CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-067

Approvable Letter (s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

5/17/04

NDA 21-067

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Ronald Garutti, M.D.
Group Vice President, Global Regulatory Affairs

Dear Dr. Garutti:

Please refer to your new drug application (NDA) dated November 30, 1998, received December 1, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asmanex Twisthaler 220mcg (mometasone furoate) Inhalation Powder.

We acknowledge receipt of your submissions dated November 14, and December 3 and 10, 2003, January 30, February 6, 17, and 18, April 12, and May 10, 13, and 14, 2004.

The November 14, 2003, submission constituted a complete response to our December 4, 2000, action letter.

We completed our review of this application, as submitted, with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies:

1. Our field investigator could not complete inspection of your Kenilworth, New Jersey, and Union, New Jersey, manufacturing facilities because the facilities were not ready for inspection. Satisfactory inspections are required before this application may be approved.

2. Clarify the differences in the [ ] data presented in the Tables A.2.1.3 and A.2.1.4 submitted on Nov. 14, 2003, and in Tables 1 and 2 submitted on Dec. 3, 2003, (hard copy and SAS transport format). Clearly state the data which were used to propose the acceptance criteria for [ ] for all future lots of drug product.

3. We acknowledge the past issues [ ] Clearly state all corrective measures added to prevent the use of [ ] during the manufacturing process of Asmanex® Twisthaler®. Provide copies of the updated Master Batch record to clearly specify these changes and recommendations.

4. Provide [ ] data on the Drug substance-[ ] that support the proposed acceptance criteria.

5. Revise the acceptance criteria for [

]

[

Alternatively, propose a [ ]for the single observation allowed outside [ ] at a given life-stage which is based on and reflective of the data gathered from all pilot and/or commercial scale batches.

]

6. Provide details on the implementation of the [ ] in the proposed drug product.

7. Revise the acceptance criteria for all impurities and degradants [ ] in accordance with the current ICHQ3A guidance (e.g., [ ] Total related compounds [ ]

8. Update the specifications for anhydrous lactose [ ]. If [ ] are used in the manufacture [ ] it may be indicated with an asterisk and a footnote.

9. Provide a recent dated letter stating that the anhydrous lactose for inhalation obtained from your supplier is free from BSE, and TSE.

10. Note that DMF [ ] has been found to be inadequate. Deficiency letter dated March 16, 2004, was issued to the DMF holder. Although the DMF holder has responded recently, it will not be evaluated within this review cycle.

In addition, you must submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the submitted labeling (package insert, patient instructions for use and pouch and carton labels submitted May 13, 2004, and container cap labels submitted May 14, 2004).

Submit the final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary and Allergy Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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

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

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

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Pulmonary and Allergy Drug Products to discuss what steps need to be taken before the application may be approved.

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

If you have any questions, call Lori Garcia, Regulatory Project Manager, at (301) 827-5580.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Badrul Chowdhury
5/17/04 04:31:54 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

12/4/00

NDA 21-067

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Joseph F. Lamendola, Ph.D.
Vice President
US Regulatory Affairs

Dear Dr. Lamendola:

Please refer to your new drug application (NDA) dated November 30, 1998, received December 1, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asmanex Twisthaler (mometasone furoate) Inhalation Powder.

We acknowledge receipt of your submissions dated May 10, June 2, and October 17 and 18, 2000. Your submission of June 2, 2000, constituted a complete response to our March 14, 2000, action letter.

Review of your submission dated November 8, 2000, will be deferred until such time that you respond to the following comments.

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

Comment numbers in parentheses following these comments below refer to the Agency discipline review letter of August 10, 2000.

1. Withdraw the [ ] packaging [ ] from the application until such time as the necessary supportive data are submitted as discussed at the September 20, 2000, meeting. The institution of the use of the — packaging should be done via a prior approval supplement containing all pertinent supportive documentation and data. (comment 2)

2. The currently proposed [ ] specification acceptance criteria should be tightened. Evaluation of the 25°C/60%RH stability and [ ] data included in your updated data set [ ] determinations from batches 8-GEN-876, 8-GEN-880, 39554-051, 39457-053-A, 39457-055-A, 39457-058-A) revealed differences between Singapore and Kenilworth batches [ ]
The [ ] testing is consistent with larger emitted and metered dosing, which is apparently not due to formulation assay differences. As indicated previously, the validation/demonstration batches from Singapore, which have now been dropped from your data set, appeared to [ ] As previously recommended, take action to reduce the variability between batches prepared at these two sites, particularly in terms of [ ] and the emitted dosing. The evaluation of the [ ] acceptance criteria based on this current combined data set is not appropriate since the added variability will tend to widen the acceptance criteria. The following acceptance criteria would be reflective of the data from the Singapore prepared product:

group I	[ ] of total recovery
group II	mcg
group III	mcg
group IV	], mcg.

We also remind you of your commitment to reevaluate the [ ] specification acceptance criteria after one year of commercial production experience. (comments 7 and 8)

3. Stability reports 032088-145-03-0200S and 032088-145-01-200KGEN indicated that various determinations of the emitted dose were out-of-specification (v.2, pp. 505-525, v.3, pp. 929-947). Report promptly to the Agency all future out-of-specification results for any release or stability parameter. Reword the withdrawal provision in the stability protocol as recommended on page 4 of the 1987 Agency guideline entitled "Submitting Documentation for the Stability of Human Drugs and Biologics." Also, in view of the observations outlined in comment 2 above, increase the number of annual batches from each site entered into the stability program from the current proposal [ ]
The number should be correlated to the yearly production rate (i.e., as a percent of annual number of batches).

4. We remind you of your commitment to revisit the flow resistance specification acceptance criteria for the device based on one year of commercial production lots. (comment 13)

5. We remind you of your commitment to record and report to the Agency any device counter failures or related complaints during future clinical trials. (comment 16)

6. We remind you of your agreement to continue the studies towards [ ]

[ ] of the device. (comment 18)

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections will be required before this application may be approved.

In addition, it will be necessary for you to submit draft labeling revised as follows:

[

]

3 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

[ ]

24. In the **ADVERSE REACTIONS** section. [ ]

ADVERSE REACTIONS: [ ]

25. In the **DOSAGE AND ADMINISTRATION** [ ]

26. Provide a copy of the Patient Package Insert (PPI) in MS Word 97 format. Note that the **Information for Patients** subsection of the package insert should be consistent with the PPI, and should be revised accordingly.

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

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

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

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

If you have any questions, call Mr. David Hilfiker, Regulatory Project Manager, at (301) 827-1084.

Sincerely yours,

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Robert Meyer
12/4/00 04:43:11 PM

Hilfiker

NDA 21-067

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

MAR 14 2000

Dear Dr. Lamendola:

Please refer to your new drug application (NDA) dated November 30, 1998, received December 1, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for mometasone furoate inhalation powder.

We acknowledge receipt of your submissions dated March 31, September 17, October 1, and December 1, 1999. Your submission of December 1, 1999, constituted a complete response to our October 1, 1999, action letter.

We also refer to your submission dated February 17, 2000. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

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

1. Provide a table that outlines the sequence, location, and timing of events for all aspects of the manufacture of the drug substance and drug product, with the various responsibilities of each site clearly identified. See related comments 9 and 36 below.

2. The [ ] data (vol. 2.2, section 4A1.2, figures 2 and 6-9) and comparison summary (p. 4, section 4A1.2) provided in the original application do not support the use of the – method for [ ] drug substance. The specificity of the – method for [ ] of the [ ] is questionable based on the data provided to date. Use the [ ] method (or other method of similar specificity) for [ ] of [ ] of the drug substance at release and at the time of retest of the drug substance. [comment 4, May 4, 1999; comment 17.d., October 1, 1999]

3. Based on the updated [ ] data for the drug substance provided in the June 30, 1999, amendment (p. 129) for the Union, Avondale, and Singapore batches of mometasone furoate [ ], the acceptance limits should be tightened. The following example is provided.

Median [ ]
At least
Not more than
At least
At least]

In this example, consideration has not been given to the [ ] data from Avondale batches that were prepared with [ ], since this equipment will not be used in production at either site (Avondale or Singapore), nor was it used to prepare any of the pivotal clinical batches of drug product. [comment 5, May 4, 1999; comment 17.e., October 1, 1999]

4. In your response to Agency comment 11.c. of the May 4, 1999, letter, you indicated that the [ ] results provided by the manufacturer [ ] of the anhydrous lactose are used for confirmation that the [ ] grade has been received. Include acceptance specifications for the [ ] of the incoming [ ] and confirm the reliability of the manufacturer's results on a periodic basis. Update and submit the acceptance specifications for the [ ] accordingly. Evaluation of your response to comment 11.f. of the May 4, 1999, amendment concerning the [ ] will be deferred until the above concerns are adequately addressed. [comments 11.c. and 11.f., May 4, 1999; comments 18.a.(3) and 18.a.(6), October 1, 1999]

5. Provide tests with appropriate acceptance criteria for pyrogens and/or bacterial endotoxins in [ ] anhydrous lactose excipient used in this drug product. [comment 11.e., May 4, 1999; comment 18.a.(5), October 1, 1999]

6. Provide a letter of authorization for a DMF for the anhydrous lactose supplied by [ ], describing the manufacturing and controls used to assure adequate identity, assay, functionality, quality, and purity of this excipient. [comment 11.e., May 4, 1999; comment 18.a.(5), October 1, 1999]

7. As previously requested, the manufacturer [ ]) of the lactose anhydrous NF should either provide a letter certifying that no organic solvents are used in the preparation/processing of the material, or delineate the solvents that are used and the appropriate tests and acceptance criteria that provide assurance that the residual levels are adequately controlled. Modify the specification sheet for the acceptance of — accordingly. [comment 11.m., May 4, 1999; comment

18.a.(13), October 1, 1999]

8. Submit [ ] data for Singapore site-specific stability drug product batches obtained at the Singapore testing laboratory [ ] Kenilworth for enrollment in the stability program. [comment 12.c., May 4, 1999; comment 19.c., October 1, 1999]

9. Submit the specific SOP requirements in the drug product manufacturing protocols (both sites) regarding the maximum lengths of time that may elapse after manufacturing is [ ] t stability testing is performed. If there is a time lag between [ ] assembly and the addition of the [ ] packaging, specify the maximum allowable period. Also, indicate how the time [ ] stability studies is determined relative to the manufacturing date. Provide verification that the [ ] preparation and [ ] assembly, and the addition of the [ ] packaging for each batch are performed at the same site. [comment 12.c., May 4, 1999; comment 19.c., October 1, 1999]

10. Provide results from a study on representative samples of drug product determining [ ] in the formulation that are of respirable size (e.g., dissolution of formulation components and microscopic counting of particles [ ]. Such data may provide justification of the position outlined in your response to comment 13.i. of the May 4, 1999, Agency letter. [comment 13.i., May 4, 1999; comment 20.i., October 1, 1999]

11. The following comments pertain to the "development" versus the "commercial" devices. [comments 13.m., 14.c., and 14.d., May 4, 1999; comments 20.m., 21.c., and 21.d., October 1, 1999]

    a. Provide a detailed comparison of any differences for any of the components of the "development device" used for the clinical batches and the stability batches from Kenilworth and the "commercial device" used in preparation of the Singapore site-specific stability batches and the various validation/demonstration batches.

    b. Outline the differences between the two inhaler types that account for the observed differences in the [ ]

    c. Provide [ ] versions of both the "commercial" and the "development" devices.

    d. Provide detailed dimensional drawings (with tolerances indicated) for any parts that differ between the "commercial" and "development" devices.

e. Provide available data for the validation/demonstration drug product batches that were prepared with the "commercial" inhaler device.

f. Revise the tables provided in the October 1, 1999, amendment to indicate which device batches were [ ] and which were used in patient use studies (designations "B" and "U").

g. Since there are **significant differences** noted in the [ ] for drug product prepared with development (Kenilworth stability batches) and commercial (Singapore site-specific stability), and since the data for the latter type of drug product are quite limited, additional comments on the associated acceptance criteria for this test parameter will be forthcoming once updated data are provided and can be evaluated. See related comment 11.e. above.

12. Take action to correct [ ] through unit life (beginning to middle to end) that is observed for both the Kenilworth and Singapore drug product. An average loss of [ ] strength is already apparent at the initial stability time-point. [comment 14.e., May 4, 1999; comment 21.e., October 1, 1999]

13. Drug master file — was found to be inadequate to support your application. The holder has been notified of the deficiencies.

14. Drug master file — was found to be inadequate to support your application. The holder has been notified of the deficiencies. [comment 15.d., May 4, 1999; comment 22.d., October 1, 1999]

15. Drug master files [ ] were previously reviewed and found to be inadequate to support your application. The holders have been notified of the deficiencies but have not responded. [comment 15.d., May 4, 1999; comment 22.d., October 1, 1999]

16. Clarify the physical, mechanical, or other differences between the various presentations of the [ ] of the 220 mcg product and the target formulation fill for each (see p. 276 of the December 1, 1999, amendment). [comment 15.f., May 4, 1999; comment 22.f., October 1, 1999]

17. Provide a letter of authorization for review of the DMF from [ ] used in the [ ] device. [comment 2, September 9, 1999]

18. Provide the test data, referred to on page 902 of the response (June 30, 1999, amendment) to comment 15.g. of the May 4, 1999, letter, that support your position that only the [ ] of the device influences the flow resistance. Additionally, provide [ ] data for representative development and

commercial [ ] so that the proposed acceptance criterion on page 654 of the amendment can be evaluated. [comment 15.g., May 4, 1999; comment 22.g., October 1, 1999]

19. Propose an acceptance test for the [ ] contained in the [ ] [comment 15.i., May 4, 1999; comment 22.i., October 1, 1999]

20. Include a limit on the number of [ ] for the acceptance criteria for the [ ] packaging supplied by [ ]. Provide clarification of the application of the [ ] acceptable quality level for [ ] in terms of the number of [ ] allowed, and provide a description of the test method performed. Provide the results of the [ ] testing performed on samples of the [ ] packaging used for the stability batches of drug product from both sites. [comment 15.j., May 4, 1999; comment 22.j., October 1, 1999]

21. Drug master file — was found to be inadequate to support your application. The holder has been notified of the deficiencies. [comment 15.l., May 4, 1999; comment 22.k., October 1, 1999]

22. Drug master file — was found to be inadequate to support your application. The holder has been notified of the deficiencies. [comment 15.m., May 4, 1999; comment 22.l., October 1, 1999]

23. Drug master file — was found to be inadequate to support your application. The holder has been notified of the deficiencies. [comment 15.n., May 4, 1999; comment 22.m., October 1, 1999]

24. Based on the updated [ ] data provided for [ ] components, the [ ] acceptance criteria are too broad and should be tightened; e.g.,

[

NMT [
NMT

NMT
NMT

]

[comment 15.o., May 4, 1999; comment 22.n., October 1, 1999]

25. Provide the emitted dose results of the — testing study performed for the end-of-unit-life doses. Pages 979-980 of your June 30, 1999, response only included beginning-of-unit-life doses [ ] [comment 16.b., May 4, 1999; comment 23.b., October 1, 1999]

26. Indicate if any of [ ] outlined on page 970 of the June 30, 1999, amendment, were used in the devices for any of the batches of drug product associated with the application. [comment 16.b., May 4, 1999; comment 23.b., October 1, 1999]

27. Elaborate on whether or not the device counter failures, referred to on page 969 of the June 30, 1999, amendment, lead to changes in the lock-out points of the devices. [comment 16.b., May 4, 1999; comment 23.b., October 1, 1999]

28. Provide a summary of patient complaints, if any, of the number of counter malfunctions reported during clinical trials. [comment 16.b., May 4, 1999; comment 23.b., October 1, 1999]

29. The emitted dose results for inhalations [ ] study samples of the 220 mcg strength were consistently [ ] than would have been expected from the control data (pp. 998 – 1001 of the June 30, 1999, amendment). At this time, the data do not support the conclusion that there was no effect on dose delivery [ ] of the inhalers [ ] Investigate the cause [ ] and report the results. Refer to comment 8 above. [comment 16.g., May 4, 1999; comment 23.g., October 1, 1999]

30. No comments on the proposed in-use period [ ] will be provided until [ ] specifications that are based on updated data have been finalized. See related comment 11.g. above. [comment 16.i., May 4, 1999; comments 23.i. and 23.j., October 1, 1999]

31. Provide [ ] data for drug product near its proposed expiration date with [ ] packaging removed and after storage under conditions of 25°C/ These data will be considered when evaluating the appropriate use period for the product after the [ ] package is removed.

32. Provide the results of your study (p. 1054 of the June 30, 1999, amendment) to [ ] when exposed to simulated in-use conditions (e.g., 25°C/). [comment 16.i., May 4, 1999; comment 23.i., October 1, 1999]

33. For the batches included in the application (stability, clinical, batches stored [ ] under conditions of 25°C/ , demonstration batches, etc.), provide the dates [ ] were prepared and filled into devices, device final assembly was done, and [ ] packages were placed on the drug product, as well as the dates for release testing and stability testing (if applicable). [comment 16.k., May 4, 1999; comment 23.k., October 1, 1999]

34. In view of the differences noted between the Kenilworth stability batches and the Singapore stability batches, particularly with respect to [ ] provide updated stability data [ ] for the Singapore stability batches prepared with the commercial design device, so that stability and an appropriate expiry period can be assessed. [comment 17.a., May 4, 1999; comment 24.a., October 1, 1999]

35. The following sentence should be removed from the stability protocol: [ ] [comment 17.b., May 4, 1999; comment 24.b., October 1, 1999]

36. In view of the limited stability data for product prepared with the commercial device, and the performance differences noted between product prepared with the commercial device versus the development device, the number of annual batches to be placed on stability should be increased from the proposed number [ ] [comment 17.c., May 4, 1999; comment 24.c., October 1, 1999]

37. Include the grade and supplier of the excipient, anhydrous lactose, in stability reports. [comment 17.f., May 4, 1999; comment 24.f., October 1, 1999]

38. A comprehensive stability protocol should include a summary or reference in the application for the statistical method of analysis used for determining the expiration dating period for a drug product. Make the appropriate modifications to the stability protocol. [comment 17.f., May 4, 1999; comment 24.f., October 1, 1999]

39. The device should bear a place for recording the date that the [ ] package was opened and a corresponding statement instructing the patient to discard the product after the in-use period has passed. [comment 19, May 4, 1999; comment 26, October 1, 1999]

40. Immediate container labels, foil [ ] package labels, and the HOW SUPPLIED section of the labeling should state that the unit should be stored in a dry place with a stated, appropriate storage temperature range. [comment 21, May 4, 1999; comment 28, October 1, 1999]

41. The DESCRIPTION section should include a statement that the amount of drug delivered to the lung will depend on patient factors such as inspiratory flow and peak inspiratory flow (PIF) through the device. This is particularly relevant for this product since [ ] dependent on the flow rate. [comments 16.f. and 22.c., May 4, 1999; comments 23.f. and 29.c., October 1, 1999]

42. Provide confirmation that the patient instructions for inhalation of the dose during the clinical trials, the instructions provided to patients during the study conducted to determine the average flow rates generated by adult and adolescent patients with varying degrees of asthma (pp. 379-380 of the December 1, 1999, amendment), and the current proposed instructions in the PATIENTS INSTRUCTIONS FOR USE section of the labeling, are identical. If not identical, clarify and justify the differences. Provide the individual data that support the mean peak inspiratory flow rate stated in the DESCRIPTION section of the labeling. [comment 22.c., May 4, 1999; comment 29.c., October 1, 1999]

43. The HOW SUPPLIED section of the labeling should be revised to include the fill weight of the various presentations. [comment 23, May 4, 1999; comment 32.a., October 1, 1999]

44. Provide updated labeling and device mock-ups.

45. Submit the case report form for patient C97-222-23/571. In addition, clarify why this patient's liver function test results, as reported on the CD-ROM included in your December 1999 submission, appear normal, yet the patient is listed as having hepatitis.

46. Submit additional information to the mometasone furoate MDI IND concerning the GCP violations that occurred at center number 8 in study C97-222.

47. In your response to comment 12.b. of our October 1, 1999, letter, , you mention that RIA data in Trial C97-049 for the cortrosyn stimulation testing is available at both Screening and Day 29. Submit a statistical analysis of the comparison between the post-cosyntropin values at Screening and the post-cosyntropin values at Day 29 for mometasone furoate DPI given 400 mcg BID and 800 mcg BID versus placebo.

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

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

have been addressed.

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

If you have any questions, call Mr. David Hilfiker, Project Manager, at (301) 827-1084.

Sincerely yours,

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 21-067
HFD-570/Div. Files
HFD-570/Hilfiker
HFD-570/Gilbert-McClain
HFD-570/Himmel/3-8-00
HFD-570/Bertha/3-8-00
HFD-570/Poochikian/3-8-00
HFD-002/ORM
HFD-102/ADRA
HFD-40/DDMAC (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

3/13/00 3-13-00 3-10-00 3/13/00 3-10-00

Drafted by: HFD-570/Hilfiker/February 28, 2000
Initialed by: HFD-570/Trout/3-7-00
HFD-570/Meyer/3-8-00
Final: HFD-570/Hilfiker/3-10-00
Filename: c:\my_documents\N21067\00-02-28.aeltr.doc

APPROVABLE (AE)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-067

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Joseph F. Lamendola, Ph.D.
Vice President, Worldwide Regulatory Affairs

OCT 1 1999

Dear Dr. Lamendola:

Please refer to your new drug application (NDA) dated November 30, 1998, received December 1, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for mometasone furoate Dry Powder Inhaler.

We acknowledge receipt of your submissions dated January 28, February 5, 9, 26, March 9, 10, 23, 30, May 14, 24, June 30, July 14, and August 2, 23, and 27, 1999.

We also refer to your submission dated June 30, 1999. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

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

1. The efficacy of the 200 µg QAM dose has not been sufficiently demonstrated as it failed to significantly improve FEV1 in 2 out of the 3 trials in which it was studied. The 200 µg QPM dose appeared effective in a single trial, but was not replicated. In addition, none of these studies utilized the 200 µg product. In order to support the efficacy of 200 µg QAM dosing and/or 200 µg QPM dosing, additional efficacy trials with the to-be-marketed 200 µg formulation are required.

2. The to-be-marketed strength of 400 µg per inhalation was not utilized in the clinical trials to provide the 400 µg QAM dose nor the 400 µg BID dose in oral steroid dependent asthmatic patients. Therefore, there is a lack of effectiveness data using this product. In addition, there is no clinical or biopharmaceutics information regarding the comparability of the 200 µg and the 400 µg products at the same nominal dose, though in vitro data suggest some disparity in dose proportionality. Perform a pharmacokinetic and pharmacodynamic study utilizing the same nominal doses from the two to-be-marketed inhalation strengths (200 µg and 400 µg).

Include evaluation of dose-response to demonstrate sensitivity of the trial. We encourage you to contact the Division to discuss the trial design prior to initiating this trial.

3. The following comments pertain to Trial C96-196.

   a. The graph for AM PEFR in Figure 3 does not reflect the same data for AM PEFR that are presented in Table 13. Clarify this discrepancy.

   b. Explain why there are so few patients included for the FEV_1 on Day 4 for the MF DPI 200 QD AM and MF DPI 200 BID treatment groups for those subjects with FEV_1 <75% predicted and for the MF DPI 200 QD PM and MF DPI 400 QD AM treatment groups for those subjects with FEV1 $\geq$ 75%.

4. For Trial C96-136, Table 50 contains a footnote indicating that the severe adverse events listed are related or possibly related to treatment. The next paragraph in the report, indicates only one subject had an adverse event that was considered treatment related and severe during the 9-month phase. Clarify this discrepancy.

5. The following comments pertain to Trial C96-137.

   a. Subjects were allowed to take other medications for their asthma (i.e. Serevent, Atrovent, and Cromolyn-like drugs) during the treatment period with appropriate washout periods. Provide these data in a summary table over the course of the treatment period.

   b. Supply the case report forms (CRF) for the five instances of fetal disorders observed in the 9-month phase. Indicate the location of adverse events within the CRF.

   c. A serious adverse event of idiopathic thrombocytopenic purpura was noted at the last visit in Subject 213. Provide follow-up data on this subject.

6. For Trial C96-186, there were baseline differences among the treatment groups in the AM and PM PEFR. Perform an analysis factoring in these baseline differences, for example, by using them as a covariate in the analysis.

7. The following comments pertain to Trial I96-111.

   a. Clarify whether baseline use of salbutamol was a covariate in the analysis.

   b. Section 11.4.1.7 indicates that clinical asthma exacerbations were reported at some time during the study by 13 subjects in the MF DPI 100 µg BID group, 11 subjects in the MF DPI 200 µg BID group, 9 subjects in the MF DPI 400 µg BID group, and 9 subjects in the Fluticasone Propionate group. It is not clear why these numbers do not match the numbers for clinical asthma exacerbations in the Time to Worsening table in Section 11.4.1.7. Clarify this discrepancy.

c. The range of weights is listed as 45-665 kg and 44-835 kg, at Week 12 and endpoint for females in the MF DPI 200 µg BID and FP group, respectively. Clarify these values, as well as the weight ranges for Caucasians in these same treatment groups.

8. For Trial C96-112, the glucose values for Site 12 (C. Bisbal, M.D.) both at screening and at Week 12 appear to be out of the normal range of 3.9 –6.4 mmol/l listed for this site. The creatinine data at Week 12 also appear to be well out of the range of 62-124 µmol/l. Submit a clarification of the glucose and creatinine data at this site.

9. For Trial I96-113, it appears that the increase in the listed weight of women on 600 µg BID is erroneous. Clarify the data.

10. For Trials I96-113 and C96-136, "menstrual disorder" was one of the adverse events listed. Clarify the definition of pain and menstrual disorder.

11. In the package labeling under Clinical Trials, a reference made to C96-136 indicates that the subjects entered into this study C
    Clarify what is meant by C
    and justify why these subjects met that criterion.

12. The following comments pertain to the evaluation of the effect of mometasone furoate on the hypothalamic-pituitary-adrenal (HPA) axis.

    a. For Trials C95-135 and C97-049, the post-cosyntropin stimulation mean serum cortisol concentration data could not be located in a table format. Supply this information as well as outlier data (subjects whose prestimulation concentration of plasma cortisol was <5 µg/dl, whose poststimulation concentration was <18 µg/dl, or whose response to stimulation was not an increase of at least 7 µg/dl) in a summary table.

    b. For Trial C97-049, submit a statistical analysis of the comparison between the post-cosyntropin values at baseline and the post-cosyntropin values at Day 29 for each active treatment versus placebo.

    c. Using mean serum cortisol $AUC_{(0\text{-}24)}$ (µg·hr/dl) data, submit an analysis comparing the change in cortisol AUC from baseline for each particular treatment arm with the change from baseline for placebo for Trials C97-049 and C95-135.

    d. There is considerable difference in the 24 hour cortisol AUC results between Trials C97-049 and C95-135. Provide an explanation for this difference. Discuss, based on pharmacokinetic data, what to-be-marketed doses and formulations would be supported by the data available in Trial C95-135.

e. For Trial C96-196, while cortrosyn stimulation testing was performed at screening, the data were only made available as individual line listings. Provide tabulated data with statistical analyses comparing the mean values at screening with those at baseline and endpoint.

13. It is stated in the Integrated Summary of Safety that ECGs were performed at Week 12 in Trial C96-134 (Section 8.2.6.1), however, the protocol did not require Week 12 ECGs. Clarify this discrepancy.

14. Based on concerns raised to the Division by the Division of Scientific Investigators (DSI), supply a re-analysis of the data for Trials C96-137 and C96-196 without Dr. Jay Grossman's subjects. Specifically, provide re-analysis of the prednisone data and FEV_1 data for Trial C96-137 and FEV_1 data and peak-flow data for Trial C96-196.

15. The assay methods and their validation reports for plasma or urinary cortisol levels were incomplete. Submit the actual assay results obtained from the following individual Trials I94-130, I95-135, and C97-049, in addition to performance data for the assay validation (copies from the commercial kits).

16. Because [ ] contains a structural alert for mutagenicity, qualify this impurity in two genotoxicity tests, one mutagenicity test and one chromosomal aberration test. Use the isolated impurity in these tests. Alternatively, you may reduce your specification in both the drug substance and drug product to less than [ ]

Note: Numbers in parentheses after each comment 17-29 refer to the corresponding comment numbers in the Agency's May 4, 1999, letter unless otherwise noted. While some comments have been rephrased, the intent of all of the comments is identical.

17. The following comments pertain to the drug substance.

a. Provide confirmation that [ ] (comment 1)

b. Provide the specifications, storage conditions, and associated retest period for the anhydrous mometasone furoate reference standard. (comment 2)

c. The acceptance criteria for recurring unidentified related compounds [ ] should be tightened to less than [ ] (comment 3)

d. There should be a quantitative and validated test and appropriate specifications for [ ] the drug substance at release and for retest or recertification [ ] (comment 4)

e. Based on the [ ] data provided (February 5, 1999, amendment, enclosure 1, p. 5) for the Union, Avondale, and Singapore batches of mometasone furoate [ ], the acceptance limits should be tightened. The following example is provided. (comment 5)

Median [
At least
Not more than
At least
At least]

f. Tighten the specifications for [ ] mometasone furoate to reflect the data presented for the batches prepared with the [ ] process and for the batches prepared with the [ ] process used for the clinical drug product batches and the Kenilworth primary stability batches of drug product. (comment 6)

g. The stability data presented for the [ ] drug substance indicated that the [ ] for most batches was about [ ] with a range from [ ] Based on these data, tighten the acceptance limit. (comment 7)

h. Tighten the acceptance criteria range for the [ ] determined in [ ] to reflect the data. (comment 8)

i. The detected individual impurities are less than [ ] in batches prepared with the [ ] process for commercial production, therefore, tighten the specification for total related substances in the drug substance to reflect these data (e.g., not more than [ ] (comment 9)

j. Container labels for the drug substance should clearly state that the compound should be protected from light. (comment 10)

18. The following comments pertain to the drug product.

a. The following comments pertain to lactose.

(1) Provide confirmation that the only source of lactose anhydrous NF will be [ ]. (comment 11a)

(2) Provide confirmation that the anhydrous lactose used at both drug product manufacturing sites will be obtained from the same supplier and will be the same grade. (comment 11b)

(3) It is apparent that [ ] supplies at least [ ] of lactose material. Specify which grade is obtained from this supplier and provide a representative certificate of analysis. Additionally, provide data establishing the ability of the acceptance testing to distinguish between the multiple grades. (comment 11c)

(4) Any post-approval change in the supplier or the grade of anhydrous lactose should be submitted with appropriate comparative and supportive data in a prior approval supplement. (comment 11d)

(5) For the anhydrous lactose excipient, there should be tests and appropriate acceptance limits for pyrogens and/or bacterial endotoxins. Once the reliability of the supplier is established, testing on a periodic basis could be proposed. (comment 11e)

(6) Specify a test with acceptance criteria for the [ ] anhydrous lactose [ ] to assure the proper [ ] (comment 11f)

(7) The following comments pertain to the assay and impurities determinations and method [ ] for the anhydrous lactose. (comment 11g)

i. Confirm that the impurities and degradant acceptance limit of "not more than [ ]" is for the total impurities and degradants monitored for the lactose. Revise the specification sheet to clarify. (comment 11g(1))

ii. Provide an explanation for the apparent increase in variability of the assay results when comparing the data for [ ] versus the [ ] Include revisions in the method if warranted. (comment 11g(2))

iii. Depending on the responses to the above two requests, the assay acceptance limit currently proposed of [ ] may need to be tightened. (comment 11g(3))

(8) For greater assurance of the reproducibility of the physical characteristics of the [ ] provide a lower limit for the [ ] that is reflective of the data for [ ] used in the clinical and primary stability batches of drug product [ ] (comment 11h)

(9) In order to complete the evaluation of [ ] method used for [ ]
provide a correlation with the actual [ ]

Revise the specifications to indicate the correlated [ ] (comment 11i)

(10) For the method used for determination of [ ] indicate what [ ] testing or calibration is performed to assure accuracy of the [ ] (comment 11j)

(11) Tighten the acceptance criteria for the [ ] for the [ ] to reflect the data provided (volume 2.3, 4B23.4, p. 12). For example: (comment 11k)

At least [ ]

At least
At least
At least
Median]

(12) Identify the sites of [ ] the equipment, and the detailed [ ] parameters ([ ]) for the lactose used in preparing the clinical batches of drug product and the Kenilworth and Singapore primary stability batches of drug product. Also, identify the source and specific grade of lactose for each of these batches. (comment 11l)

(13) The manufacturer [ ] of the lactose anhydrous NF used for the drug product formulation should either provide a letter certifying that [ ] are adequately controlled. This information may be provided directly to the Agency if it is desired that the information remain confidential. (comment 11m)

19. The following comments pertain to the drug product manufacturing.

a. Include an assay of the [ ] r the in-process tests performed during the manufacture of the drug product. Propose associated acceptance criteria. (comment 12a)

b. For release sampling, you should monitor the [ ] for inhalers from the beginning, middle, and end of a batch. (comment 12b)

c. For the primary stability batches of drug product [ ] at 25°C/60%RH and those drug product batches stored [ ] at 25°C/ [ ] provide a comprehensive list that outlines the date of manufacture and storage conditions (temperature, humidity, packaging used) before release and before initial time-point stability testing for the parameter [ ] (comment 12c)

after [ ], which would avoid the need for validation of the [ ] in terms of endotoxins/pyrogens.

6. *Provide a letter of authorization for a DMF for the anhydrous lactose supplied by [ ], describing the manufacturing and controls used to assure adequate identity, assay, functionality, quality, and purity of this excipient. [comment 11.e., May 4, 1999; comment 18.a.(5), October 1, 1999]*

Schering stated that they intend to submit the information to the NDA, rather than have [ ] create a DMF. FDA reminded Schering that a Guidance under development may eventually require a DMF to be developed, but that inclusion of the information directly to the NDA may actually be easier for now.

FDA also warned Schering that lactose is sold according to a Grade classification, but that lactose from the same supplier and of the same grade in different drug products has been much different in terms of quality and purity. FDA recommended that Schering test each batch of lactose that is used to develop specifications for its use in the drug product.

8. *Submit release data for Singapore site-specific stability drug product batches obtained at the Singapore testing laboratory [ ] to Kenilworth for enrollment in the stability program. [comment 12.c., May 4, 1999; comment 19.c., October 1, 1999]*

Schering stated that release testing is conducted at Kenilworth, because they do not believe that their Singapore test facility has the capability to perform these tests adequately. FDA requested that Schering provide a detailed description of the time intervals [ ] of the commercial manufacturing procedure, and include [ ] the drug product from Singapore to Kenilworth [ ] Schering agreed to provide that description.

FDA requested any data, including research data, that are available for the drug product from the Singapore site, [ ] to Kenilworth. Schering agreed to provide any data that is available, but emphasized the limited nature of these.

12. *Take action to correct the [ ] [ ] through unit life (beginning to middle to end) that is observed for both the Kenilworth and Singapore drug product. An average loss of [ ] for the 220 mcg strength is already apparent at the [ ] stability time-point. [comment 14.e., May 4, 1999; comment 21.e., October 1, 1999]*

20. The following comments pertain to the specifications and test methods for the drug product.

a. The description test [ ] acceptance limits allow the [ ] formulation [ ] Propose a quantitative test for [ ] with appropriate acceptance criteria for release and stability testing. (comment 13a)

b. Additional comments on [ ] specification for the drug product may be forthcoming depending on the results of the investigation of the trends and substantial differences between batches in the amount of delivered [ ] [ ] for drug product batches stored [ ] at 25°C [ ] as outlined below in comment 23.i. (comment 13b)

c. The [ ] assay method [ ] should contain [ ] in addition to [ ] and mometasone furoate. Set appropriate [ ] (comment 13c)

d. Provide an explanation for the observation that the [ ] the Mometasone Furoate [ ] for the assay and impurities methods for the drug substance and drug product are quite different [ ] [ ] even though the sample concentrations are the same and the methods nearly identical (refer to data in volumes 2.17, 4D2.6, p. 44 and 2.19, 4D3.4, p. 207). This difference is reflected in the respective [ ] limits for [ ] [ ] of this solution for the methods. (comment 13d)

e. Since the levels of all degradants were found to be below the quantitation limit of the method [ ] for the 12 months of storage under conditions of 25°C/60%RH, the proposed acceptance limits for degradant [ ] the "total for all specified degradation products," and the "total for all specified degradation products and unspecified impurities" are not justified and should be tightened. (comment 13e)

f. Revise the method [ ] for examination of the powder [ ] include [ ] both acceptable and unacceptable [ ] (e.g., as in the validation report in volume 2.7, 4B8.3, pp. 490, 493, 496, and 499). (comment 13f)

g. Revise the method [ ] for microscopic examination of the [ ] to include [ ] mometasone furoate [e.g., as in the validation report (volume 2.7, 4B8.3, pp. 507-512)]. In addition, revise the method name to indicate that it is the [ ] [ ] that are being examined. (comment 13g)

h. The [ ] data collected from the first 20 inhalations [ ] [ ] of units from your primary stability batches stored at 25°C/60%RH for both sites support a tightening of the acceptance limit of [ ] Data collected for the 12-month time-point for the Kenilworth batches and at the initial and 3-month point for the Singapore batches average approximately [ ] [ ] with a range of [ ] Tighten these limits to better reflect the data. (comment 13h)

i. Revise the specification and test for [ ] in the drug product formulation [ ] to include examination with acceptance limits for [ ] (comment 13i)

j. Revise all acceptance criteria for the [ ] for the drug product to clarify that the ±15% range for the mean applies to both stages of testing (i.e., the mean of the first stage cannot be outside of this range). (comment 13j)

k. Provide detailed drawings and descriptions of all [ ] equipment in the methods [ ] to allow Agency laboratories to perform and assess these. (comment 13k)

l. Provide data for multiple inhalers that address the repeatability and reproducibility of the entire method [ ]

For example,

[ ] (comment 13l)

m. As previously noted at the September 14, 1998, pre-NDA meeting, the acceptance criteria for [ ] for the shelf-life of the drug product are too broad. The proposed ranges for both strengths are unacceptable, particularly the wide limits. [ ] Tighten the acceptance criteria [ ] Based on the data from the clinical and primary stability batches of drug product prepared at the Kenilworth site, the following acceptance criteria would be supported. (comment 13m)

	200 µg/inhalation	400 µg/inhalation
Total Recovery	[	
Group I		
Group II		
Group III		
Group IV		]

Further tightening of these acceptance limits may be warranted depending upon your responses to comments 21a-e below.

n. The shelf-life specifications for both strengths of the product should include the [ ] testing and acceptance [ ] of the components [ ] as for the release of the drug product so that [ ] changes in either the drug substance or excipient would be noted. (comment 13n)

o. The shelf-life specifications for both strengths of the product for the [ ] should be controlled *separately* for the beginning and the end inhalations to ±15% of the label claimed delivery. (comment 13o)

21. The following comments pertain to stability and release data collected for the drug product.

a. Account for the consistently [ ] for the primary stability batches of drug product prepared in Singapore as compared to drug product batches prepared in Kenilworth. (comment 14a)

b. From the release data provided for clinical and primary stability batches it was noted that the [ ] for batches prepared in Singapore was [ ] than the average [ ] from drug product prepared at the Kenilworth site. Account for this difference and take corrective measures to address this discrepancy. (comment 14b)

c. Although the amount of stability data available from the batches of drug product prepared at the Singapore site are very limited, there appears to be an overall difference in the trend for the average [ ] life. Kenilworth product generally shows [ ] on stability at 25°C/60%RH whereas Singapore product has [ ] for this period. Additionally, the metered doses for the Kenilworth batches are generally [ ] than the label claims of 220 [ ] mcg. These observations may be related to the differences [ ] noted in the comment below. Address all differences in the performance properties of the product prepared at both sites. Take corrective actions to ensure reproducibility and comparability of the product prepared at each site. (comment 14c)

d. Based on the release and stability data presented for the Kenilworth and Singapore product, it is noted that there are distinct differences between product prepared at these two sites, particularly in terms of [ ] In general, the Singapore product displays [ ] . For example,

[ ]

[ ] is [ ] for the product prepared at Kenilworth. These substantial differences are not acceptable. Undertake measures to determine the cause and institute appropriate corrective actions. (comment 14d)

e. Based on [ ] stability data provided for both Kenilworth and Singapore drug product, there is a consistent and substantial loss [ ]]. Losses of this magnitude are considered significant and necessitate investigation and correction. [ ] testing should be performed [ ] drug product batches and for stability batches. Modify the specifications and stability protocol accordingly. (comment 14e)

f. Since the [ ] for each primary stability batch of product from both sites was only [ ] of the theoretical number that could be [ ], explain how it can be assured that the [ ] samples will be representative of drug product that would have resulted from [ ] using the total agglomerate batch. (comment 14f)

g. Provide comprehensive stability data obtained in a systematic fashion for drug product with the [ ] proposed [ ] These data will directly compared with data provided for the primary and site specific stability batches [ ] [ ] Refer to our comments below (23.i) regarding the [ ] packaging and in-use data provided in the application for [ ] product stored under simulated potential in-use storage conditions of 25°C/[ ] which highlight the need for adequate [ ] packaging of the filled inhalers. Also refer to comments 21a-e above regarding significant differences in [ ] data for the stability samples of product prepared at the Kenilworth site as compared to the Singapore site [ ] (comment 3, September 9, 1999, Agency letter)

h. Provide the description of the [ ] used for the clinical batches of drug product. (comment 15k)

22. The following comments pertain to the container and closure system of the drug product.

a. The location of the confidential information regarding the manufacturer's acceptance tests for raw materials, complete composition [ ], and manufacturer's release tests and specifications for [ ] could not be found in the referenced drug master file [ ] This information is required and letters of authorization (LOAs) should be supplied that provide specific reference with page number(s) and submission date(s). This DMF is currently considered inadequate for support of your application. (comment 15a)

b. As the acceptance specifications for [ ] lists only [ ] it is not clear what supplier of [ ] was used to prepare the clinical and stability batches of drug product or what supplier is being proposed as the source for the to-be-marketed product. Provide clarification of the sources. If both suppliers are to be used in the future, provide comparative in-use data [ ] for drug product prepared with [ ] from each (i.e., data collected on [ ] product after storage under accelerated conditions). In general, the use of alternate suppliers or materials of construction for components of the container and closure system ( ) needs to be supported by relevant performance and stability data. (comment 15b)

c. Evaluation of DMF [ ] for [ ] will not take place until clarification of the [ ] source for the clinical and primary stability batches is provided or before comparative in-use data, as outlined above, are forwarded for review (see comment 22.b. above). (comment 15c)

d. Drug master files [ ] were reviewed and found to be inadequate to support your application and the holders have been notified of the deficiencies. (comment 15d)

e. Clarify the use of [ ] from [ ] (DMF [ ]) The letter of authorization from the supplier indicates that the file includes information on [ ] The use of this material was not indicated in your container and closure component specification sheets. (comment 15e)

f. There appears to be a difference in the material/number [ ] for [ ] [ ] provided in your application as compared to that indicated in the device manufacturer's DMF [ ] Provide clarification of this discrepancy and make appropriate corrections in the relevant documents. (comment 15f)

g. There should be a test of the flow resistance of the assembled device. Acceptance criteria should be included in the appropriate specification sheets. (comment 15g)

h. Test incoming batches of container and closure components for the absence of objectionable microorganisms and for bioburden for confirmation of the [ ] procedure. Once the reliability of the [ ] is established, testing on a periodic basis could be proposed. (comment 15h)

i. Provide a [ ] test for the [ ] (comment 15i)

j. Provide the acceptance specifications for both the [ ]. (comment 15j)

k. Based on the package description for [ ] (volume 2.4, 4B6.1, p. 3), the packaging development report (volume 2.5, 4B7.3, pp. 13-14), and the LOA from [ ] for review of DMF [ ] (volume 2.4, 4B6.3, p. 21), it is not possible to determine which is the alternate [ ] material used or proposed for commercial use. The adequacy of the information provided in DMF [ ] for [ ] will

not be assessed until an LOA from [ ] is resubmitted that specifically indicates what [ ] material was supplied for the product and where the information is located (amendment date, page numbers). Also refer to the related comments 21.g, 21.h and 22.j above. (comment 15l)

l. DMF [ ] was reviewed for information on the [ ] material and was found to be inadequate. Comments have been forwarded to the holder. (comment 15m)

m. DMF [ ] is a type I file and does not contain the required detailed information on the [ ] procedures and parameters performed on the container and closure components for your drug product. [ ] may provide this information confidentially to the Agency via a type V DMF (*Federal Register*, Volume 33, No. 133, 7/11/90, p. 28378). (comment 15n)

n. [ ] testing should only be performed after [ ] There were notable differences after [ ] particularly in the levels of the [ ] [ ] Tighten the specifications accordingly to reflect the levels of [ ] obtained from the [ ] components only. For example: (comment 15o)

[
NMT —
NMT —

NMT —
NMT —

NMT —
NMT —
]

o. Include the expiration date on the portion of the device that contains the formulation. (comment 1, September 9, 1999, Agency letter)

p. Revise the color of the cap labeling (and other colored portions of associated labeling on primary and secondary packaging materials) and the plastic adapter component of the device [ ] such that it is different for the two strengths of the product (220 [ ] per metered dose). (comment 2, September 9, 1999, Agency letter)

23. The following comments pertain to characterization studies for the drug product.

a. The decrease in the average emitted dose observed after activation from non-upright positions, particularly at 90° from vertical, for later inhalations from both strengths, is significant [ ] for the 200 and 400 mcg strengths, respectively). Strengthen wording in the patient's instructions for use to ensure that activation (cap removal) is done with the unit in the vertical or upright position, e.g., "to ensure

proper dose delivery, the cap must be removed with the unit in the upright position with the [ ] base down as shown (Figure 1)." See related comment 33.b. (comment 16a)

b. Provide the results of the [ ] testing performed as per the protocol listed in volume 2.5, 4B7.3, p. 46. (comment 16b)

c. Repeat the study addressing the effects of humidity (i.e., 25°C) with equilibration periods of at least 24 hours and also for 48 and 72 hours (volume 2.5, 4B7.3, pp. 48-51). (comment 16c)

d. Repeat the study on the effects of multiple activations with the activations occurring in different orientations from the upright or vertical position (i.e. 45° and 90° from upright), and provide the resultant data. (comment 16d)

e. Provide the duration of the flow or the total volume used for each flow rate for the studies on the effect of flow rate on emitted dose [ ] (volume 2.5, 4B7.3, pp. 54-57). (comment 16e)

f. Resubmit the [ ] data versus flow rate (volume 2.5, 4B7.3, p. 57) in terms of the actual amounts of material found as opposed to percentage of recovery. (comment 16f)

g. Provide emitted dose content uniformity data [ ] from New Jersey to [ ] so that these data can be compared to the data provided for units [ ] (volume 2.5, 4B7.3, pp. 58-59). (comment 16g)

h. Submit the emitted dose test results for the 200 mcg/actuation strength product using the simulated-use test schedule for the number of doses (120) (volume 2.5, 4B7.3, p. 63). (comment 16h)

i. The examination of [ ] data for the-end-of-unit inhalations for the seven batches of drug product stored [ ] under conditions of 25°C revealed the following. (comment 16i)

(1) In terms of [ ] there appear to be two types of batches for each strength. Batches 37889-043 (400 mcg) and 37889-040 (200 mcg), which have [ ] than the remaining batches, do not display the sharp [ ] seen for the remaining batches in the first month of storage. The difference in the amount [ ] seen initially and the difference in rate of decrease seen over time should be investigated, explained and corrected. (comment 16i(1))

(2) For [ ] two of the 400 mcg strength product batches lost [ ]. Likewise, three of the 200 mcg strength product batches lost [ ] Losses of this magnitude are not acceptable. Corrective action will need to be undertaken, and details of these corrective actions provided. (comment 16i(2))

j. Comments on the appropriate in-use period will be withheld pending the appropriate modifications to the specifications and the results of the above mentioned investigation. (comment 16j)

k. Provide the [ ] data for the [ ] for the following batches of drug product 37889-040, 39457-058, 37889-043, and 37889-059 as well as any [ ] data available for these batches stored within their unopened [ ] under conditions of 25°C . (comment 16k)

24. The following comments pertain to the expiration dating period and stability protocols for the drug product.

a. Comments on the appropriate expiration dating period for the product will be withheld pending the submission of updated data with reanalysis for pertinent parameters [ ] in terms of updated specifications. (comment 17a)

b. Remove the section entitled [ ] from the protocol. Annual batches should be placed on stability as outlined in what is currently termed the [ ]. As discussed at the September 14, 1998, meeting, the section entitled [ ]' should also be removed from the stability protocol [ ] (comment 17b)

c. The placement of only one batch out of — batches of drug product on stability from each production site is not acceptable. Propose an increased number of batches from each production site that will be placed on stability relative to the number of batches produced. (comment 17c)

d. The stability protocol should specifically state that the representative samples will be obtained from each manufacturing site for each package size and type (multiple count presentations of both trade and physician samples, where applicable). (comment 17d)

e. As per comment 21.e., modify the protocol to indicate that the [ ] [ ] testing [ ] should be performed through unit life (i.e., over the labeled number of inhalations). (comment 17e)

f. Revise the stability protocol and report format for production batches (volume 2.13, 4B9.4, pp. 1-2) to indicate the following additional information:

(1) Grades and suppliers of the drug substance and excipient. (comment 17f(1))

(2) Batch size. (comment 17f(2))

(3) Source of container and closure ( ). (comment 17f(3))

(4) Specifications, (i.e., test parameters, method numbers and acceptance criteria). (comment 17f(4))

(5) Storage orientation. (comment 17f(5))

(6) Statistical analysis approach and designation of parameters examined. (comment 17f(6))

(7) Format of the stability data to be reported. (comment 17f(7))

(8) Proposed expiration dating period. (comment 17f(8))

The following preliminary comments pertain to the labeling. Additional comments will be provided when the above issues have been addressed.

25. The trademark and the established name of the product should always include the metered dose for all labels and labeling. (comment 18)

26. The device should bear a place for recording the date that the [and a corresponding statement instructing the patient to discard the product "X many days from the date of opening of the [ ]." The Patient Instructions for Use should be revised accordingly. (comment 19)

27. For all labels and labeling, the product name should be closely associated with a statement that the drug product is for oral inhalation use only. (comment 20)

28. Immediate container labels, foil [ ]labels, and the HOW SUPPLIED section of the labeling should state that the unit should be stored in a dry place, in addition to the storage temperature range. (comment 21)

29. The DESCRIPTION section of the labeling should be revised as follows.

a. Include the amount of formulation delivered with each inhalation of the device for both strengths. (comment 22a)

b. The lactose used in the formulation should be described as anhydrous. (comment 22b)

c. The range and average of peak inspiratory flow rates achieved by adult patients with varying severity of asthma should be included and the range correlated to the in vitro emitted dose delivery of the device that would be obtained for this range of flow rates and constant volume (2 L). (comment 22c)

30. The CLINICAL PHARMACOLOGY section should be revised as follows.

Pharmacokinetics: Absorption: [

]

[ ]

Distribution: Based on the study employing [ ]1000 mcg inhaled dose [ ] no appreciable accumulation of mometasone furoate in the red blood cells was found. Following an intravenous 400 mcg dose of mometasone furoate, the plasma concentrations showed a biphasic decline, with a mean terminal half-life of about 5 hours and the mean steady-state volume of distribution of 152 liters. The in vitro protein binding for mometasone furoate was reported to be 98 to 99% (in a concentration range of 5 to 500 ng/ml).

Metabolism: Studies have shown that mometasone furoate is primarily and extensively metabolized in the liver of all species investigated and undergoes extensive metabolism to multiple metabolites. In-vitro studies have confirmed the primary role of CYP 3A4 in the metabolism of this compound, however, no major metabolites were identified.

Excretion: Following an intravenous dosing, the terminal half-life was reported to be about 5 hours. Following the inhaled dose of tritiated 1000 mcg mometasone furoate, the radioactivity is excreted mainly in the feces (a mean of 74%), and to a small extent in the urine (a mean of 8%) up to 7 days. No radioactivity was associated with unchanged mometasone furoate in the urine.

Special Populations: Administration of a single inhaled dose of 400 mcg mometasone furoate to subjects with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment resulted in only 1 or 2 subjects in each group having detectable peak plasma concentrations of mometasone furoate (ranging from 50 to 105 pcg/ml). The observed peak plasma concentrations appear to increase with the severity of hepatic impairment, however, the numbers of detectable levels were few. The effects of renal impairment, age or gender on mometasone furoate pharmacokinetics have not been adequately investigated.

Drug-Drug Interaction: An inhaled dose of mometasone furoate 400 mcg was given to 24 healthy subjects twice daily for 9 days and ketoconazole 200 mg (as well as placebo) were given twice daily concomitantly on Days 4 to 9. Mometasone furoate plasma concentrations were <150 pcg/ml on day 3 prior to co-administration of ketoconazole or placebo. Following concomitant administration of ketoconazole, 4 (out of 12) subjects in the ketoconazole treatment group (n=12) had peak plasma concentrations of mometasone furoate >200 pcg/ml on Day 9 (211 to 324 pcg/ml). Since mometasone furoate plasma levels appear to increase and plasma cortisol levels appear to decrease upon concomitant administration of ketoconazole, caution should be

exercised in the co-administration of these drugs.

30. The third paragraph of the Carcinogenesis, Mutagenesis, Impairment of Fertility subsection should be revised as follows.

31. The Pregnancy subsection should be revised as follows.

Pregnancy Category C:

[

]

32. The HOW SUPPLIED section of the labeling should be revised as follows.

a. The fill weight of the various presentations should be included. (comment 23a)

b. A statement should be included in this section that the inhalers have a lock-out mechanism, that is, the inhaler will not deliver subsequent doses once the counter reaches zero ("0"). (comment 23b)

c. The in-use period [ ] may need to be revised depending on the corrective actions taken to address the [ ] and the differences between product from both sites after storage [ ] at conditions of 25°C/ [ ] (comment 23c)

33. The Patient Instructions for Use should be revised as follows.

a. A statement should be included instructing the patient to clean any remaining saliva from the mouthpiece prior to replacement of the overcap. (comment 24a)

b. The wording on the device orientation during activation (cap removal) should be strengthened [(e.g., "to ensure proper dose delivery, the cap must be removed with the unit in the upright position with the [ ] base down as shown (Figure 1)"]. (comment 24b)

c. The warning "Do not breath out through the inhaler" should be strengthened and written in bold in the patient instructions. (comment 24c)

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the invetigator's. Satisfactory inspections will be required before this application may be approved.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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

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

If you have any questions, contact Mr. Keary Dunn, Regulatory Project Manager, at (301) 827-5580.

Sincerely,

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

186 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling