patients could separate it to clean if needed.
 - The Division stated that it is important that the device be made so that both young and elderly patients are able to use the device without having the spacer separate from the actuator and having the actuator fall on the floor. This occurrence will undoubtedly result in damage to the device and possibly make it inoperative.

7.i. The following comments pertain to acceptance criteria for Fine Particle Fraction.

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.

- Forest proposed to change the grouping for the psd into four groups and asked if the Division agreed with this proposal.
 - The Division stated that the proposal cannot be evaluated without careful data analysis. We must withhold comment on the groupings for quality control

trials. All drug product impurities are qualified in ANC-MD-04. The impurity levels qualified in ANC-MD-04 are as follows:

Impurity	Qualified	Proposed by Applicant
[]]	NMT %
		NMT %
L]]	NMT %
		NMT %
		NMT %
Total		NMT %

The acceptance criteria proposed by the Agency are as follows:

[]]	NMT %
		NMT %
L]]	LT %
		NMT %
		LT %
Total		NMT %

_____ is to be controlled as Individual Unspecified.
 — limit is tentatively acceptable as proposed by applicant

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7.o. The following comments pertain to toxicological evaluation and qualification of _____ and _____ levels in the drug product.

Item i: Provide any available data on whether these compounds are metabolites in animals and humans.

- Forest indicated that there are no data suggesting that biotransformation of flunisolide hemihydrate to _____ or _____ occurs. They identified the major metabolites as _____ a derivative, and _____ compound. In human urine, 77 to 85% of the radioactivity was accounted for by free and conjugated flunisolide and _____ metabolite.

item ii: Provide data on levels of _____ 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 _____ present in the flunisolide hemihydrate batches used in the carcinogenicity studies.

- Forest indicated that they would provide this data when it is available from the innovator.

item 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.

- Forest indicated that they would provide a proposal to the Division concerning the toxicological qualification of the _____ and _____, if they can not obtain the information requested above. Forest requested that since they anticipate some time prior to obtaining the above, if they could submit the required data post approval.
 - The Division stated that the levels of impurities in general should be less than _____ % for the drug substance and less than _____ for the drug product. In case of the _____, since it is a structural alert, the levels should be less than _____ in the drug product. The Division stated that if the genotoxic tests of the _____ are found to be negative, and the proposed specifications is less than _____, then there is no need for further qualification. The Division would then set the specifications based on the data base available. The Division stated that for impurity levels of above _____ in the drug product, sponsors must conduct a 3-month inhalation study in the most appropriate species for the impurities. The Division also stated that the submission of this information is required prior to approval of this application.

The Division reminded Forest that DMF _____ is inadequate to support this NDA in issues related to specifications for related impurities, among others. No data from production-scale batches manufactured in _____ have been received. Also, no drug product has been manufactured from batches manufactured at the _____ facility.

10.e.ii. Provide identities of significant peaks in the extractables chromatogram of the actuator/spacer.

- Forest defined significant peaks in the extractables chromatogram for the actuator/spacer as those peaks whose peak area is _____ and asked if the Division agrees with this definition for significant peaks.
 - The Division stated that level of _____ needs to be more carefully defined. Also, the definition of significance is dependent on the toxicity of the component. It is impossible to define the necessary level of identification.

- Forest stated that they do not have access to the composition, therefore, can not identify any peaks on the chromatograms, and asked for the Division's advice as to how to proceed with this request.
 - The Division stated that they could identify the most prominent peaks and we could look at the DMF to see if that raises any issues.

10.i. Provide an updated Stability Protocol containing the following changes.

vi. Include microbial limits testing at the 6-month testing interval for under accelerated conditions, and at the 12-month time under 30C/60% RH conditions.

- Forest asked if the Division means that the P-A stability protocol should include testing only for microbial limits at 6 mo under accelerated conditions, and at 12 months under 30/60 with no other testing performed.
 - The Division stated that these parameters should be added to the stability protocol. No parameters should be removed.

vii. Include testing for water content and leakage in the upright storage orientation.

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- Forest asked if the Division means that the post-approval stability protocol should include testing only for water content and leakage rate in the upright storage position with no other testing performed.
 - The Division stated that these parameters should be added to the stability protocol and that no parameters should be removed.
- vii. Include a protocol for 25C/75% RH testing.**
- Forest indicated that since the flunisolide HFA Inhaler System does not require moisture-protective packaging, they do not plan to include a protocol for testing 25/75 conditions in the post-approval stability protocol and asked if that was acceptable by the Division.
 - The Division stated that the data provided in Forest's application was inadequate to assess the stability of the drug product under accelerated storage conditions. This inadequacy is reflected in our comment 7.i.(iii). of our Approvable letter.

This comment requests that you evaluate the PSD under accelerated conditions and perform additional testing at 25/75 if a significant change in PSD is observed.

The purpose of this request is for data to evaluate the effect of external moisture on the seals, the spacer hold-up (owing to static-electricity build-up), and other undefined issues. It is the observation of any significant changes at 40/75 and comparison of 25/75 with 25/60 that determines whether moisture-protective packaging is required. The comparison accomplished with PSD data will be on a stage-by-stage basis and not using combined stages as you have provided in your meeting package.

3.e. Submit test methods, validation studies, and available data for acceptance of all excipients, including validation studies for the propellant methods, to establish the reliability of the test results on the Certificates of Analysis at the NDA stage and at appropriate intervals after approval of the application.

- Forest indicated that the data requested have already been provided on pages 4-468 - 4-513 in the original application, and asked if the information submitted in the cited NDA sections satisfy the request made by the Division.
 - The Division stated that it appears that the information cited at least partially fulfills the request made. The adequacy of the information needs to be established.
- 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)

iii. The resolution between flunisolide hemihydrate and _____ for system suitability is inadequate. This criterion for system suitability needs to be increased to 1.5.

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) 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).

vi. The resolution between flunisolide hemihydrate and _____ for system suitability is inadequate and needs to be increased to 1.5.

- Forest stated that the resolution of _____ from the flunisolide peak was added as a system suitability requirement for quantitation of flunisolide and not the

_____ analog and inquired if the Division agree that a resolution of 1.2 between flunisolide hemihydrate and the _____ is acceptable for the _____ Impactor Assay (test method _____). Forest also asked if the Division agree that a resolution of 1.2 between flunisolide hemihydrate and the _____ is acceptable for the Content Uniformity/Medication Delivery and Through-Life Medication Delivery Assay (test method _____).

- The Division stated that the use of 1.2 for resolution between these two compounds is adequate in these cases.

8.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).

ii. The resolution between flunisolide hemihydrate and _____ in the Resolution Solution is inadequate and needs to be increased to at least 1.5 to decrease variability owing to peak overlap.

- Forest asked if the Division is concerned with resolution between _____ and flunisolide hemihydrate or with resolution between the _____ and flunisolide.
- The Division stated that this comment was intended to address the resolution between the _____ and flunisolide.

9. The following comments pertain to drug product characterization studies.

h. Conduct a study to determine the profiles of delivered amount 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.

- Forest indicated that they plan to conduct a study using 3 lots of drug product with 5 canisters for particle size distribution and 3 canisters for medication delivery. The following parameters will be measured: Medication delivery - test actuations 1&2 (beg), 119&120 (end), 121&122, 125&126, 129&130, 135&136, and 139&140 and Particle size distribution - test actuations 1-5 (beg), 116-120 (end), 121-125, 131-135, and 136-140. Forest asked if the Division concur that this proposal adequately addresses the profiling of actuations near canister exhaustion.
- The Division responded that the purpose of the request was to obtain individual actuation data and not data from pairs or sets of actuations. The Division stated

that the study submitted with the application for dose characterization was conducted with a two-actuation dose. This is inadequate to establish actuation-to-actuation variability changes. Individual actuation results should be detailed.

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Also, in the data provided, only data summaries were provided. For example, the PSD data was not detailed enough to provide an indication of shifting as a function of actuation and particle size. Provide the data as individual data points for evaluation of changes between individual actuations. Use the minimum possible number of actuations for these analyses.

This study needs to be conducted with both the 60-actuation and 120-actuation presentations.

Other discussion points: Forest asked if they should submit data for dose indicator to the IND for Flunisolide, and the Division agreed that it should be submitted to the IND. As for labeling, since it is similar to the CFC, it can be submitted as a prior approval supplement after approval.

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Page 13

Cc:

HFD-570/ Div.files
HFD-570/Rogers
HFD-570/Poochikian
HFD-570/Sancilio
HFD-570/Sun

Initialed by: Rogers/8-15-01
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Ladan Jafari
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Barnes
21-247

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: March 8, 2001

TO: Sandra L. Barnes, CSO, and Regulatory Project Manager
Debra L. Birenbaum, M.D., Medical Officer, Clinical Reviewer
Division of Pulmonary & Allergy Drug Products, HFD-570

THROUGH: John R. Martin, M.D., Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

FROM: H. W. Ju, M.D., GCP1 Reviewer

SUBJECT: Evaluation of Clinical Inspections

NDA: #21-247

APPLICANT: Forest Laboratories, Inc.

DRUG: Flunisolide HFA Inhaler System

INDICATION: Maintenance treatment of asthma as prophylactic therapy in adults and pediatric patients 4 years of age and older.

CONSULTATION REQUEST DATE: July 10, 2000

ACTION GOAL DATE: Date: April 27, 2001

I. BACKGROUND: Goals of inspections are as follows:

Efficacy: To determine whether the HFA and CFC formulations of flunisolide provide comparable efficacy, as measured by percent predicted FEV₁ and with respect to PRN albuterol use in patients with mild to moderate asthma.

Safety: To assess the safety of the two formations on adverse event profiles and evaluate changes from baseline in physical exam, vital signs, ECG, laboratory test results, and Cortrosyn stimulation test results.

The Medical Officer of the reviewing division randomly selected certain values of FEV₁ and FEV₁ of predicated and Cortisol levels for verification.

II. RESULTS :

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Levy, Robyn J.	Atlanta	GA	26-Jul-00	19-Sep-00	NAI
Nelson, Harold S.	Denver	CO	26-Jul-00	19-Jan-01	VAI
Grossman, Jay	Tucson	AZ	26-Jul-00	31-Jan-01	VAI
Caputo, Leonard J.	Mobile	AL	26-Jul-00	20-Nov-01	OAI

A. Protocol #ANC-MD-03-000

1. Site #34 (Robyn J. Levy, M.D., Atlanta, GA)

There were no limitations to this inspection. 34 subjects enrolled in Protocol #ANC-MD-03-000 and 33 subjects completed the study. The drug disposition list and primary parameters of 8 subjects with the source data were reviewed and no discrepancies were noted. 4 submitted case reports were compared with source data and some minor discrepancies were noted. All the consent forms were reviewed. One consent form was not signed but the subject who was old enough did write his name. The data support the drug claim.

DSI recommendation: Data from this site are acceptable to support the NDA application.

2. Site #26 (Leonard J. Caputo, M.D., Mobile, AL)

The were no limitations to this inspection. 22 subjects enrolled in Protocol #ANC-MD-03-000 and 16 subjects completed the study. Pulmonary function test results for three subjects were manually altered or were otherwise misrepresented (data falsification); without these alterations or misrepresentations, these subjects did not meet the protocol-specified criteria for inclusion in the study. Other violations included failure to conduct the study according to the approved protocol, and failure to maintain adequate and accurate records of all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.

DSI recommendation: Data from this site should be excluded from consideration in the NDA application.

B. Protocol #ANC-MD-01

1. Site #17 (Harold S. Nelson, M.D., Denver, CO)

There were no limitations to this inspection. 43 subjects were enrolled in protocol ANC-MD-01 and 19 subjects completed the study. 12 CRFs were reviewed and data were compared to raw data (e.g., laboratory reports and pulmonary function reports). Proper administration of test article was also reviewed, i.e., verification of reports of whether subjects self-administered the correct number of puffs. CRFs were evaluated to verify if the subjects met the inclusion criteria. The data verification table for 8 subjects as requested by the reviewing division were compared with the source data and no discrepancy was noted. Deficiencies included the failure to maintain adequate and accurate records (4 subjects), and failure to comply with all requirements of informed consent, The data appear acceptable for use in support of drug claims.

Telecon (1/15/98)

Record of Telephone Conversation

Date: February 20, 2001
NDA No: NDA 21-247
Product Name: Flunisolide hemihydrate Inhalation Aerosol
Firm Name: Forest Laboratories, Inc.
Jersey City, NJ 07311

**Telecon
Initiated by:** Field

Name and Title of Person with whom conversation was held:

Caryn Everly, Los Angeles DO

Telephone No: (949) 798-7722

Background:

Ms. Everly is in the process of conducting a follow-up inspection of the 3M manufacturing site in _____ . She called to discuss her preliminary findings pertaining to the flunisolide hemihydrate inhalation aerosol manufacturing process.

Content of Telecon:

Ms. Everly stated that she had discovered that batch 990560 was not manufactured by the submitted filling procedure. She inquired whether or not this unreported change in filling warranted inclusion in a FDA 483.

The difference between the filling procedure used in this batch and that described in the NDA is that the canisters in this batch were filled using a _____ instead of the _____ . It should be noted that, although the drug product is a _____ formulation, the formulation at this point of the process is being maintained at _____ and is a _____ during the filling procedure. This fact increases the likelihood of the above change having a deleterious effect on the can-to-can filling uniformity.

The batch in question was not subjected to release or stability testing, however, it is currently the only batch manufactured by this proposed process. It has not been used in any PK, Tox, or Clinical Trials. The applicant has stated to Ms. Everly that the _____ procedure is going to be used in all future batches of drug product. The _____ procedure is touted by the applicant as an improvement over the submitted filling process.

The applicant also stated that other undisclosed products have had this modified filling procedure implemented through submission in Annual Reports.

We responded that this change is not appropriate for inclusion in an Annual Report. We requested she provide us with the identities of all drug products to which this change was applied.

Brian D. Rogers, Ph.D.
HFD-570

Telecon (1/15/98)

cc:

Orig. NDA 21-247

HFD-570/Division File

HFD-570/BRogers/2/20/01

HFD-570/GPoochikian/SBarnes/RMeyer/DBirenbaum/MMann/SSuarez/KSwiss

R/D Init. by: _____

F/T by: B.Rogers/2/20/01

doc. #2-20-01.Tel.doc

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On Original

/s/

Brian Rogers

2/21/01 04:23:08 PM

CHEMIST

Appears This Way
On Original



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

MEMORANDUM

DATE: March 23, 2000

FROM: LCDR James Lindsay Cobbs
Regulatory Project Manager, DPADP

SUBJECT: Post meeting note of the End-of-Phase 2 (EOP2) meeting minutes dated
December 15, 1999.

TO: IND 51,456

The official meeting minutes of the above EOP2 meeting issued January 10, 2000. The sponsor, Forest Laboratories, Inc. (Forest), submitted a General Correspondence dated February 7, 2000, requesting an amendment to the meeting minutes dated December 15, 1999. Following review of the correspondence the team concluded that the statements in the correspondence of the discussion on the issues are not an accurate representation of the discussion at the EOP2 meeting teleconference. Although the team is not in disagreement with the statements, the team did not agree that the statements from the correspondence should be incorporated as part of the official meeting minutes but agreed that the submission should be acknowledged.

This Memo acknowledges the February 7, 2000, General Correspondence but does not amend the meeting minutes dated December 15, 1999. Please see the telephone facsimile of the February 7, 2000, General Correspondence attached, for details.

IND 51,456

Page 2

I contacted Dr. Lester Gibbs, Manager Regulatory Affairs, Thursday, March 23, 2000, to inform him of the Division's decision to issue a Memo to the file to acknowledge the February 7, 2000, General Correspondence and not to amend the meeting minutes. Dr. Gibbs agreed with the Division's decision to issue a Memo in response to their correspondence and requested a copy of this Memo.

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IND 51,456

Page 3

CC: ORIGINAL IND 51,456

DIVISION FILE

HFD-570/BARNES

HFD-570/HIMMEL

HFD-570/SANCILIO

HFD-570/SUN

HFD-570/ELASHOFF

HFD-570/WILSON

DRAFTED BY: LCOBBS/3-23-00

MY DOCUMENTS/I51456MEMO.DOC

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Forest Laboratories, Inc.

*Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311
Fax: 201-524-9711*
FAX TRANSMISSION COVER SHEET

*Date: February 7, 2000
To: Lindsay Cobbs, Project Manager, Division of Pulmonary and Allergy Drugs
Fax: 301-827-1271
Re: Comments on Pre-NDA Teleconference Minutes – IND 51,456
Sender: Lester Gibbs*

*YOU SHOULD RECEIVE 7 PAGES, INCLUDING THIS COVER SHEET. IF YOU DO NOT
RECEIVE ALL THE PAGES, PLEASE CALL 201-386-2123.*

Lindsay,

As per my phone message, attached are Forest's comments on the official FDA minutes of the Pre-NDA teleconference, as well as a copy of Forest's version of the minutes. These documents will also be sent to the IND as an official submission. Please call me with any questions.

Sincerely,

Lester S. Gibbs, PhD
Manager, Regulatory Affairs



Forest Laboratories, Inc.

Minutes of FDA Teleconference

Minutes of Pre-NDA Teleconference held on December 15, 1999 between Forest Laboratories and FDA Division of Pulmonary and Allergy Drug Products
Topic: Flunisolide HFA Inhaler System for Asthma Treatment

FDA Attendees:

Lindsay Cobbs, R.Ph., Project Manager
Barbara Elashoff, M.S., Statistical Reviewer
Martin Himmel, M.D., Deputy Division Director
Daniel O'Hearn, M.D., Medical Officer
Lawrence Sancilio, Ph.D., Pharmacology/Toxicology Reviewer
C. Joseph Sun, Ph.D., Pharmacology/Toxicology Team Leader
Steve Wilson, Ph.D., Statistical Team Leader
Young Moon Choi, Ph.D., Clinical Pharmacology Reviewer

Forest Attendees:

Im Abramowitz, Ph.D., Senior Director, Pharmacokinetics
Monica Fencik, Associate Director, Project Management
Lester Gibbs, Ph.D., Manager, Regulatory Affairs
Edward Lakatos, Ph.D., Senior Director, Biostatistics and Data Management
Charles Lindamood III, Ph.D., Senior Director, Pharmacology/Toxicology
Kenneth Newman, M.D., Director, Medical
Lawrence Olanoff, M.D., Ph.D., Executive Vice President, Scientific Affairs
Ross Rocklin, M.D., Senior Director, Medical
Shanshan Wang, Senior Statistician
Jane Wu, Ph.D., Assistant Director, Biostatistics

OVERVIEW:

This teleconference was held to discuss with the Division the NDA that will be submitted in support of the approval of Flunisolide HFA Inhaler System. Topics discussed included the pharmacology/toxicology, clinical pharmacokinetics, and clinical/statistical programs. Agreements reached and outstanding issues are summarized below.

Clinical Pharmacokinetics

Agreements reached:

The Agency indicated that the labeling included in the NDA should include available information on the metabolism of flunisolide, pharmacokinetics in special populations, such as children, the elderly, gender differences, and any information on drug interactions. All information available, including published data, should be considered.

Pharmacology/Toxicology

Agreements reached:

As agreed to at the 5/24/99 Type C meeting, there are no fileability issues regarding the current pharmacology/toxicology program, which is satisfactory for NDA submission.

Outstanding issue:

Dr. Sancilio asked that the apparent differences in corticosterone levels between animals treated with flunisolide HFA vs. flunisolide CFC be addressed in the NDA.

Clinical/Statistical

Agreements reached:

1. Forest agreed to provide the clinical safety and efficacy data sets in SAS transport format as per the current guidance document (1/99).
2. Forest agreed to emphasize what is new and relevant in the flunisolide literature database (both clinical and preclinical) when providing a literature summary in the NDA.
3. Regarding the content of ISS and ISE, and shell tables:
 - Although not required for submission, Forest was asked to provide a table that lists transaminase increases of ≥ 20 IU/L above baseline for each formulation and dose.
 - Although not required for submission, Forest was asked to provide shift tables for chemistry, hematology and urinalysis parameters. An example of such a table was provided by the Division via fax. Forest will summarize the shift from

screening visit to the final visit (the only two scheduled visits with lab tests) and categorize the "high" values into 2xULN, 3xULN, 5xULN, and 8xULN (where ULN = Upper Limit of Normal).

4. In the proposed ISS Tables 10a, 10b and 10c, Forest agreed to include minimum and maximum values, change and % change from screening visit for each formulation as well as each dose of formulation. The "n" in the proposed tables will refer to the number of patients who had assessments at both screening and endpoint, and this definition will be provided in the footnote of the tables.
5. Listings of all laboratory abnormalities according to the original laboratory normal ranges will be submitted in the NDA.
6. All study reports and tables will be available in Word 97 format.
7. In the demographics profile provided as an ISS table, Forest will include duration of asthma, and smoking history. Values for percent predicted FEV₁ at baseline as well as screening will be provided for Studies ANC-MD-01 and ANC-MD-03. Values for actual FEV₁ at baseline and screening will be provided for Study ANC-MD-01 only. Values for in-clinic PEFR at screening and baseline will be provided for Study ANC-MD-03. Diary values of AM PEFR at baseline will be provided for Studies ANC-MD-01 and ANC-MD-03.
8. In proposed ISS Table 4, the incidence of dropouts will be presented for each formulation, as well as each dose of the formulation. In addition to the proposed ISS Table 2, the demographic profile in studies ANC-MD-01 and ANC-MD-03 will be presented for each formulation as well as each dose of the formulation. In proposed ISS Tables 8, 9e, 9f and 9g, adverse events for each dose of each formulation will be presented, as well as adverse events for each formulation (all doses together).
9. Data on HPA axis testing will be made available on "outliers" (i.e., those subjects with pre-Cortrosyn < 5 mcg/dl, post Cortrosyn values < 18 mcg/dl, or the difference between pre and post-Cortrosyn < 7 mcg/dl) within each treatment group at Baseline and at Endpoint. The available data on urine and cortisol levels will also be tabulated. HPA axis tests were performed only at baseline and the end of the study (Endpoint).
10. The Division has no preference regarding how the data is presented with respect to age subgroups. Forest will use the following age subgroups: pediatric (≤ 11 years of age), adolescent (12 - 17 years of age), adult (18 - 64 years of age), and ≥ 65 years of age. (Please note that this represents a slight difference from what was proposed in the ISS and ISE table of contents (Appendices I and II of the Briefing Book)).
11. The Division remains in concurrence with the NDA submission plan originally proposed: final reports for Studies ANC-MD-01 and ANC-MD-03, an ISE including

IND# 51456
Div File

Forest Laboratories, Inc.
Pre-NDA Teleconference
Aerobid (flunisolide hemihydrate) Inhaler System Hfa
December 15, 1999

Memorandum of Telephone Facsimile Correspondence

Date: January 7, 2000

To: Lester S. Gibbs, PhD.
Manager, Regulatory Affairs
(201) 524-9711

From: J. Lindsay Cobbs, R.Ph.
Regulatory Project Manager

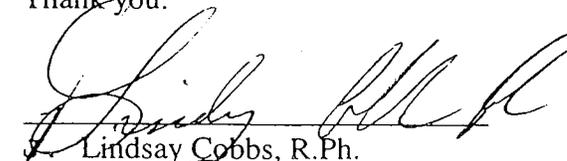
Subject: Pre-NDA Teleconference, Aerobid (Flunisolide hemihydrate) Inhaler System Hfa.

Reference is made to the teleconference held between representatives of your company and this Division on December 15, 1999. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at FDA, 5600 Fishers Lane, HFD-570, DPADP, Rockville, MD 20857.

Thank you.


Lindsay Cobbs, R.Ph.

1-7-00
Date

Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products

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Aerobid (flunisolide hemihydrate) Inhaler System Hfa
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Forest Laboratories, Inc Pre-NDA Teleconference

IMTS # 5312

Representing Division of Pulmonary & Allergy Drug Products (DPADP)

Young-Moon Choi, Clinical Pharmacology & Biopharmaceutics Reviewer
Lindsay Cobbs, Regulatory Project Manager
Barbara Elashoff, Biometrics Reviewer
Dan O'Hearn, Clinical Reviewer
Marty Himmel, Deputy Director DPADP
Larry Sancilio, Pharmacology Reviewer
Joe Sun, Pharmacology Team Leader
Steve Wilson, Biometrics Team Leader

Representing Forest Laboratories, Inc.

Im Abramowitz, Senior Director, Pharmacokinetics
Monica Fencik, Associate Director, Project management, and Team Leader
Lester S. Gibbs, Manager, Regulatory Affairs
Edward Iakatos, Senior Director, Biostatistics and Data Management
Chalres Lindamood III, Senior Director, Pharmacology/Toxicology
Kenneth Newman, Director, medical
Lawrence Olanoff, Executive Vice President, Scientific Affairs
Ross Rocklin, Senior Director, medical
Shanshan Wang, Senior Statistician
Jane Wu, Assistant Director, Biostatistics

Background

A PreNDA teleconference was granted to discuss the Pre-clinical Pharmacology/Toxicology, Human Pharmacokinetic (PK) and Bioavailability, and Clinical issues. No CMC issues were raised for discussion in the briefing package dated November 12, 1999, provided by Forest. Please see the briefing package for details.

Question 3

Based upon the Type C meeting with the Division on May 24, 1999, Forest understands that there are no outstanding issues concerning the acceptability of the nonclinical pharmacology and toxicology program that will interfere with filing the submission with the FDA. Does the Division remain in concurrence with this statement?

1. The Division noted that from the PK standpoint there are no fileability issues at this time. However, Forest was reminded that the labeling should be updated and include gender analysis.

Question 2

Based upon the Type C meeting with the Division May 24, 1999, Forest understands that there are no outstanding issues concerning the acceptability of the human pharmacokinetics and bioavailability program that will interfere with filing the submission with the FDA. Does the Division remain in concurrence with this statement?

2. The Division noted that from the Pharm/tox standpoint there are no fileability issues at this time.
 - a. The Division noted that the corticosterone levels in the flunisolide HFA-treated animals tended to show an increase while those in the flunisolide CFC-treated animals as expected were decreased. Nevertheless, both formulations showed the characteristic histological changes for glucocorticoids. Forest was asked to comment on the difference in corticosterone levels between the two formulations.
 - (1) Forest stated that they could not draw definitive conclusions on the corticosterone levels and that they believed that there were adequate

function levels in reserve and that there would probably not be a noticeable change.

- (2) The Division asked if Forest had observed this in previous studies. Forest stated that they had observed variability but that a high dose is required to detect suppression.
- (3) The Division noted that this would be a review issue.

Question 9

SAS datasets will be provided in standard transport format with SAS code to assist the Division in copying the datasets to their system. Would the Division prefer to see safety data only, efficacy data only, or both safety and efficacy data?

3. The Division noted that both safety and efficacy data should be in SAS transport format as detailed in the guidance to industry.

Question 4

As there are few publications regarding the HFA flunisolide formulation, the literature summary will be based on available clinical publications for the CFC flunisolide formulation. Is the scope of the literature search acceptable to the Division?

4. The Division noted that Forest emphasize new and relevant data in the flunisolide literature database and added that some pre-clinical data from the literature would also be helpful, particularly with HPA axis issues.

Question 5

- a. Does the Division have any comments or suggestions regarding the proposed organization and/or contents of these documents?
 - b. Does the Division have any comments regarding the shell tables for the ISS?
 - c. With regard to the ISE and ISS Data, does the Division have any comments on the definition of the age subgroups?
5. Parts a. and b. of Question 5.

steroid naïve subjects because it reflects the HPA axis before the two weeks of Aerobid 500 mcg twice daily that is to be administered during the trial's run-in period.

- Forest stated that there were no steroid naïve patients at baseline.

6. Part c. of Question 5.

The Division noted the differences in the age subgroups without additional comment.

Question 6

Based upon the meeting with the Division on May 24, 1999, Item 8 (the clinical section) of the NDA submission for flunisolide HFA will consist of the following: reports for Studies ANC-MD-01 and ANC-MD-03, an ISE including data from these studies, and an ISS including all safety data from ANC-MD-01 and ANC-MD-03 and narratives for deaths, serious adverse events or adverse event dropouts in patients treated for ≤ 6 months in Studies ANC-MD-02 and ANC-MD-04. Does the Division remain in concurrence with this agreement?

7. The Division noted concurrence with the statement in question 6., and reiterated the stipulation of the 12 month review clock.

Question 7

Does the Division agree that the case report form tabulations can be submitted as an electronic filing only? If yes, is the PDF format acceptable?

8. The Division stated that case report form tabulations should be submitted as SAS transport files, and restated that Forest follow the January 1999 Electronic Submissions guidance to industry. PDF files do not conform to the current Guidance.

Question 8

Case report form tabulations will be organized by center, and within each center, by patient. Is this acceptable to the Division?

9. As recommended in the Division's response to Question 7, the sponsor should

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submit case report tabulations as SAS transport files to include variables identifying patients and centers per the January 1999 guidance.

Question 10

Labeling for the CFC formulation Aerobid contains a great deal of information that is also applicable to the HFA formulation. Appropriate information from the labeling for the CFC formulation will be transferred to the package insert for the HFA formulation along with updates specific to the HFA product. Is this acceptable to the Division? {Please note that information shaded in the draft proposed package insert was taken from the Aerobid package insert. Sections that are not shaded may contain information that was presented in the Aerobid package insert, however, these sections have been updated or are presented in a new format.}

10. The Division stated that this question is addressing review issues and noted that the Division can better address them during the review cycle following a complete labeling review.

Question 11

For Studies ANC-MD-01 and ANC-MD-03, a combined table of AE's from the two studies will be constructed for the package insert. Is this acceptable to the Division?

11. The Division agreed that this proposal is acceptable and that such a table should identify specific age groups and doses.

Question 12

The Dosage and Administration section of the package insert will contain instructions for starting patients at an HFA flunisolide dose equivalent to 500 mcg bid CFC flunisolide dose and titrating down (step down approach) once asthma control is achieved. Is this acceptable to the Division?

12. The Division noted that this issue will need further discussion following review of the specific efficacy data, and was told that such a statement may be justified if titration was performed in the clinical trial. Forest stated that such titration was done in Trials ANC-MD-02 and ANC-MD-04. The Division cautioned that the data from