

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-067**

**Administrative/Correspondence**

**Patent Information Pursuant to 21 CFR § 314.53**

Re: Use of TRADEMARK (mometasone furoate inhalation powder) product to Treat Asthma

Tradename: TRADEMARK  
Active Ingredient: Mometasone Furoate  
Strength: 220mcg/inhalation  
Dosage Form: Dry Powder Inhaler

Pursuant to the provisions of 21 CFR § 314.53 Applicant provides the following patent information for the caption Schering Corporation ("Schering") NDA:

U.S. Patent No.: 4,472,393  
Expiration Date: September 18, 2001  
Type of Patent: Mometasone Furoate as the compound per se; mometasone furoate, the active ingredient in the drug product, TRADEMARK (mometasone furoate inhalation powder) product, for which approval is being sought.  
Patent Owner: Schering Corporation

U.S. Patent No: 5,394,868  
Expiration Date: March 12, 2012  
Type of Patent: Inhaling device for powdered medicaments including mometasone furoate, the active ingredient in the drug product, TRADEMARK (mometasone furoate inhalation powder) product, for which approval is being sought.  
Patent Owner: Schering Corporation

U.S. Patent No.: 5,829,434

Expiration Date: November 3, 2015

Type of Patent: Powder inhaler for powdered medicaments including mometasone furoate, the active ingredient in the drug product, TRADEMARK (mometasone furoate inhalation powder) product, for which approval is being sought.

Patent Owner: Schering Corporation

U.S. Patent No.: 5,740,792

Expiration Date: April 21, 2015

Type of Patent: A dry powder inhaler dose counter including the drug product, TRADEMARK (mometasone furoate inhalation powder) product equipped with a dose counter, for which approval is being sought.

Patent Owner: Schering Corporation

U.S. Patent No.: 5,687,710

Expiration Date: November 18, 2014

Type of Patent: A dry powder inhaler nozzle including the drug product, TRADEMARK (mometasone furoate inhalation powder) product equipped with a nozzle, for which approval is being sought.

Owner of Records: Schering Corporation



U.S. Patent No.: DE 348,928

Expiration Date: July 19, 2011

Type of Patent: Design covering the drug product, TRADEMARK (mometasone furoate inhalation powder) product, for which approval is being sought.

Owner of Record: Schering Corporation

The undersigned declares that (a) the above listed U.S. Patent No. 4,472,343 covers mometasone furoate as the compound per se, and that (b) mometasone furoate is the active ingredient in the TRADEMARK (mometasone furoate inhalation powder) product for which approval is being sought under Section 505 of the Federal Food Drug and Cosmetic Act (FFD&C Act) 21 USC § 355.

The undersigned declares that (a) the above listed U.S. Patent No. 5,394,868 covers an inhalations device for powdered medicaments including the TRADEMARK (mometasone furoate inhalation powder) product, and that (b) the TRADEMARK (mometasone furoate inhalation powder) product is the drug product for which approval is being sought under Section 505 of the FFD&C Act.

The undersigned declares that (a) the above listed U.S. Patent No. 5,829,434 covers a powder inhaler for powdered medicaments including TRADEMARK (mometasone furoate inhalation powder) product and that (b) the TRADEMARK (mometasone furoate inhalation powder) product is the drug product for which approval is being sought under Section 505 of the FFD&C Act.

The undersigned declares that (a) the above listed U.S. Patent No. 5,740,742 covers a dry powder inhaler dose counter including the TRADEMARK (mometasone furoate inhalation powder) product equipped with dose counter and that (b) the TRADEMARK (mometasone furoate inhalation powder) product equipped with a dose counter is the drug product for which approval is being sought under Section 505 of the FFD&C Act.



The undersigned declares that (a) the above-listed U.S. Patent No. 5,687,710 covers a dry powder inhaler nozzle including the TRADEMARK (mometasone furoate inhalation powder) product equipped with a nozzle and that (b) the TRADEMARK (mometasone furoate inhalation powder) product equipped with a nozzle is the drug product for which approval is being sought under Section 505 of the FFD&C Act.

The undersigned declares that (a) the above listed U.S. Design Patent DE 348,928 covers the design of the TRADEMARK (mometasone furoate inhalation powder) product and that (b) the TRADEMARK (mometasone furoate inhalation powder) product is the drug product for which approvals being sought under Section 505 of the FFD&C Act.

The undersigned further declares that a claim of patent infringement under U.S. Patent Nos. 4,472,393, 5,394,868, 5,829,434, 5,740,792 and 5,687,710 and U.S. Design Patent DE 348,928 could reasonably be asserted if a person not licensed by Schering Corporation, the owner of each of the above listed patents, engaged in manufacture, use, sale, or offer for sale of the TRADEMARK (mometasone furoate inhalation powder) product.



## 19. Claim for Exclusivity

1. Pursuant to the provisions of Sections 505 (c) (3) (D) (iii) and 505 (j) (4) (D) (iii) of the Food, Drug and Cosmetic Act (FDCA) and 21 CFR 314.108 (b) (4), the applicant claims three (3) years of exclusivity for its TRADEMARK (mometasone furoate inhalation powder) product and its use for the treatment of asthma.
2. The applicant certifies that to the best of the applicant's knowledge each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in 21 CFR 314.108 (a).
3. There are no published studies or publicly available reports of clinical investigations known to the applicant through a computer-assisted literature search that are relevant to the conditions for which the applicant is seeking approval.
4. The applicant certifies that it has thoroughly searched the scientific literature through a computer-assisted search of the Scholar database, encompassing MEDLINE, BIOSIS, EMBASE, DERWENT DRUG FILE, CHEMICAL ABSTRACTS SEARCH, and SCISEARCH databases, for English and non-English literature relating to clinical studies of mometasone furoate in asthma.
5. To the best of the applicant's knowledge, the list of scientific literature pertaining to mometasone furoate and asthma is complete and accurate and, in the opinion of the applicant, the publicly available information does not provide a sufficient basis for the approval of the use of mometasone furoate inhalation powder. The applicant's opinion that the studies or reports are insufficient is based on the following:
  - The literature does not contain characterization of the safety or efficacy profiles of mometasone furoate inhalation powder, which are established by the data from the new clinical investigations conducted by the sponsor under IND 46,216 and included in the submission.
  - Clinical studies as recommended in the Division of Pulmonary Drug Products' September 19, 1994 "Points to Consider: Clinical Development Programs for MDI and DPI Drug Products", are not addressed by the available literature.
6. The applicant was the sponsor named in the Form FDA-1571 for IND 46,216 under which the new clinical investigations were conducted.



EXCLUSIVITY SUMMARY FOR NDA # 21-067

SUPPL # \_\_\_\_\_

Trade Name Asmanex Twisthaler\_Generic Name Mometasone furoate\_inhalation powder

Applicant Name Schering HFD # 570

Approval Date If Known -Mar-2005

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES / x / NO /     /

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / x / NO /     /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

\_\_\_\_\_  
\_\_\_\_\_

d) Did the applicant request exclusivity?

YES /  / NO /  /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /  / NO /  /

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /  / NO /  /

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other

than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	___N20-762_____	___Nasonex Nasal Spray_____
NDA#	___N19-543_____	___Elocon 0.1% Ointment_____
NDA#	___N19-625_____	Elocon 0.1% Cream
NDA#	___N19-796_____	Elocon 0.1% Lotion

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	_____	_____
NDA#	_____	_____
NDA#	_____	_____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or

supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /  / NO /  /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /  / NO /  /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

---

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/ NO /\_x\_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/ NO /\_x\_/

If yes, explain:

---

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /\_x\_/

If yes, explain:

---

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

C98-475, P01545, C96-136, C96-196, C96-137

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied

on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_x_/
Investigation #2	YES /___/	NO /_x_/
Investigation #3	YES /___/	NO /_x_/
Investigation #4	YES /___/	NO /_x_/
Investigation #5	YES /___/	NO /_x_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

\_\_\_\_\_

\_\_\_\_\_

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_x_/
Investigation #2	YES /___/	NO /_x_/
Investigation #3	YES /___/	NO /_x_/
Investigation #4	YES /___/	NO /_x_/
Investigation #5	YES /___/	NO /_x_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

\_\_\_\_\_  
\_\_\_\_\_

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

C98-475, P01545, C96-136, C96-196, C96-137

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	!		
IND # <u>46,216</u>	YES / <u>x</u> /	!	NO / ___ / Explain: _____
Investigation #2	!		
IND # <u>46,216</u>	YES / <u>x</u> /	!	NO / ___ / Explain: _____
Investigation #3	!		
IND # <u>46,216</u>	YES / <u>x</u> /	!	NO / ___ / Explain: _____
Investigation #4	!		
IND # <u>46,216</u>	YES / <u>x</u> /	!	NO / ___ / Explain: _____
Investigation #5	!		



## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21067 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: 30-Nov-1998 Action Date: 30-Mar-2005

HFD 570 Trade and generic names/dosage form: Asmanex Twisthaler 220mcg (mometasone furoate) inhalation powder

Applicant: Schering Therapeutic Class: Corticosteroid

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- xx No:** Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

### Section B: Partially Waived Studies

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 0 Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 3 Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

**xx Other:** The formulation is a cap-activated inhalation-driven multi-dose dry powder inhaler. The amount of drug delivered to the lung depends (in part) on the inspiratory flow through the device. Pediatric patients less

than 4 years of age would not be expected to generate the minimum inspiratory flow necessary to receive the medication.

\_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 4 Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 11 Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- xx Products in this class for this indication have been studied/labeled for pediatric population**
  - Disease/condition does not exist in children
  - Too few children with disease to study
  - There are safety concerns
  - Adult studies ready for approval
  - Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): 04/01/2007

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 12 Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 17 Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

{See appended electronic signature page}

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA 21-067  
HFD-960/ Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: \_\_\_\_\_

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: \_\_\_Partial Waiver \_\_\_Deferred \_\_\_Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA #-###  
HFD-960/ Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

(revised 10-14-03)

FDA Links Tracking Links Check Lists Searches Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) View Word Document

NDA Number: 021067 Trade Name: MOMETASONE FUROATE INHALATION POWDER 220  
 Supplement Number: 000 Generic Name: MOMETASONE FUROATE INHALATION POWDER 220  
 Supplement Type: N Dosage Form:  
 Regulatory Action: AE COMIS Indication: TREATMENT OF ASTHMA  
 Action Date: 10/1/99

Indication # 1 Long-term control of asthma

Label Adequacy: Other - See Comments

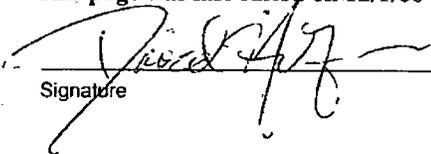
Formulation Needed: NO NEW FORMULATION is needed

Comments (if any): To my knowledge, the applicant has not requested a waiver of the pediatric requirements for patients under 12 yrs. The Division has not discussed the requirements for patients under 12 yrs. D. Hilfiker

	<u>Lower Range</u>	<u>Upper Range</u>	<u>Status</u>	<u>Date</u>
12 years	Adult	Completed	12/5/00	
0 years	11 years	Deferred	12/5/00	

Comments: The Division has not discussed pediatric requirements to study this dosage form in children under 12 yrs. of age. The applicant has not requested waiver or deferral of pediatric requirements to my knowledge. DH, 12-1-00

This page was last edited on 12/1/00

  
 \_\_\_\_\_  
 Signature

12/1/00  
 \_\_\_\_\_  
 Date

### Debarment Certification

Schering Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

*Appears This Way  
On Original*





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

---

---

**FACSIMILE TRANSMITTAL SHEET**

---

---

**DATE:** March 30, 2005

<b>To:</b> Mike Belman	<b>From:</b> LT Lori Garcia Regulatory Project Manager
<b>Company:</b> Schering	Division of Pulmonary and Allergy Drug Products
<b>Fax number:</b> 908-740-2243	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 908-740-4997	<b>Phone number:</b> 301-827-5580

**Subject:** N21-067

---

**Total no. of pages including cover:** 33

**Comments:**

---

---

**Document to be mailed:**           xxYES           NO

---

---

**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, or a person authorized to deliver this document to 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 have received this document in error, please notify us immediately by telephone at (301) 827-1050. Thank you.**

**Garcia, Lori**

---

**From:** Marques, Brenda  
**Sent:** Wednesday, March 02, 2005 11:25 AM  
**To:** Garcia, Lori  
**Cc:** Wang, Jialynn; Purohit-Sheth, Tejashri; Bertha, Craig M; Gilbert McClain, Lydia I; Hu, Elaine J  
**Subject:** Additional comments for the ASMANEX PIU

**Importance:** High

Hi Lori,

In addition to my review dated, February 18, 2005, below are my suggestions.

1. Remove the claim [ ]

The term [ ] has promotional connotations. Their claim implies that ASMANEX is [ ], which is not the case. In fact, the use of this product requires the ability of the patient to adequately follow numerous instructions and have good coordination skills, in order to receive a therapeutic dose of ASMANEX. Therefore, [ ] to use. Lastly, the original version of the PIU contained [ ]. In their latest version, Schering has [ ] which is misleading. Therefore, I suggest that the sponsor remove the aforementioned claim and refer to the "close the inhaler" instructions as Step 3, as reflected in their other proposal (15-Nov, 2004 EDR submission).

2. Move the statements "It is important to repeat steps 1 and 2 each time you Inhale" and "rinse your mouth after using" to the last section under Step 2 (after the statement "Important: Do not breathe out through the inhaler" and before the "close the inhaler" section). Furthermore, the statement [ ] should be revised to the following: "Important: Repeat steps 1 and 2 [ ]"

3. The use of uppercase words should be limited, since they are difficult to read. Therefore, to enhance consumer comprehension and emphasis of important information, the following revisions are suggested:

**Important: Do not breathe out through the inhaler.**

**Important: Repeat steps 1 and 2 . [ ]**

4. Since a PA or NP may also oversee the patient's therapy, I suggest replacing "Doctor" with healthcare provider throughout this PIU.

Thanks,

Brenda

**Brenda Marques, Pharm.D.**  
**LT, US PHS**  
**Regulatory Review Officer**  
**FDA/CDER/OMP/DDMAC**  
**Main: 301-827-2831**  
**Fax: 301-594-6771**  
**Email: marquesb@cder.fda.gov**

-----Original Message-----

**From:** Garcia, Lori  
**Sent:** Wednesday, March 02, 2005 9:31 AM  
**To:** Marques, Brenda  
**Cc:** Wang, Jialynn; Purohit-Sheth, Tejashri; Bertha, Craig M; Gilbert McClain, Lydia I; Hu, Elaine J  
**Subject:**

3/30/05

NDA 21-067

## Regulatory Project Management Labeling Review

### Background

Schering's complete response for their new drug application for Asmanex (mometasone furoate inhalation powder) Twisthaler was submitted on September 29, 2004, in response to the approvable letter dated May 17, 2004. Labeling was not included in the September 29, 2004, submission. Draft labeling (PI, Patient's Instructions for Use, carton and immediate container labels) was requested and submitted by Schering on November 15, 2004. The labeling provides for the use of Asmanex (mometasone furoate inhalation powder) Twisthaler for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older, as well as the treatment of asthma patients who require oral corticosteroid therapy, where adding Asmanex Twisthaler therapy may reduce or eliminate the need for oral corticosteroids.

### Review

The majority of the labeling review was done during the last approvable cycle. The labeling text that was agreed upon at that time was resubmitted on November 15, 2004, for final review.

The draft labeling, submitted November 15, 2004, was reviewed by the Clinical, Chemistry, Manufacturing, and Controls, Pharmacology/Toxicology, Clinical Pharmacology and Biopharmaceutics, Biostatistics, DDMAC, and Project Management teams. The Pharmacology/Toxicology, Biostatistics, and Clinical Pharmacology/Biopharmaceutics teams found the draft labeling text to be acceptable from the standpoint of their individual discipline, and did not recommend any revisions. Revisions to the draft labeling text (PI and Patient's Instructions for Use) were made by the Clinical, CMC, and DDMAC teams and were sent to Schering in a facsimile dated March 9, 2005. Schering agreed to all of the proposed FDA revisions to the labeling text, except for the proposed deletion of Line 541 of the PI. A teleconference was held on March 16, 2005, to discuss this proposed revision and Schering agreed at that time, to all of the FDA's proposed revisions to the labeling text as indicated in the March 9, 2005, facsimile.

The agreed-upon revised draft labeling (PI and Patient's Instructions for Use) was submitted by Schering on March 17, 2005. This submission was sent to the Clinical and CMC teams for verification that all proposed revisions had been made by Schering, as requested by the Division. The labeling was found to be acceptable. I compared the draft labeling submitted March 17, 2005, to the agreed-upon labeling from the facsimile dated March 9, 2005. All of the changes requested by the FDA to the labeling were made by Schering, with one exception in the Patient's Instructions for Use:

In the 4<sup>th</sup> bullet in the IMPORTANT POINTS TO REMEMBER ABOUT ASMANEX TWISTHALER section, the sentence 'C

⌈ It should have been changed to "Whether or not you are able to sense delivery of a dose, do not take extra doses unless your healthcare provider has told you to" as requested in the facsimile dated March 9, 2005.

This was discussed with Schering's representative Mike Belman, who noted that they had failed to make this change due to an oversight, and Schering does agree to revise the label as proposed by the Division in the March 9, 2005, facsimile. A few minor editorial errors were noted in the PI and will be included in the labeling enclosed with the action letter, along with the change to the PIU as noted above. Otherwise, the revised draft labeling submitted March 17, 2005, is identical to the agreed-upon labeling text in the facsimile dated March 9, 2005.

### Conclusion

The revised draft labeling text (PI and Patient's Instructions for Use) submitted March 17, 2005, is acceptable with the agreed-upon change noted above, and the minor editorial changes which will be enclosed in the labeling in the action letter. The carton and immediate container labels submitted on November 15, 2004, are acceptable.

---

Lori Garcia, R.Ph.  
Regulatory Project Manager  
Division of Pulmonary and Allergy Drug Products

Initialed: SBarnes/March 30, 2005

Finalized: LGarcia/March 30, 2005

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

/s/

-----  
Lori Garcia  
3/30/05 03:42:16 PM  
CSO

19 Page(s) Withheld



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

     § 552(b)(5) Deliberative Process

     § 552(b)(4) Draft Labeling



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

---

**FACSIMILE TRANSMITTAL SHEET**

---

**DATE:** March 9, 2005

<b>To:</b> Mike Belman	<b>From:</b> LT Lori Garcia Regulatory Project Manager
<b>Company:</b> Schering	Division of Pulmonary and Allergy Drug Products
<b>Fax number:</b> 908 740 2243	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 908 740 4997	<b>Phone number:</b> 301-827-5580

**Subject:** N21-067/Asmanex/proposed labeling revisions

**Total no. of pages including cover:**

**Comments:**

---

**Document to be mailed:**                      YES                      XX NO

---

**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, or a person authorized to deliver this document to 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 have  
received this document in error, please notify us immediately by telephone at (301) 827-  
1050. Thank you.**

N21-067

Dear Mr. Belman:

We have reviewed the labeling submitted November 15, 2004. Our proposed revisions to the Package Insert and Patient's Instructions for Use are enclosed along with the following comment.

1. Re: Figures 1 and 2. The legends should include the number of patients in each of the treatment arms. The numbers can be noted within parentheses, e.g., (n=xx).

We request that you provide your response to the FDA revised labeling within 1 week from the date of this facsimile.

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

29 Page(s) Withheld

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

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(4) Draft Labeling

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

/s/

-----  
Lori Garcia  
3/9/05 03:14:58 PM  
CSO

Garcia, Lori

---

**From:** Al Habet, Sayed  
**Sent:** Wednesday, March 02, 2005 1:51 PM  
**To:** Garcia, Lori  
**Cc:** Fadiran, Emmanuel O  
**Subject:** RE: N21-067

Lori,

The labeling looks good and I have no comments at this time. In the meantime, please keep me posted with any meetings. I know the action date any time soon, but I can not remember what day?

Thanks

Sam

---

-----Original Message-----

**From:** Garcia, Lori  
**Sent:** Wednesday, March 02, 2005 10:57 AM  
**To:** Al Habet, Sayed  
**Subject:** RE: N21-067

Ok, thanks

-----Original Message-----

**From:** Al Habet, Sayed  
**Sent:** Wednesday, March 02, 2005 9:17 AM  
**To:** Garcia, Lori  
**Cc:** Fadiran, Emmanuel O  
**Subject:** RE: N21-067

Yes.

I will discuss with Tayo and let you know today.

Thanks

Sam

---

-----Original Message-----

**From:** Garcia, Lori  
**Sent:** Wednesday, March 02, 2005 8:34 AM  
**To:** Al Habet, Sayed  
**Cc:** Fadiran, Emmanuel O  
**Subject:** RE: N21-067

Hi Sam,

Have you had a chance to look at the labeling?

Thanks,

Lori

-----Original Message-----

**From:** Garcia, Lori  
**Sent:** Wednesday, February 23, 2005 12:05 PM  
**To:** Al Habet, Sayed  
**Cc:** Fadiran, Emmanuel O  
**Subject:** RE: N21-067

The submission is in the edr (<http://edr/>). Dated 15-Nov-2004.

We would like to wrap up the labeling ASAP so we can take action within the next few days. The labeling was also reviewed in the last cycle, so there should not be much that you need to do except make sure that nothing for your section has changed and make sure that you do not have any new comments.

Lori

-----Original Message-----

**From:** Al Habet, Sayed  
**Sent:** Wednesday, February 23, 2005 10:25 AM  
**To:** Garcia, Lori  
**Cc:** Fadiran, Emmanuel O  
**Subject:** RE: N21-067

Lori,

Please send me a copy of the most recent label.

P.S. When is the deadline? Our review is in the DFS since February 2004. NO PK issues.

Thanks

Sam

-----Original Message-----

**From:** Garcia, Lori  
**Sent:** Wednesday, February 23, 2005 9:17 AM  
**To:** Gebert, James R; Al Habet, Sayed  
**Subject:** N21-067

Good morning,

We are getting ready to wrap this up. I just want to be sure that there are no new comments from stats or biopharm for the labeling submitted 11/15/04 (in EDR) for this review cycle. Please let me know if the labeling is acceptable from your perspective.

Thanks,

Lori

**From:** Gebert, James R  
**Sent:** Wednesday, February 23, 2005 9:21 AM  
**To:** Garcia, Lori  
**Subject:** RE: N21-067  
No comments from stats.

-----Original Message-----

**From:** Garcia, Lori  
**Sent:** Wednesday, February 23, 2005 9:17 AM  
**To:** Gebert, James R; Al Habet, Sayed  
**Subject:** N21-067

Good morning,

We are getting ready to wrap this up. I just want to be sure that there are no new comments from stats or biopharm for the labeling submitted 11/15/04 (in EDR) for this review cycle. Please let me know if the labeling is acceptable from your perspective.

Thanks,

Lori

RE EDR - NDA021067 from SCHERING drug name MOMETASONE FUROATE INHALATION POWDER 220.txt  
From: Whitehurst, Virgil E  
Sent: Tuesday, November 30, 2004 10:16 AM  
To: Garcia, Lori  
Subject: RE: EDR - NDA021067 from SCHERING drug name MOMETASONE FUROATE INHALATION POWDER 220

Labeling is fine from a nonclinical perspective  
VEW

-----Original Message-----

From: Garcia, Lori  
Sent: Tuesday, November 30, 2004 8:42 AM  
To: Purohit-Sheth, Tejashri; Bertha, Craig M; Whitehurst, Virgil E; Al Habet, Sayed; Gebert, James R  
Subject: FW: EDR - NDA021067 from SCHERING drug name MOMETASONE FUROATE INHALATION POWDER 220

FYI:

Labeling for N21-067/Asmanex TwiSthaler (labeling was not submitted originally with the complete response as it should have been).

Major review of the labeling was done in the last AE cycle.

Lori

-----Original Message-----

From: EDRAAdmin@cder.fda.gov [mailto:EDRAAdmin@cder.fda.gov]  
Sent: Wednesday, November 24, 2004 12:55 PM  
To: GARCIAL@cder.fda.gov; BARNES@cder.fda.gov; PRATHERM@cder.fda.gov; REDDYB@cder.fda.gov; SAUNDERSJA@CDER.FDA.GOV; TAGOEI@cder.fda.gov  
Cc: schumaker@cder.fda.gov; esub@cder.fda.gov; nathanj@cder.fda.gov; talastash@cder.fda.gov; emmonsp@cder.fda.gov; Tokoli@cder.fda.gov; EDRAAdmin@cder.fda.gov  
Subject: EDR - NDA021067 from SCHERING drug name MOMETASONE FUROATE INHALATION POWDER 220

Hi !

The EDR has received an Electronic Document on CD-ROM for division HFD-570:

NDA# N21067  
Incoming Document Type: N  
Incoming Document Type Sequence Number: 000  
Supplement Modification Type: BL  
Letter Date: 11/15/2004

It has sections 1, 2, 20.

The network path location is: \\CDSESUB1\N21067\N\_000\2004-11-15  
It is now available on the network. You can review this submission by entering EDR in your browser.

Please address any questions concerning this electronic submission to:

EDRAAdmin@cder.fda.gov

Thanks,  
Prentiss

1-28-05

NDA 21-067

Attention: Carol B. Shichman  
Manager  
Global Regulatory Affairs, CMC

Dear Ms. Shichman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asmanex (mometasone furoate inhalation powder) Twisthaler, 220mcg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and we are requesting your written agreement to the statements listed below. If you concur, submit an amendment to this NDA within 1 week of the date of this facsimile affirming your agreement to each statement.

1. Submit a prior approval supplement containing all pertinent supportive documentation for [ ] of Singapore as a manufacturing site for the drug product.
2. Re-evaluate the [ ] acceptance criteria after one year of commercial experience.
3. Re-evaluate the specifications for resistance to flow-by pressure drop after one year of commercial production experience.
4. Commence within three (3) months of approval, post-approval studies to determine the underlying factors leading to the shift in the [ ] stage grouping deposition that is seen when comparing batches prepared at Kenilworth in 2002 with those recently made in 2004, i.e., increase in Group I and decrease in Group II and III deposition. You agree to a projected completion date of no more than twelve (12) months.
5. Submit three copies of an updated methods validation package containing the following information: a). composition of the drug product formulation; b). acceptance criteria and methods for the drug substance; c). acceptance criteria and methods for the drug product; d). supporting validation data for drug substance and drug product methods; e). a list of available samples with their respective sample numbers; f). analytical results for available samples. It is requested that these be submitted within a reasonably short time after approval (e.g., within 3 months).

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

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 Lori Garcia, Regulatory Project Manager, at 301-827-5580.

Sincerely,

Richard Lostritto, Ph.D.  
Chemistry Team Leader for the  
Division of Pulmonary and Allergy Drug Products,  
HFD-570  
DNDC II, Office of New Drug Chemistry  
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/

-----  
Lori Garcia  
1/28/05 08:41:43 AM  
CSO

## MEMO

**To:** Badrul A. Chowdhury, M.D.  
Director, Division of Pulmonary and Allergy Drug Products, HFD-570

**From:** Charlie Hoppes, R.Ph., M.P.H.  
Safety Evaluator, Division of Medication Errors and Technical Support  
Office of Drug Safety, HFD-420

**Through:** Alina Mahmud, R.Ph., Team Leader  
Carol Holquist, R.Ph., Director  
Division of Medication Errors and Technical Support  
Office of Drug Safety, HFD-420

**CC:** Lori Garcia  
Project Manager, Division of Pulmonary and Allergy Drug Products  
HFD-570

**Date:** December 8, 2004

**Re:** ODS Consult 04-0015-1; Asmanex® Twisthaler™  
(Mometasone Furoate Inhalation Powder), 220 mcg per inhalation  
NDA 21-067

---

This memorandum is in response to a November 8, 2004 request from your Division for a re-review of the proprietary name, Asmanex® Twisthaler™. DMETS acknowledges the Division's comments that labeling was not available for review at the time of this consult and that a separate consult to assess the labeling of this product will be forwarded. However, DMETS notes that labeling submitted by the sponsor (letter dated, November 15, 2004), is now available in the electronic document room. Therefore, DMETS will forward comments regarding the sponsor's labeling with this consult.

The proprietary name of Asmanex® Twisthaler™ was reviewed by DMETS on February 6, 2004, and found to be acceptable. However since this review, the name Anzemet has been identified as a name that may lead to confusion with the proposed name Asmanex Twisthaler.

## I. SOUND-ALIKE/LOOK-ALIKE NAME

Anzemet may look similar to Asmanex when scripted and sound similar to Asmanex when spoken, especially if "Twisthaler" is inadvertently omitted from the name "Asmanex Twisthaler". Anzemet is the proprietary name for dolasetron mesylate available in injection and tablet dosage forms. Anzemet is indicated for nausea and vomiting associated with chemotherapy and postoperative nausea and vomiting. The usual adult dose is 100 mg intravenously or orally. The look-alike similarities stem from the shared letters "A" and "e" in the names (see writing sample below). The cursive "s" and "x" in Asmanex may look like the cursive "n" and "t" in Anzemet. It is also possible for the "m" in Asmanex to look like the "z" in Anzemet.

The image shows two words written in cursive: 'Asmanex' on the left and 'Anzemet' on the right. The letters are slanted and connected, illustrating the visual similarities between the two names, particularly the 's' and 'x' in Asmanex which resemble 'n' and 't' in Anzemet.

The names may also sound alike. Each name has three syllables and begins with the short "a" sound. The beginning of each name, "As" vs. Anz" may sound alike if, especially if the "n" is not given verbal prominence. The name endings "nex" vs. "met" may also sound alike due to strong phonetic similarities between "ne" and "me", each sharing the short "e" sound. Despite look-alike and sound-alike properties of the proprietary names, the Anzemet and Asmanex Twisthaler have product differences which may serve to distinguish them including, dosage form (injection and tablet vs. metered dose inhaler), route administration (intravenous and oral vs. oral inhalation), indication of use (against nausea and vomiting vs. for asthma), and dose [Dolasetron Mesylate Injection; 100 mg (base)/5 mL, 12.5 mg (base)/.625 mL, 500 mg (base)/25 mL Dolasetron Mesylate Tablet; 50 mg (base), 100 mg (base) vs. 220 mcg per inhalation], respectively. These differences will minimize the potential for error.

## II. LABELS AND LABELING

In review of the Asmanex Twisthaler container labels (cap labels and pouch labels), carton, insert, and patient instruction labeling, DMETS has attempted to focus on safety issues relating to possible medication errors and have identified the following areas of possible improvement.

### A. CONTAINER LABELS (Cap Labels, 30, 60, 120 actuations, Institutional Use, Sample)

1. The green colors selected to differentiate the 30 actuation and 120 actuation sizes are very similar. DMETS recommends selection of a more distinctive color for one of these package sizes to minimize selection errors.
2. DMETS recommends that the expression of strength be relocated to follow the established name on the principal display and that it be revised to read, "220 mcg per dose", (add "per dose"). This format will be consistent with Center conventions where the strength follows the proprietary and established names (rather than appearing between those names), and will define the strength in terms of one dose (rather than total unit strength).
3. Since the performance of the drug product is dependent upon moisture content, it is important to increase the prominence of the statement, "Store in a dry place", perhaps by using bold face type.
4. Please also increase the prominence of the statement, "Discard inhaler...", perhaps by using bold face type.

B. CONTAINER LABELS (Pouch Labels, 30, 60, 120 actuations, Institutional Use, Sample)

1. See comments for CONTAINER LABELS, Cap Labels, above.
2. Increase the prominence of the boxed statement, "For more than...", appearing with the number of doses on the 30 and 60 dose labels. This important information is very difficult to read due to smallness of type.

C. CARTON LABELING (30, 60, 120 actuations, Institutional Use, Sample)

See comments for CONTAINER LABELS, Pouch Labels, above.

D. PROFESSIONAL INSERT LABELING

1. TITLE

Relocate the strength to follow the established name and revise to read, "220 mcg per dose", (add "per dose").

2. DESCRIPTION

Add information in this section that explains the short expiration date of the product once the foil pouch is opened. Is this product \_\_\_\_\_ If so, does \_\_\_\_\_ alter powder flow characteristics?

3. DOSAGE AND ADMINISTRATION

Add information, perhaps as another column for the table, clearly explaining which product should be dispensed and why. For example, it should be clear that the 120 dose product should not be dispensed to patients receiving one or two doses a day because the 45 day period will be exceeded.

E. PATIENT INSTRUCTIONS

1. Inhale dose

Should an instruction that the patient first exhale completely prior to inhalation accompany this instruction?

2. Bold the statement, "Keep the inhaler in a dry place."

In summary, DMETS has no objections to the proprietary name Asmanex Twisthaler. DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-2102.

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

/s/

-----  
Charles Hoppes  
12/16/04 01:24:32 PM  
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud  
12/16/04 01:29:12 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
12/17/04 10:31:48 AM  
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

## REQUEST FOR CONSULTATION

(Division/Office):

**Director, Division of Medication Errors and  
Technical Support (DMETS), HFD-420  
PKLN Rm. 6-34**

FROM: LORI GARCIA  
REGULATORY PROJECT MANAGER  
ODEI/DPADP, HFD-570

DATE November 8, 2004	IND NO.	NDA NO. 21067	TYPE OF DOCUMENT AZ/Complete Response	DATE OF DOCUMENT September 29, 2004
NAME OF DRUG Asmanex Twisthaler	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Corticosteroid	DESIRED COMPLETION DATE <b>January 9, 2005</b>	
NAME OF FIRM: Schering Corporation				

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER                       |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                              |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                                   |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                         |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                                  |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

#### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

#### III. BIOPHARMACEUTICS

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

#### IV. DRUG EXPERIENCE

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

#### COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

Please re-review the tradename Asmanex Twisthaler for this 9/29/04 re-submission to NDA 21-067. Your review (ODS consult # 04-0015) dated 3/4/04, had no objection to the use of the proprietary name, Asmanex Twisthaler, in the last cycle. PDUFA goal date=3/31/05, however, **we would like to take action by the end of January 2005**. This submission is available in the EDR at <http://edr/> Please note that labeling was not submitted with this complete response and has been requested from Schering. A separate consult to ODS will follow once the labeling is received. Labeling recommendations made by DMETS in consult # 04-0015 were agreed to by Schering in the last cycle. The labeling to be submitted should be identical to the package insert and carton labels submitted 5/13/04 and the container cap labels submitted 5/14/04. The patient instructions for use will be revised and should be identical to the patient instructions for use submitted 5/10/04 (this was not reviewed in the last cycle). These submissions are available in the EDR as well.  
PDUFA DATE: March 31, 2005 (\*\*Plan to take action in January 2005, if possible).  
ATTACHMENTS: See EDR CC:  
Archival NDA 21-067

HFD-570/Reviewers and Team Leaders

HFD-570/Garcia, Lori  
HFD-570/Division File

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

-----  
Lori Garcia  
11/8/04 02:12:21 PM

25 Page(s) Withheld

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

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(4) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-067

9/3/04

Schering Corporation  
2000 Galloping Hill Road  
Kenilworth, NJ 07033

Attention: Carol B. Shichman  
Regulatory Affairs, Manager  
Global Regulatory Affairs, CMC

Dear Ms. Shichman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asmanex (mometasone furoate) Twisthaler.

We refer to your June 29, 2004, submission containing revised specifications [ ] and a proposal to [ ]

[ ] We also refer to your other June 29, 2004, submission containing the response to the CMC deficiencies identified in our action letter dated May 17, 2004.

We have reviewed the referenced material and have the following comments and recommendations.

1. Satisfactory inspections of the Union and Kenilworth, NJ sites are required before this application may be approved. We acknowledge your expected PAI readiness date of September 30, 2004, for the Union and Kenilworth, NJ sites.
2. Provide updated stability data from drug product manufactured at the Kenilworth site as well as the results of the statistical analysis used to support your proposal of 18 months for the expiration dating period in light of the newly proposed acceptance criteria for both the emitted dose [ ]  
[ ] The eighteen month data provided on just two batches, 8-GEN-876 and 8-GEN-880, are insufficient for a determination of the appropriate expiration dating period, especially with regard to the [ ]  
[ ]
3. Resubmit the complete specification sheet for the drug product, revised to include the new specification acceptance criteria [ ] [ ]
4. Confirm your agreement with the following comments pertaining to [ ] [ ] testing and acceptance criteria.
  - a. Examine and revise, if necessary, the controls on the environmental conditions



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

/s/

-----  
Richard Lostritto  
9/3/04 03:32:01 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office) <b>Director, Division of Drug Marketing, Advertising and Communications HFD-244 PKLN Rm. 17B-17</b>		FROM: <b>Lori Garcia, Regulatory Project Manager Division of Pulmonary and Allergy Drug Products HFD-570</b>		
DATE <b>September 1, 2004</b>	IND NO <b>46,216</b>	NDA NO	TYPE OF DOCUMENT	DATE OF DOCUMENT <b>August 17, 2004</b>
NAME OF DRUG <b>Mometasone Furoate DPI</b>	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG <b>Steroid</b>	DESIRED COMPLETION DATE <b>September 18, 2004</b>	
NAME OF FIRM				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> PAPER NDA <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> CONTROL SUPPLEMENT <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): <input type="checkbox"/> MEETING PLANNED BY				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: DDMAC review of the August 17, 2004, submission to IND 46,216 is requested by the sponsor. This submission contains <input type="checkbox"/> for Asmanex Twisthaler. Comments are requested within approx. 4 weeks from the submission date. A copy of the submission is enclosed.				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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

/s/

-----  
Lori Garcia  
9/1/04 03:28:30 PM



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

---

---

**FACSIMILE TRANSMITTAL SHEET**

---

---

**DATE: July 6, 2004**

<b>To: Carol Shichman</b>	<b>From: Lori Garcia, Project Manager</b>
<b>Company: Schering</b>	Division of Pulmonary and Allergy Drug Products
<b>Fax number: 908-740-5100</b>	<b>Fax number: 301-827-1271</b>
<b>Phone number: 908-740-2953</b>	<b>Phone number: 301-827-5580</b>
<b>Subject: Meeting minutes from 6/18/04 meeting/RE: Draft proposal to Revise Specifications . [ ]</b>	

**Total no. of pages including cover: 4**

**Comments:**

---

---

**Document to be mailed:**                      YES                      XXNO

---

---

**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, or a person authorized to deliver this document to 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 have received this document in error, please notify us immediately by telephone at (301) 827-1050. Thank you.**

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** June 18, 2004  
**TIME:** 12:30pm-12:45pm  
**MEETING LOCATION:** Bethesda Marriott, 5151 Pooks Hill Road, Bethesda, MD 20814  
**APPLICATION:** N21-067  
**DRUG NAME:** Asmanex  
**MEETING RECORDER:** Richard Lostritto, Ph.D.

### FDA ATTENDEES: (Title and Office/Division)

Division of Pulmonary and Allergy Drug Products:  
Richard Lostritto, Ph.D., Chemistry Team Leader  
Prasad Peri, Ph.D., Chemistry Reviewer

### EXTERNAL CONSTITUENT ATTENDEES:

Schering Corporation:  
Galen Radabaugh  
Nicholas Pelliccione

### BACKGROUND:

Subject: 30 page Fax dated 6/17/04 regarding the applicant's DRAFT proposal to widen [ ] stage grouping acceptance criteria. Schering asked the Agency to provide feedback regarding the scientific merit of their DRAFT proposed widening of [ ] criteria and to provide the proposal into their upcoming complete response amendment to NDA 21-067 (Asmanex DPI). Schering also wanted to know if they should submit this package for review with their complete response package to this NDA or as a separate amendment afterwards.

### DISCUSSION POINTS:

The Agency indicated that Schering could submit their finalized [ ] criteria proposal with their complete response amendment without prejudice towards the determination of a complete response. It is more efficient in this case to have all the information in one amendment.

The following technical feedback was provided by the Agency:

1. Tabulated data and acceptance criteria should be presented in a format that permits a ready comparison to currently proposed versus newly proposed.
2. Trends were noted in the data from dose [ ] SP should explain this and may consider conducting separate statistical analyses to see if the means at [ ] are different statistically; and to see if the added variability of these three life stages is more or less than the equivalent variability (e.g., as standard deviation) of the pooled data set.

3. The three sigma approach is not necessarily acceptable. This is a review issue to be consulted to Biometrics when the amendment is submitted. SP may wish to consider and present additional/alternate statistical approaches (e.g., + - 95% CI) in the amendment.

4. SP should submit the results of the mass balance determinations for all  $\bar{x}$  determinations to be discussed in the submission regarding the change in acceptance criteria. This data should be provided in a comparative format as well.

5. SP should provide a discussion of the method modification control which includes a change in the  $\bar{x}$  device to  $\bar{x}$  which increase variability of the results.

6. The adequacy of SP's proposal to widen the  $\bar{x}$  acceptance criteria is a review issue that can only be determined when the totality of the data are provided.

---

Richard Lostritto, Ph.D.  
Chemistry Team Leader

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

/s/

-----  
Richard Lostritto  
7/7/04 02:30:58 PM



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

---

---

**FACSIMILE TRANSMITTAL SHEET**

---

---

**DATE: May 5, 2004**

<b>To: Mike Belman</b>	<b>From: Lori Garcia, Project Manager</b>
<b>Company: Schering</b>	Division of Pulmonary and Allergy Drug Products
<b>Fax number: 908-740-2243</b>	<b>Fax number: 301-827-1271</b>
<b>Phone number: 908-740-4997</b>	<b>Phone number: 301-827-5580</b>

**Subject: FDA revised labeling/comments for N21067**

**Total no. of pages including cover: 31**

**Comments:**

---

---

**Document to be mailed:** YES XNO

---

---

**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, or a person authorized to deliver this document to 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 have received this document in error, please notify us immediately by telephone at (301) 827-1050. Thank you.

We have reviewed the draft package insert, patient instructions for use, and carton/container/pouch labels for NDA 21067. We have the following comments followed by our edits to your draft labeling:

1. The placement of the established and proprietary names on the carton labeling is different than that on the container and pouch label. The Division recommends repositioning the proprietary and established name so that on both labels, the names are configured above the metered dose information (14, 30, 60, and 120 metered dose) as done in the professional sample.
2. Increase the font size of the in-use statement on the cap label to make it commensurate with that of the storage statement.
3. Revise the storage statement to the following on all packaging labels and cartons as per the Stability Guidance: Store in a dry place at 25°C (77°F). [See USP Controlled Room Temperature].
4. The illustrations accompanying the patient instructions for use are not aligned with the instructions. The Division recommends revising the layout so that the illustrations are adjacent to the instructions.
5. In order to identify and distinguish the number of doses per device, clearly color code the backgrounds of the number of inhalations on the cap label as you did for the pouch and carton labels (e.g., indicate the number 60 metered doses in white on dark blue background even on the cap label).
6. The established name is less than half the size of the proprietary name. Additionally, the font type and coloring de-emphasize the prominence of the established name. Revise the label accordingly.
7. For the pouch labels, the product strength, 220mcg, is placed on the label immediately following "Twisthaler" and also above the metered dose content. This information is redundant. We recommend removing the product strength positioned above the metered dose strength.

29 Page(s) Withheld

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

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(4) Draft Labeling

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

/s/

-----  
Lori Garcia  
5/5/04 04:07:14 PM  
CSO

Lori Garcia  
5/5/04 04:09:15 PM  
CSO

## DIVISION DIRECTOR'S MEMORANDUM

Date: May 17, 2004

To: NDA 21-067

From: Badrul A. Chowdhury, MD, PhD  
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Asmanex Twisthaler 220 mcg (mometasone furoate inhalation powder)

Applicant: Schering Corporation

### **Administrative and Introduction**

Schering Corporation submitted a 505(b)(1) new drug application (NDA 21-067) on November 30, 1998, for use of mometasone furoate dry powder inhaler (subsequently given the trade name Asmanex Twisthaler) for use in patients 12 years of age and older with asthma. The application received an approvable action on October 1, 1999, primarily due to CMC deficiencies. Review of the clinical section of the original submission concluded that from an efficacy standpoint the proposed doses of 400 mcg twice daily, 400 mcg once daily, and 200 mcg twice daily (ex-mouthpiece doses) were supported by the submitted data, but the dose of 200 mcg once daily (ex-mouthpiece dose) was not supported. The action letter stated that to support the 200 mcg once daily dose additional clinical trials will be required. The action letter also pointed out that the 400 mcg strength product was not used in the clinical trials. Since the original submission the application has gone through two review cycles and stayed approvable due the CMC deficiencies. The most recent response was submitted by Schering on November 14, 2003, which was received by the Agency on November 17, 2003. The PDUFA due date on this submission is May 17, 2004. In addition to CMC information this response includes results from two new clinical studies submitted to bolster the clinical database and to support the 220 mcg once daily (200 mcg ex-mouthpiece) dosing. The proposed to-be-marketed product is now a single strength 220 mcg product that delivers 200 mcg mometasone furoate from the mouthpiece. The new clinical studies submitted support the 220 mcg QD PM dosing. The major CMC deficiencies are also resolved, except that the manufacturing site is not ready for inspection. The application will remain approvable because the manufacturing site is not ready.

### **Chemistry, Manufacturing, and Controls, and Establishment Evaluation**

The drug substance mometasone furoate is a well known compound that is already approved in several commercial drug products. The DMF associated with the manufacture of the drug substance intermediate is adequate. The final drug substance is manufactured by Schering Plough in Singapore. The drug product is a dry powder formulation of mometasone furoate and anhydrous lactose contained in a cap-activated inhalation-driven multi-dose device. Closing and opening action of the cap of the device

meters a dose and activates the dose counter. When a patient closes the cap by twisting clockwise a dose is metered into the delivery chamber, which is available for inhalation on next dosing. The counter-clockwise opening action of the cap triggers the device counter that counts down the number of remaining doses. Each actuation of Asmanex Twisthaler 220 provides a nominal dose of 220 mcg of mometasone furoate, which results in delivery of 200 mcg of mometasone furoate from the mouthpiece to the patient. Asmanex Twisthaler 220 is proposed to be supplied as 14, 30, 60, and 120 actuations per inhaler versions. The fill for all are the same, the label claim number of actuations is controlled by the device lock-out mechanism.

The drug product was originally proposed to be manufactured in Kenilworth, NJ, and in Singapore. During early reviews, differences and inconsistencies were noted in the attributes, [redacted] of the drug product manufactured in two sites. These differences could not be satisfactorily addressed and were the major approval issues. Schering is now proposing to remove the Singapore site as a drug product manufacturing site. The [redacted] is now more consistent and also the applicant has made reasonable efforts to tighten these. The applicant proposed acceptance criterion for [redacted] that is slightly outside the range that the Agency has accepted in the past for inhaled products, but given the drug class the proposed specifications are reasonable. The drug is intended for chronic administration and is not for acute relief of symptoms; therefore, slightly higher variations between doses will not be a safety or efficacy risk.

The major outstanding issue with the application is that the proposed Kenilworth, NJ, drug product manufacturing site, and the Union, NJ, drug product quality control operation site are not ready for inspection. All other CMC issues that would preclude approval are resolved. The CMC review team is recommending an approvable action primarily because of lack of readiness of inspection of manufacturing site, and I concur with that recommendation.

#### **Clinical and Statistical**

The pivotal clinical studies submitted to the NDA included three studies in patients previously maintained on bronchodilators alone (C96-136, C96-186, C98-475), three studies in patients previously maintained on inhaled corticosteroids (C96-196, C96-134, P01545), and one study in patients previously maintained on oral corticosteroids (C96-137). Studies C98-475 and P01545 were included in the most recent submission; other studies were submitted with the original application. In subsequent sections of this memorandum these studies and an HPA axis safety study (C97-049) are briefly reviewed. Detailed review of the original application can be found in Dr. Daniel O'Hearn's Medical Officer Review from 1999, and detailed review of the two new studies can be found in Dr. Purohit-Sheth's Medical Officer Review of 2004. In this memorandum all doses are mentioned as the nominal dose. Note that in the Medical Officer Reviews the doses are mostly referred to as the ex-mouth piece dose. For the proposed to be marketed 220 mcg product, the ex-mouthpiece dose is 200 mcg.

Studies in patients previously maintained on bronchodilators alone:

C96-136 was a double-blind, placebo-controlled, parallel group study conducted in patients 12 years of age and older who were previously maintained on inhaled beta-agonists only. The study was conducted in 21 centers in the United States. The study had a 1-2-week run-in period, followed by a 12-week double-blind treatment period where patients were treated with mometasone furoate at doses of 220 mcg QD AM, 440 mcg QD AM, or placebo. Study subjects were then continued on to a 9-month phase where morning and evening dosing of 220 mcg and 440 mcg were compared. For the 12-week treatment period, the primary efficacy endpoint was change in pre-dose FEV1 at endpoint (last observation) compared to baseline. Secondary efficacy variables included recording of PEFr in the morning, asthma symptom scores on a 0-3 scale, nocturnal awakening, and rescue medication use. Safety variables included recording of adverse events, physical examination, laboratory tests, and ECG. A total of 236 patients were randomized, approximately equally to the three treatment arms. Approximately 80% of patients completed the study, with slightly more completers in the active treatment arms compared to the placebo arm. Both doses of mometasone were effective in this study. Mean FEV1 at endpoint compared to baseline increased by 0.35 L (14.8%) in the mometasone 220 mcg QD AM arm, 0.35 L (14.2%) in the mometasone 400 mcg QD AM arm, compared to 0.06 L (2.5%) in the placebo arm. Differences between both active treatment arms and placebo were statistically significant. Secondary endpoints also supported efficacy, although the 400 mcg QD AM dose tended to be superior to the 200 mcg QD AM dose for most secondary efficacy variables. For morning PEFr at endpoint and nocturnal awakenings, the 400 mcg QD AM dose was statistically significantly different than placebo, but the 200 mcg QD AM dose was not. Both doses were statistically significantly different than placebo for asthma symptoms, and rescue albuterol use. Both doses were well tolerated in the study.

C96-186 was also a double-blind, placebo-controlled, parallel group study conducted in patients 12 years of age and older who were previously maintained on inhaled beta-agonists only. The study was conducted in 21 centers in the United States. The design and conduct of this study was similar to C96-136 with the notable difference that the study was limited to a 12-week treatment period and there was an additional treatment arm of mometasone 220 mcg BID. A total of 306 patients were randomized, approximately equally to the four treatment arms. Approximately 85% of patients completed the study, with slightly more completers in the active treatment arms than the placebo arm. In this study mometasone 440 mcg QD AM and 220 mcg BID were effective, but 220 mcg QD AM was not. Mometasone 220 mcg QD AM dose did not reach statistical significance for mean change in FEV1 at endpoint compared to baseline. Mean FEV1 at endpoint compared to baseline increased by 0.27 L (10.4%) in the mometasone 220 mcg QD AM arm, 0.41 L (16.0%) in the mometasone 440 mcg QD AM arm, 0.40 (16.1%) in the mometasone 220 mcg BID arm, compared to 0.14 L (5.5%) in the placebo arm. The numerical values for the 440 mcg QD AM and 220 mcg BID arms were similar for FEV1 and for most secondary efficacy variables. All three doses were well tolerated in the study.

C98-475 was also a double-blind, placebo controlled, parallel group study conducted in patients 12 years of age and older who were previously maintained on inhaled beta-agonist only. The primary objective of this study was to support the 200 mcg once daily dose, because in the previously submitted studies efficacy of the 200 mcg once daily dose was not replicated. Interestingly, in the previous studies 200 mcg dose was given in the morning, whereas in this study 200 mcg dose was given in the evening. The study was conducted in 18 centers in the United States. The design and conduct of this study was similar to studies C96-136 and C96-186. This was also a 12-week study and the treatment arms were mometasone 200 mcg QD PM and placebo. A total of 195 patients were randomized approximately equally between the two treatment arms and close to 90% of patients in both treatment arms completed the study. Mometasone 200 mcg QD PM was effective in this study. Mean FEV1 at endpoint compared to baseline increased by 0.43 L (16.8%) in the mometasone 200 mcg QD PM arm, compared to 0.16 L (6.0%) in the placebo arm. The difference was statistically significant. Secondary efficacy variables, such as morning and evening PEFr, symptom scores, nocturnal awakening, and rescue albuterol use all favored mometasone 200 mcg QD PM over placebo. Mometasone was well tolerated in this study.

Studies in patients previously maintained on inhaled corticosteroids:

C96-196 was a double-blind, placebo-controlled, parallel group study conducted in patients 12 years of age and older who were previously maintained on inhaled corticosteroids. The study was conducted in 16 centers in the United States. The study had a 1-2-week run-in period during which the patients continued on their inhaled corticosteroids, followed by a 2-week open-label period during which all patients were switched to mometasone furoate dry powder inhaler 200 mcg BID, followed by a 12-week double-blind treatment period where patients were treated with mometasone at doses of 220 mcg QD AM, 220 mcg QD PM, 400 mcg QD AM, 200 mcg BID, or placebo. Efficacy and safety variables were similar to the studies described above. A total of 286 patients were randomized to double-blind treatment divided approximately equally to the five treatment arms. Approximately 80% of patients completed the study, with more completers in the active treatment arms (72% to 88%) compared to the placebo arm (59%). Mean FEV1 at endpoint compared to baseline decreased by 0.22 L (8.4%) in the mometasone 200 mcg QD AM arm, 0.03 L (1.5%) in the mometasone 200 mcg QD PM arm, 0.01 L (1.4%) in the mometasone 400 mcg QD AM arm, 0.03 L (0.6%) in mometasone 200 mcg BID AM arm, compared to 0.30 L (9.8%) for the placebo arm. The mometasone 200 mcg QD PM and 400 mcg QD AM arms were statistically significantly different from placebo, and other active treatment arms were not. Secondary efficacy variables tended to numerically favor the active treatment arms. All doses were well tolerated in the study.

C96-134 was also a double-blind, placebo-controlled, parallel group study conducted in patients 12 years of age and older who were previously maintained on inhaled corticosteroids. The study was conducted in 20 centers in the United States. The design and conduct of this study was similar to C96-196 with the notable difference that the mometasone treatment arms were 110 mcg BID, 220 mcg BID, 440 mcg BID, and the study included an active comparator beclomethasone MDI 168 mcg BID. The study had

a 1-2-week run-in period during which the patients continued on their inhaled corticosteroid, followed by a 12-week double blind treatment period. A total of 365 patients were randomized to double-blind treatment divided approximately equally to the five treatment arms. Approximately 75% of patients completed the study, with more completers in the active treatment arms (79% to 87%) compared to the placebo arm (47%). Mean FEV1 at endpoint compared to baseline increased by 0.22 L (8.4%) in the mometasone 110 mcg BID arm, 0.28 L (12.1%) in the mometasone 220 mcg BID arm, 0.12 L (4.2%) in mometasone 440 mcg BID arm, 0.22 L (8.4%) in the beclomethasone MDI arm, compared to a decrease of 0.17 (7.9%) in the placebo arm. Difference between all active treatment arms and the placebo were statistically significant. Secondary efficacy variables also tended to numerically favor the active treatment arms. One of the problems in the study was a large number of patient dropouts, particularly from the placebo arm. All doses were well tolerated in this study.

P01545 was also a double-blind, placebo-controlled, parallel group study conducted in patients 12 years of age and older who were previously maintained on inhaled corticosteroids. The primary objective of this study was to support the mometasone 400 mcg QD PM dose given as one inhalation of 400 mcg. The study was conducted in 45 centers in North America. The design and conduct of the study was similar to study C96-134. The treatment arms were mometasone 200 mcg BID, 400 mcg QD PM (given from one device as 400 mcg per inhalation), 400 mcg QD PM (given from two different devices as 200 mcg per inhalation), 200 mcg QD PM, and placebo. The study also addressed the 400 mcg device issue raised in the original action letter, but this is not relevant because the applicant is not proposing to market that device. A total of 400 patients were randomized approximately equally among the five treatment arms. Approximately 75% of patients completed the study, with more completers in the active treatment arms (83% to 90%) compared to the placebo arm (52%). Mean FEV1 at endpoint compared to baseline increased by 0.51 (23.7%) in the mometasone 200 mcg BID arm, 0.41 (19.2%) in the mometasone 400 mcg QD PM (1 inhalation) arm, 0.49 (21.3%) in the mometasone 400 mcg QD PM (2 inhalations) arm, 0.41 (19.2%) in mometasone the 200 mcg QD PM arm, compared to 0.16 (7.8%) in the placebo arm. All active treatment arms were statistically significantly super to placebo. Secondary efficacy variable all favored different doses of mometasone over placebo. Mometasone was well tolerated in the study.

Studies in patients previously maintained on oral corticosteroids:

C96-137 was a double-blind, placebo-controlled, parallel group study conducted in patients 12 years of age and older who were previously maintained on oral corticosteroids. The mean prednisone dose for patients enrolled in the study was 11.83 mg/day and ranged from 4 mg to 35 mg/day. Patients were also on inhaled corticosteroids. The study was conducted in 21 centers in the United States. The study had a 1-2-week run-in period, followed by 12-week double-blind treatment period where patients were treated with mometasone furoate 440 mcg BID or 880 mcg BID or placebo. Study subjects were then continued on to a 9-month phase where all received open label treatment with mometasone 880 mcg BID, which could be tapered down to 440 mcg BID once the subject had been weaned off prednisone. Efficacy and safety variables were

similar to other studies with the notable exception that prednisone dose tapering was the primary efficacy variable, and an ACTH stimulation test was done at baseline and at the end of 12 weeks of treatment. A total of 132 patients were randomized, approximately equally to the three treatment arms. Approximately 70% of patients completed the study, with more completers in the active treatment arms (83% and 84%) compared to the placebo arm (47%). Both doses of mometasone were effective in this study. Mean percentage reduction of prednisone use was 46% in the 400 mcg BID arm, 24% in the 800 mcg BID arm, compared to an increase of 164% in the placebo arm. Mean FEV1 at endpoint compared to baseline increased by 0.25 L (14.0%) in mometasone 440 mcg BID arm, 0.17 L (9.5%) in mometasone 880 mcg BID arm, compared to a decrease of 0.19 L (12%) in the placebo arm. Differences between both active treatment arms and placebo were statistically significant. Other efficacy variables also favored mometasone over placebo. Both doses were well tolerated in this study.

HPA axis safety study:

C97-049 was a single center randomized, parallel-group, placebo- and active-controlled study conducted in patients 18 to 50 years of age with asthma to assess the effect of mometasone inhaler on adrenal axis. A total of 64 patients were divided equally to receive 29 days of treatment with mometasone 440 mcg BID, mometasone 880 mcg BID, oral prednisone 10 mg QD, or placebo. All patients were domiciled for the duration of the study. The primary endpoint was change in serum cortisol level between pre- and 30 minute post treatment with 250 mcg of Cosyntropin on day 29. Secondary endpoints were 24-four hour serum cortisol and 24-hour urine cortisol assessed every week. Both doses of mometasone appeared to suppress the adrenal axis. The 30 minute post-Cosyntropin stimulation serum cortisol concentration was 23.2 mcg/dL for mometasone 440 mcg BID, 20.8 mcg/dL for mometasone 800 mcg BID, 14.5 mcg/dL for oral prednisone 10 mg, and 25 mcg/dL for placebo. The difference between the mometasone 800 mcg BID and placebo was statistically significantly different. Serum cortisol also tended to reduce on mometasone treatment, but the difference at endpoint was not impressive. Mean serum cortisol AUC 0-24 hr (mcg.hr/dL) was 242.0 at baseline and 185.3 at day 28 for mometasone 400 mcg BID (reduction of 57.6), 210.9 at baseline and 163 at day 28 for mometasone 800 mcg BID (reduction of 47.9), 215.6 at baseline and 74.3 at day 28 for oral prednisone 10 mg (reduction of 141.3), and 255.5 at baseline and 206.4 at day 28 for placebo (reduction of 49.1). The reduction seen in the placebo arm makes interpretation of this result difficult. Unfortunately, urine collection was not complete and did not give any useful data.

Summary efficacy conclusion, dose recommendation, and safety findings:

Various dosage regimens of mometasone were studied in three different patient groups based on prior asthma therapy as reviewed above. The dosage regimen studied in the three patients groups in different studies are summarized in Table 1. Studies that supported a specific dosage regimen based on a statistically significant difference in the primary efficacy endpoint between treatment and placebo is highlighted in the Table. Dosages at the two extreme ends, 110 mcg BID and 880 mcg BID, are not supported because these doses are not replicated. The dosage of 220 mcg QD PM is replicated, but 220 mcg QD AM is not. Although the 440 mcg QD PM dose is not replicated, the 440

mcg QD AM dose is replicated, and dosages above and below the 440 mcg dose is replicated. Therefore, substantial evidence for approval is available for the 220 mcg QD PM dose, the 440 mcg total daily dose given either as a one time dose in the morning or in the evening or given as a divided dose of 220 mcg BID, and the 440 mcg BID dose. For patients who were previously on oral bronchidilators or inhaled corticosteroids, the recommended starting dose will be 220 mcg QP PM and the highest daily dose will be 440 mcg given either as a one time dose in the morning or evening or in a divided doses of 220 mcg BID. For patients on oral corticosteroids, the recommended dose will be 440 mcg BID. The 880 mcg BID dose did not show any efficacy advantage over the 440 mcg BID dose and has a higher safety burden. The recommended doses will be for patients ages 12 years and above because that was the age group studied so far in the clinical program.

Table 1. Efficacy support of various dose regimens from the pivotal studies\*

	Active Treatment Arms							
	110 mcg BID	220 mcg QD AM	220 mcg QD PM	220 mcg BID	440 mcg QD AM	440 mcg QD PM	440 mcg BID	880 mcg BID
Inhaled bronchodilator		<b>C96-136</b> C96-186		<b>C96-186</b>	<b>C96-136</b> <b>C96-186</b>			
Inhaled corticosteroid	<b>C96-134</b>	C96-196	<b>C96-196</b> P-01545	C96-196 <b>C96-134</b> P-01545	<b>C96-196</b>		<b>C96-134</b>	
Oral Corticosteroid							<b>C96-137</b>	<b>C96-137</b>

\* Studies where the primary endpoint was statistically significantly different than placebo is bolded and underlined

All doses of mometasone studied in the pivotal efficacy and safety studies were generally well tolerated. Adverse events that occurred more frequently in the mometasone treatment arms than the placebo arm were typical events seen with orally inhaled corticosteroids, such as oral candidiasis, and pharyngitis and upper respiratory tract infections. In the clinical efficacy and safety studies no evidence of adrenal axis suppression was seen, but in one controlled study (C97-049, reviewed above) mometasone at doses of 440 mcg BID and 880 mcg BID appeared to have an affect on adrenal axis.

The effect of mometasone on bone mineral density was assessed in two 2-year studies ( [ ] not reviewed elsewhere in this document). In both the studies mometasone 440 mcg BID was compared to placebo. Study [ ] did not show any difference between mometasone and placebo. In study [ ] the lumbar spine bone mineral density decreased from baseline to endpoint by 0.015 g/cm<sup>2</sup> (1.43%) for mometasone 400 mcg BID compared to 0.002 g/cm<sup>2</sup> (0.25%) for placebo. The difference was statistically significantly different. Bone mineral density for the total femur and femoral neck did not change.

#### Clinical Pharmacology and Biopharmaceutics

Schering submitted results from a fairly comprehensive clinical pharmacology program with the original submission. The program addressed the key biopharmaceutics issues, such as pharmacokinetic parameters after single and multiple dose, in vitro metabolism, drug interaction with ketoconazole, and effect of hepatic impairment. These studies were reviewed in detail in Dr. Tien-mein Cheng's review and were found to be adequate. One point of interest was the observation that the systemic bioavailability of mometasone from the lung was very low. In one study in 18 adult subjects, when 400 mcg of mometasone was given by intravenous route the mean plasma AUC was 8012 pg.hr/mL, whereas when the same dose was given by inhalation route only one subject had one value above the limit of quantification of 50 pg/mL. This contrasts with clinical studies that showed fairly well defined systemic corticosteroid effects with inhaled mometasone, such as measurable suppression of cortisol production in the Cosyntropin stimulation test after 29 days of treatment with inhaled mometasone 400 mcg BID and 800 mcg BID, and decrease in bone mineral density in one 2-year study with mometasone 400 mcg BID.

#### **Pharmacology and Toxicology**

Schering submitted complete preclinical general toxicology studies with the original submission. These were reviewed in detail by Dr. Misoon Chun and were found to be adequate. Preclinical inhalation toxicity studies conducted with dry powder formulations with and without lactose did not show any unique toxicology findings. All findings were typical glucocorticoid effects and were consistent with effects seen with other formulations of mometasone. Studies addressing the reproductive toxicity, genotoxicity, and carcinogenicity of mometasone furoate were submitted to the NDA for mometasone furoate nasal spray (Nasonex, NDA 20-762) and reviewed under that NDA. Many genotoxicity studies were conducted and most were negative. Positive findings were observed in an in vitro chromosome aberration study, a response observed with other glucocorticoids. Nose only inhalation carcinogenicity studies in rats and mice with mometasone were negative. Reproductive toxicology studies showed some known teratogenic effects of corticosteroids, such as cleft palate in mice and rabbits. There were no unique findings with mometasone. The pregnancy category for Asmanex Twisthaler will be C, which is same as other mometasone containing products.

#### **Data Quality, Integrity, and Financial Disclosure**

DSI audited three study sites during review of the original submission. There was some concern with one investigator who participated in two studies. DSI recommended that data from that investigator not be relied upon for approval purpose. Reanalysis of data excluding that investigator did not change the overall results of the two studies. During review of the original submission and subsequent submissions no irregularities that would raise concerns regarding data integrity were found. No ethical issues were present. All studies were performed in accordance with accepted clinical standards. The applicant submitted acceptable financial disclosure statements for the two new studies submitted with this application. No financial disclosure statements were submitted for the studies submitted with the original application because most of the studies were conducted before that requirement went into effect.

**Pediatric Considerations**

The current development program for Asmanex studied patients 12 years of age and older and the applicant is seeking approval for ages 12 and above. [

J

[

J

**Product Name**

The product name Asmanex Twisthaler was reviewed by the Office of Drug Safety and found to be acceptable. The review team of this Division also finds the name acceptable.

**Labeling**

During previous review cycles the label was not extensively reviewed because the application stayed approvable. With this review the Division has extensively reviewed the label because the application is essentially ready for approval, except the lack of an approved manufacturing site. Also with this submission, Schering has included results from two new clinical studies to support the 220 mcg once daily dose. The Division and Schering have agreed on a final labeling text that adequately reflects the drug product and the clinical program.

**Action**

The action on this application will be APPROVABLE because Schering is not ready for inspection of the manufacturing site. The application can be approved once the manufacturing establishment is ready for inspection and is found to be acceptable.

-----  
**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 04:28:36 PM  
MEDICAL OFFICER

**DIVISION DIRECTOR'S MEMORANDUM**

Date: March 30, 2004

To: NDA 21-067

From: Badrul A. Chowdhury, MD, PhD  
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Asmanex Twisthaler 220 mcg (mometasone furoate inhalation powder)

Applicant: Schering Corporation

This memorandum comments on the review findings of the September 30, 2004, complete response to our previous approvable action taken on this application on May 17, 2004. The application was not approved in the previous cycle because some sites related to this application were not ready for inspection. There were no other outstanding issues. All manufacturing and testing sites are now ready and have been inspected and found to have acceptable status. Therefore, the action on this application will be an APPROVAL.

My previous memorandum that summarizes the whole development program for this application is appended to this summary.

The product label was extensively reviewed by all disciplines of this Division and other relevant Divisions of the Agency in one of the previous review cycles. The label was further reviewed in this cycle and some minor updates and changes were made. The Division and Schering have agreed on a final labeling text.

*Appears This Way  
On Original*

**REQUEST FOR CONSULTATION**

TO (Division/Office):

**Director, Division of Medication Errors and  
Technical Support (DMETS), HFD-420  
PKLN Rm. 6-34**

FROM: LORI GARCIA, REGULATORY PROJECT MANAGER  
DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCT, HFD-570

DATE JANUARY 13, 2004	IND NO.	NDA NO. 21067	TYPE OF DOCUMENT Class II resubmission	DATE OF DOCUMENT NOVEMBER 14, 2003
NAME OF DRUG ASMANEX TWISTHALER		PRIORITY CONSIDERATION STANDARD	CLASSIFICATION OF DRUG CORTICOSTEROID	DESIRED COMPLETION DATE MARCH 1, 2004
NAME OF FIRM: SCHERING CORP				

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER                       |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                              |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input checked="" type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION                                   |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                         |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input checked="" type="checkbox"/> PAPER NDA    | <input type="checkbox"/> FORMULATIVE REVIEW                                  |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

**II. BIOMETRICS**

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

**III. BIOPHARMACEUTICS**

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

**IV. DRUG EXPERIENCE**

- |   |  |
|---|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                  | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES      | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input checked="" type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)   | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input checked="" type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP |  |

**V. SCIENTIFIC INVESTIGATIONS**

- |  |                                      |
|--|--------------------------------------|
| <input checked="" type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|--|--------------------------------------|

**COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:**

Requesting follow-up evaluation of trade name for Class II resubmission for NDA 21-067 for ASMANEX TWISTHALER. Last consult was completed on 11/29/00 and there were no objections at that time to the proprietary name, ASMANEX TWISTHALER. Draft labeling for product information has been requested. We will forward this to you as soon as we receive it.

PDUFA DATE: MAY 18, 2004

ATTACHMENTS: patient instructions for use; carton/container labels; 12/4/00 action letter and complete response from sponsor regarding labeling(11/14/03).

CC:

Archival NDA 21-067  
HFD-570/Division File  
HFD-570/RPM  
HFD-570/Reviewers and Team Leaders

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF DRUG SAFETY  
(DMETS; HFD-420)**

<b>DATE RECEIVED:</b> 01/15/04	<b>DESIRED COMPLETION DATE:</b> 03/01/04 <b>PDUFA DATE:</b> 05/18/04	<b>ODS CONSULT #:</b> 04-0015
-----------------------------------	--	-------------------------------

**TO:** Badrul A. Chowdhury, M.D.  
Director, Division of Pulmonary and Allergy Drug Products  
HFD-570

**THROUGH:** Lori Garcia  
Project Manager  
HFD-570

<b>PRODUCT NAME:</b> Asmanex® Twisthaler™ (Mometasone Furoate Inhalation Powder) 220 mcg	<b>NDA SPONSOR:</b> Schering Corporation
---	--

**NDA#:** 21-067

**SAFETY EVALUATOR:** Jinhee L. Jahng, Pharm.D.

**RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary name, Asmanex® Twisthaler™. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, Asmanex® Twisthaler™, acceptable from a promotional perspective.

Carol Holquist, R.Ph. Deputy Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242	Fax: (301) 443-9664	Jerry Phillips, R.Ph. Associate Director Office of Drug Safety Center for Drug Evaluation and Research Food and Drug Administration
---	---------------------	---

Division of Medication Errors and Technical Support (DMETS)  
Office of Drug Safety  
HFD-420; PKLN Rm. 6-34  
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

**DATE OF REVIEW:** February 6, 2004  
**NDA#:** 21-067  
**NAME OF DRUG:** Asmanex® Twisthaler™ (Mometasone Furoate Inhalation Powder)  
220 mcg  
**NDA HOLDER:** Schering Corporation

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Pulmonary and Allergy Drug Products (HFD-570) for a re-review of the proprietary name, "Asmanex Twisthaler", regarding potential name confusion with other proprietary or established drug names. The proposed name was found acceptable by DMETS on November 1, 2000 (ODS Consult #99-070). Additionally, during that consult, DMETS provided suggestions for improvements on the labels and labeling. Revised container labels, carton and insert labeling were provided for review and comment at this time.

PRODUCT INFORMATION

Mometasone furoate, the active component of the Asmanex Twisthaler product, is an anti-inflammatory corticosteroid indicated in the maintenance treatment of asthma as prophylactic therapy. The Asmanex Twisthaler is also indicated for asthma patients who require systemic corticosteroid administration. Each actuation of the Asmanex Twisthaler provides a measured dose of 1.5 mg mometasone furoate inhalation powder, containing 220 mcg of mometasone furoate. The recommended starting dose for most patients is two 220 mcg metered inhalations, administered once daily or one 220 mcg metered inhalation twice daily. The Asmanex Twisthaler product will be available with 14, 30, 60, or 120 inhalation units.

**II. RISK ASSESSMENT:**

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2</sup>, as well as several FDA databases<sup>3</sup> for existing drug names

<sup>1</sup> MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

which sound-alike or look alike to Asmanex Twisthaler to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>4</sup>. The Saegis<sup>5</sup> Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

**A. EXPERT PANEL DISCUSSION (EPD)**

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Asmanex Twisthaler. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have concerns with the name, Asmanex Twisthaler, in regard to promotional claims.
2. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with Asmanex Twisthaler. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Asmanex Twisthaler	Mometasone Furoate	Inhale 440 mcg day.	
Nasonex Nasal Spray	Mometasone Furoate Monohydrate	Inhale 200 mcg per day	LA
Azelex	Azelaic Acid Cream 2%	Apply to affected area twice daily.	SA

\*Frequently used, not all-inclusive.  
 \*\*L/A (look-alike), S/A (sound-alike)

<sup>4</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

<sup>5</sup> Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Asmanex Twisthaler were discussed by the Expert Panel (EPD).

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Asmanex Twisthaler, the primary concerns related to look-alike and sound-alike confusion with Azelex and Nasonex.

1. Azelex and Asmanex Twisthaler have potential for sound-alike confusion. Azelex contains azelaic acid and is available as a 2% cream. Typically, Azelex is applied twice daily. Asmanex Twisthaler is an anti-inflammatory corticosteroid indicated in the maintenance treatment of asthma as prophylactic therapy and is administered once or twice daily. Azelex and Asmanex both have three syllables, share and the same suffix ("-ex") and similar sounding prefixes ("Az-" vs. "As-"). However, the middle letters ("-el-" in Azelex vs. "-man-" in Asmanex) in each respective name phonetically differentiate the two names from one another. Azelex and Asmanex have an overlapping administration schedule (twice daily), but they differ in route of administration (topical vs. oral), dosage form (cream vs. inhalation powder), and dosage strength (2% vs. 220 mcg). Given the phonetic and product differences between Azelex and Asmanex, the likelihood for sound-alike confusion between these two products is minimal.
2. Nasonex and Asmanex Twisthaler may look-alike when scripted. Nasonex is a corticosteroid demonstrating anti-inflammatory properties and it is indicated for the treatment of the nasal symptoms of seasonal allergic and perennial allergic rhinitis, in adults and pediatric patients 2 years of age and older. Although both products contain the active ingredient mometasone furoate, Nasonex is available as a nasal spray, whereas Asmanex will be available as an oral inhalation powder. Nasonex and Asmanex contain seven letters and share similar suffixes, "-onex" in Nasonex vs. "-anex" in Asmanex, but their prefixes are distinguishable (see below). The "A-" may resemble an "N", however, the placement of the other letters, "-as-" vs. "-sm-", help distinguish one name from the other. Nasonex and Asmanex share a similar dosage schedule (once daily), but differ in respect to route of administration (nasal vs. oral), dosage form (nasal spray vs. inhalation powder), and dosage strength (50 mcg/inhalation vs. 220 mcg/inhalation). DMETS believes that the likelihood for confusion between Nasonex® and Asmanex® Twisthaler™ is minimal due to the aforementioned reasons.

*Asmanex  
Nasonex*

### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Asmanex Twisthaler, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

#### A. GENERAL COMMENTS

1. The established name is less than half the size of the proprietary name. Additionally, the font type and coloring deemphasize the prominence of the established name. Revise the label accordingly.
2. Modify the layout of the container and pouch label, and carton labeling so that each metered dose container (14, 30, 60, 120 metered doses) is distinguishable from one another (i.e. contrasting color, boxing, or some other means).

#### B. CONTAINER LABEL

See GENERAL COMMENTS.

#### C. POUCH LABEL

1. See GENERAL COMMENTS.
2. The product strength, 220 mcg, is placed on the label immediately following "Twisthaler" and also above the metered dose content. This information is redundant. DMETS recommends removing the product strength positioned above the metered dose content.
3. The statements, "For more than 1 inhalation daily" and "For more than 2 inhalations daily", are placed below the metered dose content for the 60 Metered Doses and 120 Metered Doses device respectively. This statement seems superfluous, since all recommended doses require a minimum of two inhalations per day. Please clarify and comment.

#### D. CARTON LABELING

1. See GENERAL COMMENTS, C2, and C3.
2. The placement of the established and proprietary names on the carton labeling is different than that on the container and pouch label (see page 6). DMETS recommends repositioning the proprietary and established name so that on both labels, the names are configured above the metered dose information (14, 30, 60, and 120 metered dose) as done in the professional sample shown below.

- [
- ]
3. The "Contents" section of the carton label includes the same net content for each metered dose device, irrespective of the number of total metered doses. Please revise the statement to accurately reflect the net content or fill weight of the formulation for each metered dose device (14, 30, 60, and 120 metered dose).

E. PATIENT INSTRUCTIONS

The illustrations accompanying the patient instructions are not aligned with the instructions. DMETS recommends revising the layout so that the illustrations are adjacent to the instructions.

*Appears This Way  
On Original*

**IV. RECOMMENDATIONS:**

- A. DMETS has no objections to the use of the proprietary name, Asmanex Twisthaler. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
- B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary name Asmanex Twisthaler acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

---

Jinhee L. Jahng, Pharm.D.  
Safety Evaluator  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Concur:

---

Alina Mahmud, R.Ph.  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

cc: NDA 21-067  
HFD-570: Lori Garcia, Project Manager  
HFD-570: Badrul A. Chowdhury, Division Director  
HFD-040: Andy Haffer, Senior Regulatory Review Officer, DDMAC  
HFD-430: Quynh Nguyen, Project Manager  
HFD-420: Sammie Beam, Project Manager, DMETS  
HFD-420: Jinhee Jahng, Safety Evaluator, DMETS  
HFD-420: Alina Mahmud, Team Leader, DMETS

L:\ODS04\Jahng\Pre-Marketing\04-0015.ASMANEX.Twisthaler(F).doc

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

/s/

-----  
Jinhee Jahng  
2/26/04 12:35:55 PM  
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud  
2/26/04 12:40:55 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
2/26/04 04:12:20 PM  
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips  
3/4/04 07:50:01 AM  
DRUG SAFETY OFFICE REVIEWER



U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF DRUG EVALUATION II

## Division of Pulmonary and Allergy Drug Products

Parklawn Building, Room 10B-45  
5600 Fishers Lane HFD - 570  
Rockville, MD 20857

To:

Name: Ravi Chivukula

Organization Name/Dept: Schering Corp.

CC: \_\_\_\_\_

Phone number: \_\_\_\_\_

Fax number: 908-740-5100

From: David Hiltiker

FAX: 301 - 827 - 1271

Phone: 301 - 827 - 1050

- Urgent
- For Review
- Please Comment
- Please Reply
- OTHER: \_\_\_\_\_

Date sent: 8/20/01

Number of pages including cover page: 5

Message:

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, or a person authorized to deliver the document to 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 have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail.

MEETING MINUTES

Date: December 18, 2000  
Time: 3:30-4:00 pm  
Place: Parklawn Building, 3<sup>rd</sup> floor conference room "M"

Company: Schering Corporation  
Drug: Asmanex Twisthaler (mometasone furoate inhalation powder)  
NDA #: 21-067

Subject: Discussion of December 4, 2000, AE letter comments

**Background:**

NDA 21-067 was originally submitted on November 30, 1998, for Asmanex Twisthaler (220 mcg mometasone furoate) Inhalation Powder. The NDA was issued its third approvable letter on December 4, 2000. Schering requested a meeting to discuss CMC comment 2 of the December 4 approvable letter.

**Meeting Attendees**

FDA:	Craig Bertha	CMC Reviewer
	David Hilfiker	Regulatory Project Manager
	Guirag Poochikian	CMC Team Leader
	Mary Purucker	Clinical Team Leader
	Kevin Swiss	CMC Reviewer
Schering:	Michael Belman	Regulatory Affairs
	John Hart	Development Operations
	Alice Loper	Development Operations
	David Mazzo	Development Operations
	Nicholas Pelliccione	Regulatory Affairs

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 [ 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 [ from Singapore-produced product). The [ in [ ] 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, [ As previously recommended, take action to reduce the variability between batches prepared at these two sites, particularly in [ 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 [ ]  
group II  
group III  
group IV ]

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

Schering's proposal [ ] prior to this comment incorporated data from [ ] batches produced at both Kenilworth and Singapore. They proposed limits that incorporated all mean data from these batches but limits that they believed to be more rigorous that the typical three standard deviations above and below the mean. They additionally proposed that specifications would be revised, and in their estimation, tightened, after one year of commercial production batch stability data was evaluated. They asked FDA why this proposal was inadequate.

FDA stated that [ ] difference between the two production sites varied between [ ] mean values. Individual groupings differed between the two production sites between [ ] These mean differences are not acceptable. FDA offered that specifications could be set based on the data from one of the two sites and Schering would be at a high risk of batch failure from the other commercial site if [ ] differences persist.

FDA stated that it will be difficult to agree to Schering's proposed widened specifications without knowing why the mean differences are observed. Schering anticipated that the variations between sites would cease to exist once more commercial batch data could be generated, now that operations at both sites are practically identical.

FDA advised that Schering may want to review data from commercial batches produced with different lots of lactose. Lactose has, in past experience, contributed to [ ] variation in other dry powder products.

At the meeting, Schering asked FDA to consider the following proposal for comment 3 of the December 4 approvable letter, which reads:

NDA 21-067

December 18, 2000, meeting minutes

Page 3

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).*

Schering is prepared to offer monitoring of the first 3 commercial batches produced post-approval (as per ICH guidelines), then one out of every — batches for the next — batches produced, and then one out of every — batches thereafter. Schering estimated that their commercial production rate, if both Kenilworth and Singapore manufacturing facilities are operational, would amount to approximately — commercial batches per year.

FDA commented that stability monitoring for — of batches produced [ ] is better, but the determination of the adequacy of this proposal will be part of the overall CMC review once the response to the approvable letter is submitted.

THE MEETING ADJOURNED.

Cc: Original NDA 21-067  
HFD-570/Div File

Initialed by: HFD-570/Bertha/1-8-01  
HFD-570/Swiss  
HFD-570/Poochikian/8-20-01  
HFD-570/Purucker

Draft by: HFD-570/Hilfiker/1-2-01  
Final by: HFD-570/Hilfiker/8-20-01  
C:\data\my documents\N21067\001218mtgmin

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

/s/

-----  
David Hilfiker  
8/20/01 08:32:58 AM

## Telephone Facsimile Correspondence

Date: November 16, 2000  
To: Mike Belman, Schering Corporation  
Fax No.: 908-740-2982  
From: David Hilfiker  
Project Manager  
Subject: Preliminary Labeling Comments  
# of Pages: 3

We are providing the attached information via telephone facsimile to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

**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 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

David Hilfiker  
Project Manager  
Division of Pulmonary Drug Products

Mike:

The following are preliminary labeling comments for NDA 21-067, mometasone furoate inhalation powder. These comments represent some larger labeling issues that need to be addressed before we begin to discuss specific language. More labeling comments will be provided once you have responded to these comments. Your response to these comments should be provided electronically as a MS Word file, to the NDA.

1. In the **CLINICAL PHARMACOLOGY** section, **Clinical Trials** subsection, paragraph 2, in the first sentence, delete [ ]  
] These parameters are not measurements of lung function.
2. In the **CLINICAL PHARMACOLOGY** section, **Clinical Trials** subsection, paragraph 2, second sentence, delete the sentence that begins [ ]  
] This statement implies an onset of action claim, and the data do not support an onset of action within 24 hours of the start of treatment.
3. In the **CLINICAL PHARMACOLOGY** section, **Clinical Trials** subsection, under the heading, "Patients Not Receiving Corticosteroid Therapy," in the second sentence, delete [ ]  
] Statements regarding reduction in  $\beta_2$  agonists rescue medication are only acceptable without the statement that this is a measure of significant improvement in asthma control.
4. In the **CLINICAL PHARMACOLOGY** section, **Clinical Trials** subsection, under the heading, "Patients Previously Maintained on Inhaled Corticosteroids," in the third sentence, delete [ ]  
] for reasons stated in the preceding comment.
5. In the **WARNINGS** Section, [ ]  
] update the third sentence as follows to reflect the availability of a vaccine for Varicella/chicken pox (Varivax<sup>®</sup>): "In such children or adults who have not had these diseases *or who are not properly immunized...*"
6. In the **PRECAUTIONS** section, **General** subsection, include class labeling for orally inhaled corticosteroids with regard to growth suppression in children:  
  
**General:** Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see **PRECAUTIONS, Pediatric Use** section).
7. In the **PRECAUTIONS** section, **Pediatric Use** subsection, include class labeling for orally inhaled corticosteroids with regard to growth suppression in children:

**Pediatric Use:** Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth in pediatric patients. In these studies, the mean reduction in growth velocity was approximately one cm per year (range 0.3 to 1.8 cm per year) and appears to depend upon dose and duration of exposure. This effect was observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied. The growth of children and adolescents receiving orally inhaled corticosteroids, including [insert product name], should be monitored routinely (e.g. via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including [insert product name], each patient should be titrated to his/her lowest effective dose.

8. In the **PRECAUTIONS** section, **Pediatric Use** subsection, in accordance with 21 CFR 201.57 (f)(9)(i-viii), provide any additional information regarding the safe and effective pediatric use of this drug, or provide reasons for the omission of such information.
9. In the **PRECAUTIONS** section, **Geriatric Use** subsection, in accordance with 21 CFR 201.57 (f)(10)(i-vi), provide information regarding the safe and effective geriatric use of this drug, or provide reasons for the omission of such information. Include the number of geriatric patients (age 65 years and older) who were also age 75 years or older.
10. In the **ADVERSE REACTIONS** section, if applicable to your drug product, include class labeling for orally inhaled corticosteroids with regard to growth suppression in children:

**ADVERSE REACTIONS:** Cases of growth suppression have been reported for orally inhaled corticosteroids [(including (insert product name, if appropriate))] [

11. In the **DOSAGE AND ADMINISTRATION** section, in the third sentence, delete [ ] and in the fourth sentence, delete [ ] " See above for rationale (second comment).
12. 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.

/s/

-----  
David Hilfiker

11/16/00 02:42:39 PM

CSO

## Telephone Facsimile Correspondence

Date: November 15, 2000  
To: Nicholas J. Pelliccione, Schering Corporation  
Fax No.: 908-740-5100  
From: David Hilfiker  
Project Manager  
Subject: Information Request – Stability Data Format  
# of Pages: 3

We are providing the attached information via telephone facsimile to expedite the progress of our review of your pending NDA. This information request will not be sent in a letter. Please feel free to contact me if you have any questions regarding the contents of this transmission.

**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 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

NDA 21-067  
November 15, 2000, information request

Dr. Pelliccione:

To aid in our evaluation of your pending NDA 21-067, mometasone furoate inhalation powder, please respond to the following information request as soon as possible. We would like you to resubmit the following stability data:

Singapore data are located in volume 2 of 3 (19.2, pp. 482-622) of the 10/17/00 amendment. The statistical analysis is located in volume 2 of 3 (19.2, pp. 623-893) of the same amendment following the data section.

Kenilworth data are located in volume 3 of 3 (19.3, pp. 894-1031) of the 10/17/00 amendment and the statistical analysis is located in volume 3 of 3 (19.3, pp. 1032-1321) of the 10/17/00 amendment.

The stability evaluation, in particular, the estimation of drug expiry-dating period, requires that the sponsor submit stability data in certain formats. The following tables describe how the stability data should be submitted.

Table 1 illustrates a sample standard stability data set. A standard stability data set includes both required and optional variables.

Table 1. Sample standard stability data

TEST	TEMPER	RH	PACKAGE	CLLEVEL	CLSIDE	LOWSPEC	UPPSPEC	BATCH	TIME	LEVEL
ASSAY	25	40	A	0.05	2	90	110	BCH_A	0	101.6
ASSAY	25	40	A	0.05	2	90	110	BCH_A	0	99.5
ASSAY	25	40	A	0.05	2	90	110	BCH_A	3	92.1
ASSAY	25	40	A	0.05	2	90	110	BCH_A	3	94.8
ASSAY	25	40	A	0.05	2	90	110	BCH_A	6	88.6
ASSAY	25	40	A	0.05	2	90	110	BCH_A	6	90.1
ASSAY	25	40	A	0.05	2	90	110	BCH_A	9	84.1
ASSAY	25	40	A	0.05	2	90	110	BCH_A	9	86.9
More data...										
IMPURITY	25	40	A	0.05	1	.	0.4	BCH_A	0	0.1
IMPURITY	25	40	A	0.05	1	.	0.4	BCH_A	0	0.0
IMPURITY	25	40	A	0.05	1	.	0.4	BCH_A	3	0.3
IMPURITY	25	40	A	0.05	1	.	0.4	BCH_A	3	0.2
More data...										

Table 2 and Table 3 specify recommended formats for the required and optional variables that appeared in Table 1.

Table 2. Description of Required Variables in Stability Data

VARIABLE NAME	LABEL	FORMAT	VALID VALUE
TEST	Test parameter	\$8.	Character string
BATCH	Batch	\$8.	Character string
TIME	Time in months	3.	Numeric
LEVEL	Measurement	8.4	Numeric

Table 3. Description of optional variables in stability data

VARIABLE NAME	LABEL	FORMAT	VALID VALUE
TEMPER	Storage temperature	3.	Numeric
RH	Relative humidity	3.	Numeric
PACKAGE	Package type	\$8.	Character string
CLLEVEL	1-Confidence level	4.2	Numeric
CLSIDE	Number of sides of confidence limits	3.	Numeric
LOWSPEC	Lower specification	8.2	Numeric
UPPSPEC	Upper specification	8.2	Numeric
More variables ...			

In addition to the descriptions of standard stability data set, the following points are worth noting:

- If the incoming data set includes the required variables alone, this program will enable you to standardize the data online.
- Other variables (e.g., strength) may be included in the data. However, the sponsor is expected to meet the minimal requirements (required variables).
- The sponsor should submit a document (usually no more than 2 pages) that clearly describes the variables included in each file. A data set without appropriate documentation is not acceptable.
- In conformance with the current guidance (Regulatory Submissions in Electronic Format; New Drug Applications -- issued 1/1999, posted 1/27/1999), all data should be submitted as SAS transport files.

/s/

-----  
David Hilfiker  
11/15/00 04:24:32 PM  
CSO

## Memorandum of a Teleconference

**NDA:** [ ] , 21-067 **Date:** October 18, 2000

**Products:** [ ]

Mometasone furoate inhalation powder

**Subject:** Request from Schering Corp to [ ]

**Attendees:**

NJ District Office (NJDO): Abrahams, Ellsworth, Givens, Price, Radice, Roa-Remache

Office of Compliance: Alcock, Blumenschein, Famulare

DPADP (HFD-570): Jani, Mann, Meyer, Poochikian, Schroeder, Swiss

ONDC (HFD-820): Gibbs, Hoiberg, lange

---

**Background:** (See the attached copy of the letter from Schering Corp)

**Discussion:**

- Schering claims: [ ]
- Renovation [ ] is completed.
- Schering claims that because of [ ]
- NJDO would like to see data from the actual commercial production [ ]
- [ ]
- Schering has submitted stability data from the Kenilworth facility for NDA 21-067, which Schering did not know existed (discussed first time with the Division at the September 20, 2000, meeting). The Division would like the NJDO to investigate it.
- [ ]

**Action Items:**

- The Division agreed to provide a list of issues that need to be investigated during the inspection, by October 20, 2000.
- The NJDO will find out as to when exactly the validation [ ] was completed.
- The NJDO, Division, OC, and ONDC were in agreement that the inspection should not be delayed.

- The NJDO will start the cGMP inspection
- The due dates for various products are as follows;
  - [ ]
  - NDA 21-067/mometasone inhalation powder/due 12-5-00
  - [ ]
- The NJDO will provide the final recommendation for the above listed products before the listed due dates.

---

Parinda Jani  
Project Manager

CC:  
Orig NDAs [ ] /21-067, [ ]  
Div File HFD-570 (4)  
HFD-570/Meter, Mann, Jani, Schroeder, Bertha, Swiss, Poochikian  
HFD-820/Hoiberg, Gibbs, Lang  
NJ District Office  
Office of Compliance/Famulare, Alcock, Blumenschein

/s/

-----  
Parinda Jani  
11/14/00 08:32:54 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

*Fin (S) Hilfinger*

Food and Drug Administration  
Rockville MD 20857

OCT - 4 2000

Jay Grossman, M.D.  
698 East Wetmore  
Tucson, Arizona 85705

Dear Dr. Grossman:

Between April 29 and June 28, 1999, Mr. Armando Chavez, representing the Food and Drug Administration (FDA), met with you to review your conduct of the following clinical studies:

"Placebo-controlled efficacy and safety study of Mometasone Furoate Dry Powder, once daily vs. twice daily, in asthmatic subjects previously maintained on inhaled corticosteroids," Protocol No. C96-19609, performed for Schering-Plough Research Institute;

[ ..... ]

[ ..... ]

[ ..... ]

[ ..... ]

This inspection is part of FDA's Bioresearch Monitoring Program which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and your written response through The Law Firm of Karp, Heurlin and Weiss, P.C., dated July 9, 1999, that you addressed to Mr. Chavez, we conclude that you did not adhere to all pertinent Federal regulations and/or good clinical investigational practices. We note that at the close of the inspection, Mr. Chavez presented and discussed with you his findings, which were listed on Form FDA 483 Inspectional Observations.

Page 2 – Jay Grossman, M.D.

We wish to emphasize the following observations:

1. [

2.

3.

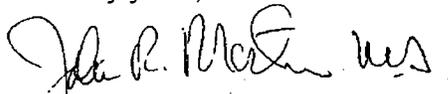
]

Page 3 – Jay Grossman, M.D.

These violations, in aggregate, are of concern to us because they may reflect a lack of supervision. Although your written response, dated July 9, 1999, acknowledges several of these findings, it does not adequately address our concerns regarding your plans for specific corrections. Because of the departures from FDA regulations discussed above, we request that you notify this office, in writing, of actions you have taken, or plan to take, to prevent similar violations in the future.

We appreciate the cooperation shown Investigator Chavez during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,



John R. Martin, M.D.  
Branch Chief  
Good Clinical Practice I, HFD-46  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place  
Rockville, MD 20855

Page 4 – Jay Grossman, M.D.

cc:

HFD-510 Doc. Rm. NDA:  
HFD-510 Review Div.Dir.  
HFD-510 MO O'HEARN  
HFD-510 PM CSO HILFIKER

HFD-510 Doc. Rm. IND:  
HFD-510 Review Div.Dir.  
HFD-510 MO O'HEARN  
HFD-510 PM CSO BARNES

HFD-510 Doc. Rm. IND:  
HFD-510 Review Div.Dir.  
HFD-510 MO JOHNSON  
HFD-510 PM CSO PARINA

HFD-510 Doc. Rm. IND:  
HFD-510 Review Div.Dir.  
HFD-510 MO PURUCKER  
HFD-510 PM CSO HILFIKER

HFD-588 Doc. Rm. BB-IND:  
HFD-588 Review Div.Dir.  
HFD-588 MO ESSAYAN  
HFD-588 PM CSO SCHNAIDER

HFD-45/Reading File  
HFD-46/Chron File  
HFD-46/GCP/CIB File 09938  
HFD-46/GCP/CIB/REVIEWER/JU  
HFD-46/GCP/CIB/CSO/CM/PRAGER  
HFD-46/GCP/CIB/BC/MARTIN

HFR-PA250 DIB KOZICK  
HFR-PA250 BIMO MONITOR KOLLER  
HFR-PA2540 FIELD INVESTIGATOR CHAVEZ

Page 5 - Jay Grossman, M.D.

CFN: #

PDUFA - Protocol No. #C96-19609

Field Classification: VAI

Headquarters Classification: VAI

Deficiency noted : deviation from protocol

FOR CAUSE - Protocol Nos. C

Field Classification: OAI

Headquarters Classification:

1)NAI

2)VAI no response required

3)VAI-R response requested

4)VAI-RR adequate response received prior to issuance of VAI-R letter

5)OAI warning letter

6)OAI NIDPOE letter

If Headquarters classification is a different classification, explain why: Not all the points on the FDA-483 were well documented in the exhibits.

Deficiencies noted:

inadequate consent form

inadequate drug accountability

deviations from protocol

inadequate records

failure to report ADRs

lack of supervision

*O:\ju\GrossmanForCause11hwj.doc*

drafted/hwj/1/19/00

reviewed/dal,sww/2/16/00

reviewed/hwj/6/2/00

re-draft/GAP/6/19/00

re-draft/hwj/6/19/00

draft/jrm/8/21/00

re-draft/hwj/8/22/00

revised/hwj/8/23/00

revised/hwj/8/25/00

revised/hwj/8/30/00

finald/mrb/8/31/00

revised/gap/9/7/00

revised/jrm/10/02/00

f/t/jau/10/02/00

Page 6 – Jay Grossman, M.D.

Note to Review Division and DSI Recommendation:

For the PDUFA study, the field inspector inspected the study-related records for 14 of the 30 subjects enrolled in Protocol C96-196-09 at Vivra Asthma and Allergy, Inc. The data appear acceptable for use in support of drug claims.

[

]

1   Page(s) Withheld



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

       § 552(b)(5) Deliberative Process

       § 552(b)(4) Draft Labeling

## MEETING MINUTES

Date: September 20, 2000  
Time: 10:00-11:30 am  
Place: Parklawn Building Conference Room "Q"

Company: Schering Corporation  
Drug Product: mometasone furoate 220 mcg inhalation powder  
NDA #: 21-067

## ATTENDEES

Schering	Alex Giaquinto	Regulatory Affairs
	John Hart	Director, Inhalation Products
	Alice Loper	Pharmaceutical Development
	David J. Mazzo	Development Operations
	Nicholas Pelliccione	CMC Regulatory Affairs
	Lois Singer	Director, Package Development
	Jonathan Spicehandler	President, SPRI
FDA	Craig Bertha	CMC Reviewer
	David Hilfiker	Project Manager
	Marianne Mann	Acting Deputy Division Director
	Robert Meyer	Division Director
	Guirag Poochikian	CMC Team Leader
	Mary Purucker	Clinical Team Leader

## BACKGROUND

NDA 21-067, mometasone furoate inhalation powder, was submitted on November 30, 1998, for the chronic prophylactic treatment of asthma. Letters identifying CMC deficiencies were sent to the applicant on May 4, September 9, and October 1, 1999, and January 24, March 14, and August 10, 2000. The October 1, 1999, and March 14, 2000, letters were approvable (AE) letters.

On September 8, 2000, Schering requested a meeting to discuss proposals for resolution of some of the CMC deficiencies identified in the most recent August 10, 2000, discipline review letter.

## MINUTES

Schering presented data and proposals for addressing several of the comments provided in the August 10, 2000, CMC discipline review letter (see hard copy attachment for slides). The deficiency comments that were discussed are included in italics followed by the discussion.

2. The following comments pertain to [ ] in product performance.
- a. Provide complete information [ ] of in-process tests for [ ] used during [ ] from the Singapore manufacturing site to the Union, NJ site.
- b. Conduct a systematic study to demonstrate the adequacy of [ ] packaging in terms of product performance [ ] The study should address adverse [ ] conditions that might be [ ] from the Singapore site to Union, NJ, where they are repackaged with [ ] Although your response to comment 8 in the June 2, 2000, amendment may have provided limited data addressing this issue [ ] were not defined and the reliability of the results from Singapore are in question as per your admission at the February 14, 2000, meeting.
- c. Please note that the [ ] the drug product from Singapore to Union, NJ is subject to the periodic testing (annual batches) described in the stability protocol. Furthermore, long term and accelerated stability data for this [ ] product should be submitted to the application for evaluation. For comparison to these data, stability data (long term and accelerated) for drug product [ ] should be included in the application or reference made to such data if already provided.
8. From the data [ ] provided for the validation/demonstration batches (v.1, pp 127-18 amendment dated June 2, 2000) it is seen that the Singapore product generally displays [ ] MF for the groups III and IV [ ] At the same time group I deposition for the Singapore product is [ ] than Kenilworth for these demonstration/validation batches. In essence these differences represent [ ] for Singapore. Corrective action should be taken to limit these differences in product prepared at the two manufacturing sites. Because of these noted differences, provide, for these batches,

[ ] data with [ ]  
Schering presented [ ] from batches manufactured at both Kenilworth, NJ, and Singapore. Schering stated that the data from Kenilworth validation/stability batches represents 18 months of stability. Apparently this data was accessible at the time of the June 2, 2000, response to the NDA, but was not submitted, because Schering's data quality assurance contractor did not communicate that the data was available to the Regulatory Affairs group. This process has since been corrected so that this mistake will not happen again.

Schering stated that the further data supports tightening the [ ] for Group II [ ] to [ ]

Schering stated that the further data demonstrates a greater comparability [ ] between batches manufactured at Kenilworth and Singapore than what was suggested by the data presented in the June 2 response. Dr. Bertha requested more information on the differences that were seen at the early time points presented in the June 2 response (see comment 8 of the August 10, 2000, Agency letter). With that information, Schering should clearly indicate how the primary Singapore stability batches [ ] to New Jersey, and provide the approximate timetable of events that occurred from the [ ] until testing occurred. Schering agreed to provide this information.

In regard to the [ ] packaging of product manufactured in Singapore [ ] in New Jersey, Dr. Poochikian stated that Schering should provide full information for all components of the [ ] packaging. Dr. Poochikian clarified that Schering should provide all of the same information that is normally provided [ ]

Schering stated that suppliers for some of the components do not have DMFs, and only certain information is available at this time (see attachment, slide 9). Dr. Bertha noted that testing [ ] should be conducted.

Schering clarified that [ ] packaging was used, because the drug product has to be [ ] once in New Jersey for release testing and labeling before the product is repackaged. Even if drug product is [ ] before it is repackaged [ ]

To address comment 2.b., Schering can supply stability data from Singapore at 1 and 6 month time points under ambient conditions (25°C/60%RH). Stability samples used to provide this data were [redacted] but were [redacted] at Kenilworth prior to testing. Schering stated that they can also provide comparative data for [redacted] [redacted] to demonstrate that there is no difference in drug product performance [redacted] [redacted]. Dr. Bertha asked for this information in the next response, and requested that Schering also provide approximate timetables to show the timecourse of events from the point of manufacture in Singapore until the point of testing in Kenilworth for each of the stability batches.

Schering asked if this information would suffice as a response to comment 2.b. Dr. Bertha stated that he cannot agree until the data is reviewed.

Schering stated that they are considering two other options, in the interest of avoiding further delays towards NDA approval. Schering can commit to [redacted] all drug product manufactured in Singapore [redacted]. In the meantime, Schering can work with FDA to establish a suitable study to demonstrate the viability of the [redacted] [redacted] materials. After NDA approval, Schering can submit a prior approval supplement for the use of [redacted] [redacted] from Singapore to Kenilworth.

The other option is not to supply from Singapore at all until [redacted] process can be approved from that facility. Schering stated that they favored the former option as a compromise, if the stability information that is currently available will not be adequate to support [redacted] [redacted].

Schering clarified that the [redacted] [redacted] are identical between the Kenilworth and Singapore facilities.

Dr. Poochikian expressed his concern about the potential effects on the dry powder performance due to the additional handling of Singapore samples when they are [redacted] [redacted].

17. The following comments pertain to the proposed [redacted] [redacted] for the drug product [redacted] [redacted].

- a. The 6 weeks of data provided in response to comment 31 for aged drug product batches 39457-055-XU and 39457-058-XU stored [redacted] [redacted] under conditions of 25°C, [redacted] are not sufficient to justify [redacted] [redacted]. Generally a dataset of longer duration (e.g., 12 weeks)

than the proposed duration, that displays suitable stability, is necessary. Provide such updated data.

- b. Depending on the data supported by the updated studies of drug product performance after storage under conditions of 25°C, the appropriateness of the higher proposed presentation counts (e.g., 60 and 120) may need to be reconsidered.

Schering presented data (not provided in the June 2, 2000, response) for (see attachment 1, slides 13-16). Schering stated that this new data demonstrates no difference in performance between beginning- and end-of-shelf-life product. Dr. Bertha noted that the Group I results demonstrate a (Groups III and IV, slides 15 and 16) demonstrate. This could indicate

Schering acknowledged this but stated that the proposed for the product does fall within specifications for beginning, middle, and end of the total actuations for product. Schering added that the projected for each device should only be if used as labeled, since the 60-actuation unit will be labeled for BID use only and the 120-actuation unit will be labeled for QID use only.

Dr. Poochikian noted that there is a significant versus the beginning (dose 1 and 2) and middle (dose 60) actuations. Schering stated that this trend is only evident beyond the proposed for these products, and therefore should not be a problem.

13. Based on the limited data provided (pp. 149-151 of your June 2, 2000, amendment) for the acceptance testing of devices for flow rate, the criterion of is broad and should be tightened in the interim, We remind you of your agreement to provide the final acceptance criterion and the validated method for the determination of the flow rate for incoming device components by June, 2001. The final limits proposed should be reflective of the collected data to provide a reasonable level of quality control for this important parameter, upon acceptance of the device.

Schering presented new flow rate data on commercial lots of (see attachment 1, slides 18 and 19). Based on the average lot measurements (slide 18), Schering proposed an interim specification of Dr. Bertha stated that the data will be reviewed to determine if this interim specification is acceptable.

Schering requested an extension of the commitment to provide final acceptance criterion and the validated method by June, 2001. Schering proposed a final specification based upon data from one year of commercial production lots. Dr. Bertha stated that if the proposed interim specification is reasonable, an extension of the final specification will be considered.

9. Drug master file [ ] was reviewed, was found to be inadequate to support your application, and a letter dated February 5, 1999, was forwarded to the holder. After a telephone conversation with the holder representative ( [ ] ), a telephone facsimile copy of the February 5, 1999, letter was forwarded on May 19, 2000. The holder has not responded as of August 8, 2000.
10. Drug master file [ ] was reviewed, was found to be inadequate to support your application, and a letter dated March 13, 2000, was forwarded to the holder. The holder has not responded as of August 8, 2000.
11. Drug master files [ ] were reviewed, were found to be inadequate to support your application, and letters dated February 5, 1999, were forwarded to the holder. After a telephone conversation with the holder representative ( [ ] ), a telephone facsimile copy of each letter was forwarded on May 23, 2000. The holder has not responded as of August 8, 2000.
12. Drug master file [ ] was reviewed, was found to be inadequate to support your application, and a letter dated April 13, 2000, was forwarded to the holder. The holder has not responded as of August 8, 2000.

Dr. Bertha stated that he last checked the document room electronic log on September 18, 2000, and the above DMFs had not been amended. Dr. Bertha requested that Schering contact their suppliers. If the suppliers have amended their DMFs to respond to these deficiencies, the DMF holders may send a desk copy directly to the attention of Dr. Bertha.

6. Any future stability reports that include an "initialized" time zero data point as opposed to release should be identified as such and should include or give reference to the data from the corresponding release testing.

Dr. Bertha stated that it was unclear whether the zero time point used in stability reports referred to the release time point. Dr. Bertha requested that Schering clarify the procedure for stability testing, and Schering agreed. Dr. Poochikian noted that elapsed time in between release and the zero stability time point could be misleading if there is a significant drop [ ] within that period of time that is not captured in the data set.

NDA 21-067

Page 7

September 20, 2000, Meeting Minutes

Dr. Poochikian noted that Schering has responded to deficiencies in this application by proposing an alternate pathway to avoid the problem rather than addressing the problem. These alternate pathways have raised new and significant concerns that were not raised in previous deficiency letters. To avoid further delays, Dr. Poochikian suggested that Schering consider addressing the concerns outlined in the FDA letter rather than changing plans to avoid the problems.

Attachment: Schering presentation: 19 slides, hard copy only

RD by: D Hilfiker/9-22-00

RD initialed by: R Meyer/9-29-00  
M Purucker/9-25-00  
M Mann/9-26-00  
C Bertha/9-28-00  
G Poochikian/9-28-00

Final: D Hilfiker/9-29-00

C:\data\my documents\N21067\000920mtgmin

Hilbiter

NDA 21-067

AUG 10 2000

Schering Corporation  
2000 Galloping Hill Road  
Kenilworth, New Jersey 07033

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

Dear Dr. Lamendola:

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

We also refer to your submissions dated May 10, and June 2, 2000.

Our review of the Chemistry, Manufacturing and Controls section of your submissions is complete, and we have identified the following deficiencies. Numbers in parentheses following the comments below refer to the numbering in the March 14, 2000, Agency letter.

1. As previously requested, provide a table that outlines the sequence, location, and timing of events for all aspects of the manufacture of the [ ] drug substance, with the various responsibilities of each site clearly identified. (comment 1)
  
2. The following comments pertain to [ ] product performance.
  - a. Provide complete information [ ]  
 [ ] description of in-process tests for control [ ] used during [ ]  
 [ ] manufacturing site to the Union, NJ site. [ ] from the Singapore
  
  - b. Conduct a [ ] study to demonstrate the adequacy [ ]  
 [ ] The study  
 should address [ ]  
 Singapore site to Union, NJ, [ ]  
 [ ] Although your response to

comment 8 in the June 2, 2000, amendment may have provided limited data addressing this issue [ ]

[ ] were not defined and the reliability of the results from Singapore are in question as per your admission at the February 14, 2000, meeting.

- c. Please note that the [ ] the drug product from Singapore to Union, NJ is subject to the periodic testing (annual batches) described in the stability protocol. Furthermore, long term and accelerated stability data for this [ ] product should be submitted to the application for evaluation. For comparison to these data, stability data (long term and accelerated) for drug produc. [ ]

[ ] should be included in the application or reference made to such data if already provided. (comment 1)

3. Provide data on prepared drug product demonstrating the affect on the performance [ ] and [ ] as a result of the proposed [ ] storage period for the agglomerates (anhydrous mometasone furoate and lactose). (comment 1)

4. Once appropriate drug product data validating the agglomerate hold period of up to [ ] hold period for product packaged in [ ] (Singapore) are provided, submit updated master batch records from each site that have been revised, if necessary, that indicate these maximum holding periods. (comment 1)

5. [ ] should provide a commitment that they will notify their customers of changes to the chemistry, manufacturing, or controls for the supplied lactose that may result in changes in the drug products to be formulated with this material. As indicated at our February 14, 2000, meeting, future guidance from the Agency may recommend that drug master files be submitted for major excipients (e.g., lactose) for drug products to be taken by the inhalation route. (comment 6)

6. Any future stability reports that include an "initialized" time zero data point as opposed to release should be identified as such and should include or give reference to the data from the corresponding release testing. (comment 9)

7. Tighten the acceptance criterion [ ] for the mometasone furoate found on the Group II stages [ ] to be reflective of the data provided [ ]

[ ] (comment 11.e)

8. From the data [redacted] provided for the validation/demonstration batches (v.1, pp 127-18 amendment dated June 2, 2000) it is seen that the Singapore product generally displays [redacted] MF for the groups III and IV. [redacted] At the same time group I deposition for the Singapore product is [redacted] than Kenilworth for these demonstration/validation batches. In essence these differences represent [redacted] for Singapore. Corrective action should be taken to limit these differences in product prepared at the two manufacturing sites. [redacted]
  
- [redacted] (comment 11.e)
  
9. Drug master file [redacted] was reviewed, was found to be inadequate to support your application, and a letter dated February 5, 1999, was forwarded to the holder. After a telephone conversation with the holder representative [redacted] a telephone facsimile copy of the February 5, 1999, letter was forwarded on May 19, 2000. The holder has not responded as of August 8, 2000. (comment 15)
  
10. Drug master file [redacted] was reviewed, was found to be inadequate to support your application, and a letter dated March 13, 2000, was forwarded to the holder. The holder has not responded as of August 8, 2000. (comment 15)
  
11. Drug master files [redacted] were reviewed, were found to be inadequate to support your application, and letters dated February 5, 1999, were forwarded to the holder. After a telephone conversation with the holder representative [redacted] a telephone facsimile copy of each letter was forwarded on May 23, 2000. The holder has not responded as of August 8, 2000. (comment 15)
  
12. Drug master file [redacted] was reviewed, was found to be inadequate to support your application, and a letter dated April 13, 2000, was forwarded to the holder. The holder has not responded as of August 8, 2000. (comment 17)
  
13. Based on the limited data provided (pp. 149-151 of your June 2, 2000, amendment) for the acceptance testing of devices for flow rate, the criterion of [redacted] is broad and should be tightened in the interim, [redacted] We remind you of your agreement to provide the final acceptance criterion and the validated method for the determination of the flow rate for incoming device components by June, 2001.

The final limits proposed should be reflective of the collected data to provide a reasonable level of quality control for this important parameter, upon acceptance of the device. (comment 18)

14. We acknowledge your removal of [ ] from the application (section 4.B.6.2). (comment 20)
15. DMF [ ] was reviewed on May 2, 2000, and was found to be inadequate to support your application. The holder has been notified by letter of the deficiencies. As the [ ] has been removed from section 4.B.6.2 of the application and you have stated that you will not use this [ ] for future production of the drug product, DMF [ ] reference should be withdrawn from the application. (comment 22)
16. Your response to comment 27 of the March 14, 2000, letter indicates that the counter controls the lock-out point of the device. As you have previously indicated that there were device counter failures and that modifications have been made to optimize the reliability of the mechanisms (pp. 969-970 of June 30, 1999, amendment), it is important that the reliability of the counter be established, e.g., report on any counter failures or related complaints from any future clinical trials such as an open label study. (comment 27 and 28)
17. The following comments pertain to the proposed in-use period for the drug product [ ]
  - a. [ ]  
  
Provide such updated data. ]
  - b. [ ]  
  
] ]
18. The results of your studies involving improvement of the sealing consistency of the inhalers (p. 372 of your June 2, 2000, response) are encouraging and we recommend that they continue as outlined in your response to our comment 32 of the March 14, 2000, letter. (comment 32)

19. Aside from the label on the overcap, which identifies the drug and strength, this information should also be included on the body of the device as well. Whereas the [ ] is probably sufficient for your identification of the correct 220 mcg dosing, [ ] it is not sufficient for identification of the drug substance and strength in the marketplace once the overcap is separated from the remainder of the device. (amendment 3 of your June 2, 2000, response)
  
20. Revise the following sentence in the DESCRIPTION section of the labeling from:  
[ ]  
to  
  
"The amount of mometasone furoate emitted from the inhaler in vitro did not differ significantly for flow rates ranging from 28.3 L/min to 70 L/min for fixed intervals of 2 seconds." (comment 41)
  
21. The HOW SUPPLIED section of the labeling should be revised to include the fill weight of the various presentations. Please make the appropriate revisions to the product labels and labeling and submit the revised mock-ups for our evaluation. (comment 43)
  
22. Please note that once agreement is reached with regard to the drug product specification acceptance criteria, you should submit four copies of an updated methods validation package containing the following information: a). composition of the drug product formulation; b). acceptance criteria and methods for the drug substance; c). acceptance criteria and methods for the drug product; d). supporting validation data for drug substance and drug product methods; e). a list of available samples with their respective sample numbers; f). analytical results for available samples.

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

NDA 21-067

Page 6

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 Mr. David Hilfiker, 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

NDA 21-067

Page 7

cc:

Archival NDA 21-067

HFD-570/Div. Files

HFD-570/D. Hilfiker

HFD-570/Bertha

HFD-570/Poochikian

HFD-820/DNDC Division Director

DISTRICT OFFICE

Drafted by: sb/August 8, 2000

Initialed by: P. Jani 8/9/00

C. Bertha 8/10/00

G. Poochikian 8/10/00

*CR 8/10/00*

*[Signature] 8/10/00*

*CB 8/10/00*

filename: N21067IR

DISCIPLINE REVIEW LETTER (DR)

Hilfiker

### Record of Telephone Conversation

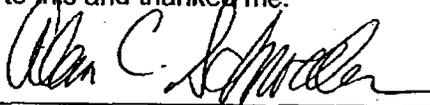
**Date:** August 22, 2000  
**Subject:** NDA 21-067 and NDA [ ]  
**Initiated by:** Applicant  
**Product Name:** mometasone furoate DPI, 220 mcg and [ ]  
**Firm Name:** Schering Corporation  
**Contact:** Dr. Alex Giaquinto; Dr. Diane Zezza  
**Telephone Number:** 908-740-5770

First call: I was called by Dr. Giaquinto, who was looking to speak with Dr. Poochikian. I said that Dr. Poochikian was away this week. He indicated that they had received a letter for their mometasone furoate DPI NDA, and they wished to have a meeting or a teleconference for clarification. They would like to avoid multiple cycles. I said that I thought that Dr. Poochikian should be involved in such a meeting. Dr. Giaquinto would like to meet with us next week. He didn't know who is the reviewer for this product. I indicated that for simple clarification it might be possible to have a teleconference next week but that the primary reviewer needs to be here.

Second call: I called Dr. Giaquinto's office, and I found that he was not available but that he had asked Dr. Zezza to speak with me. I told her of Dr. Giaquinto's earlier conversation with me, and I indicated that Dr. Craig Bertha is the primary reviewer for mometasone furoate DPI, 220 mcg. Dr. Bertha is away this week. Since various people involved are on leave or will be on leave at this time of year, it would be best for her to contact the project manager for mometasone furoate DPI, Mr. David Hilfiker. Mr. Hilfiker can check schedules and set up the meeting. They should indicate in writing the purpose of the meeting and the specific issues that they would like to have clarified.

I indicated that [ ]

] She agreed to this and thanked me.



Alan C. Schroeder, Ph.D.

<p>cc: Orig. NDA #21-067          Dup. NDA 21-165          HFD-570/Division file          HFD-570/ACSchroeder/8-22-2000          HFD-570/GPoochikian          HFD-570/CSO DHilfiker          HFD-570/KSwiss          HFD-570/GTrout</p>	<p>HFD-570/CBertha          R/D init. by: ACS for GP 8/22/00          F/T by: ACSchroeder/8-22-2000          ACSfile: N21067_2000_08_22_tel.doc</p>
---	---

Hilfiker

NDA 21-067

Schering Corporation  
2000 Galloping Hill Road  
Kenilworth, NJ 07033

JUL 26 2000

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

Dear Dr. Lamendola:

We acknowledge receipt on June 5, 2000, of your June 2, 2000, resubmission to your new drug application (NDA) for Asmanex Twisthaler (220 mcg mometasone furoate) Inhalation Powder.

This resubmission contains additional information submitted in response to our March 14, 2000, action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is December 5, 2000.

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

Sincerely yours,



*to* Sandy Barnes  
Chief, Project Management Staff  
Division of Pulmonary and Allergy Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

NDA 21-067

Page 2

cc:

Archival NDA 21-067

HFD-570/Div. Files

HFD-570/Hilfiker

HFD-570/Barnes/7-14-00

HFD-570/Bertha

HFD-570/Gilbert-McClain

HFD-570/Chun

HFD-570/Choi

*JAH 7/26/00*

*EST 7/26/00*

DISTRICT OFFICE

Drafted by: HFD-570/Hilfiker/July 14, 2000

Final: HFD-570/Hilfiker/7-26-00

Filename: c:\my documents\N21067\000714acltr

CLASS 2 RESUBMISSION ACKNOWLEDGEMENT (AC)

(DDR: Update the user fee goal date based on the class of resubmission.)

2800 for R/M 7/24/00

Hilfiker

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): HFD-400/OPDRA/Assoc. Director for Medication Prevention		FROM: HFD-570/DPADP/Hilfiker		
DATE: July 14, 2000	IND NO.:	NDA NO.: 21-067	TYPE OF DOCUMENT : Class 2 Resubmission	DATE OF DOCUMENT: June 2, 2000
NAME OF DRUG: Asmanex Twisthaler	PRIORITY CONSIDERATION: standard	CLASSIFICATION OF DRUG: 5S	DESIRED COMPLETION DATE: November 1, 2000	
NAME OF FIRM: Schering Corporation				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Tradename Consult				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input checked="" type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER:		<input type="checkbox"/> CHEMISTRY REVIEW <input checked="" type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER:		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input checked="" type="checkbox"/> DEFICIENCY LETTER RESPONSE <input checked="" type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input checked="" type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input checked="" type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<p><b>COMMENTS/SPECIAL INSTRUCTIONS:</b> The Division has previously consulted the former LNC about the tradename Asmanex (see attached LNC evaluation.) LNC did not recommend the use of Asmanex, because of other similar tradenames and the implication of the indication in the name. The Division did not receive Center-level support for rejecting Asmanex based on the indication as part of the tradename.</p> <p>The applicant has just filed a complete response to the most recent approvable letter. The new PDUFA due date is December 5, 2000. The Division hereby requests follow-up evaluation of the tradename with the potential that this NDA may be approved within 6 months.</p> <p>cc: Original NDA 21-067 HFD-570/Div. Files HFD-570/Hilfiker, Gilbert-McClain, Bertha</p>				
NATURE OF REQUESTER:		METHOD OF DELIVERY (Check one):		
SIGNATURE OF REQUESTER: <i>[Signature]</i> 7-14-00		<input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER:		SIGNATURE OF DELIVERER:		

Orig NDA 21-067  
HFD-570/Div. Files

REQUEST FOR TRADEMARK REVIEW

To: The Office of Post-Marketing Drug Risk Assessment  
Attention: Associate Director for Medication Error Prevention (HFD-400)

From: Division of Pulmonary and Allergy Drug Products	HFD-570
Attention: David Hilfiker	Phone: (301) 827-1084
Date: July 14, 2000	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Asmanex Twisthaler	NDA 21-067
Established name, including dosage form: mometasone furoate inhalation powder	
Other trademarks by the same firm for companion products: Nasonex Nasal Spray	
Indications for Use (may be a summary if proposed statement is lengthy): <input type="checkbox"/> 7 asthma	
Initial Comments from the submitter (concerns, observations, etc.): There is no support for the argument against Asmanex because of the indication implied in the tradename. We have not previously requested an evaluation for the tradename Twisthaler.	

Attachments: (1) 7-16-97 LNC evaluation of the tradename,    
(2) Draft labeling submitted 6-2-00 (package insert, carton/container labeling)

Appears This Way  
On Original

7 Page(s) Withheld



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

       § 552(b)(5) Deliberative Process

       § 552(b)(4) Draft Labeling

Hilfiker

NDA 21-067

JAN 24 2000

Schering Corporation  
2000 Galloping Hill Road  
Kenilworth, NJ 07033

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

Dear Dr. Lamendola:

Please refer to your November 30, 1998, new drug application for mometasone furoate inhalation powder.

We also refer to your submissions dated June 30, August 23, September 17, October 1, and December 1, 1999.

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 comment numbers and dates in brackets following these comments refer to comments in previous FDA letters dated May 4 and October 1, 1999, regarding this application.

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 commercial 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 the 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 direct tablet (DT) 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 [ ]

[ ] are adequately controlled. The specification sheet for the acceptance of lactose should be modified accordingly. [comment 11.m., May 4, 1999; comment 18.a.(13), October 1, 1999]

8. Submit release data for Singapore site-specific stability drug product batches obtained at the Singapore testing laboratory [redacted] 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 finished before release and initial time-point stability testing is performed. If there is a time lag between [redacted] assembly and the addition of the [redacted] packaging, specify the maximum allowable period. Also, indicate how the time "zero" point for stability studies is determined relative to the manufacturing date. Provide verification that the [redacted] preparation and [redacted] assembly, and the addition of the [redacted] 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 [redacted] in the formulation that are of respirable size (e.g., dissolution of formulation components and microscopic counting of particles [redacted]). 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 to 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 [redacted]
  - c. Provide [redacted] 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 unwrapped 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 [ ] for the [ ] 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

[ ]  
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 11 and 12 of the ( ) study samples of the 220 mcg strength were ( ) 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 due to ( ) Investigate the cause of this ( ) 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 unwrapped under conditions of 25°C, demonstration batches, etc.), provide the dates when the agglomerates 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 [redacted] provide updated stability data [redacted] 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: [redacted] [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 [redacted] [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 [redacted] 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 [redacted] package labels, and the HOW SUPPLIED section of the labeling should state that the unit should be stored in a dry place with a given 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 [redacted] 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. 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.

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 Mr. David Hilfiker, Project Manager, at (301) 827-1084.

Sincerely yours,

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

cc:

Archival NDA 21-067

HFD-570/Div. Files

HFD-570/Hilfiker

HFD-570/Bertha/1-18-00 *B 1/24/00*

HFD-570/Poochikian/1-19-00 *1-21-00*

HFD-820/DNDC Division Director *1/24/00*

DISTRICT OFFICE

Drafted by: HFD-570/Hilfiker/January 12, 2000

Initialed by: HFD-570/Jani/1-14-00/1-21-99

Final: HFD-570/Hilfiker/1-20-00

Filename: c:\my\_documents\N21067\00-01-12.irltr.doc

DISCIPLINE REVIEW LETTER (DR)

---

---

INTEROFFICE MEMORANDUM

---

---

TO: NDA 21-067

FROM: MARTIN H. HIMMEL, MD, MPH - DEPUTY DIRECTOR, HFD-570 *m Himmel 2/28/00*

SUBJECT: MEDICAL REVIEW OF RESPONSE TO APPROVABLE LETTER OF OCTOBER 1999;  
SECONDARY REVIEW OF DR. O'HEARN'S MEDICAL OFFICER REVIEW DATED FEBRUARY 19, 2000

DATE: FEBRUARY 28, 2000

CC: HFD-570: DIVISION FILE, HILFIKER, MEYER, GILBERT-MOCLAIN, HIMMEL

---

This memo is being written as the medical review of volumes 2 and 3 of the sponsor's response to the Division's approvable letter dated October 7, 1999. The first volume, which contains the sponsor's specific responses to each of the clinical comments in the October 7, 1999, letter was reviewed by Dr. O' Hearn, the medical officer assigned this NDA. I agree with his conclusions regarding the sponsor's responses in volume one. Of note, however, I don't think Dr. O'hearn's comment number 1 at the end of his review needs to be conveyed to the sponsor, as we have already made this comment to them. The second and third volumes of the submission contain the safety update on mometasone.

The safety update addresses new safety information regarding the mometasone dry powder formulation, the HFA 227 based metered dose inhaler formulation and the HFA 227 based nasal formulation.

Completed Mometasone DPI Asthma Trials:

New safety data submitted for the dry powder formulation included three completed trials in adults involving 144 subjects and 3 completed trials in children (an HPA axis study, short-term growth study and a 12-week safety and efficacy trial). The safety report includes information on common adverse events, serious adverse events, adverse events that led to patient withdrawal, median laboratory data, clinically significant laboratory abnormalities and results from physical exams. These summaries were reviewed, and the adverse events seen were similar, overall, to those seen in the original NDA database. In addition, there were only 100 new patients in adult placebo controlled trials, thus this new information need not be integrated into the original database for labeling purposes. Overall, the safety data reported does not alter the approvability decision for this NDA.

Ongoing Mometasone DPI Asthma Trials:

The following are the asthma trials using the dry powder formulation that the sponsor reports are still underway:

- 2 year studies evaluating bone density
- P682 and P683: Clinical pharmacology studies
- P98-602, P98-603, P98-598, P98-601: active comparator marketing studies
- C97-380, C97-384, C97-385: pediatric studies evaluating safety and efficacy, long term safety, and long term growth.

For these ongoing studies, only serious adverse event information was submitted by the sponsor. These events were reviewed and they too do not change the clinical determination that this NDA is approvable.

Completed Mometasone HFA Asthma Trials:

Concerning the HFA metered dose inhaler formulation, there are eight completed studies that are discussed in this safety update involving approximately 2031 patients that received active drug. The sponsor presented pooled data for six of the trials that were similar in design. Two studies, one involving patients that were already on prednisone when enrolled and one that was not placebo controlled were presented separately, as was the data on two 9 month extension trials. In addition, one pediatric phase I clinical pharmacology study was completed and is reported here. The information from these trials that was presented included common adverse events, serious adverse events, adverse events resulting in patient withdrawals from the trials, median laboratory value changes clinically significant laboratory abnormalities and findings on physical exams and vital signs. In general, the findings were similar to the dry powder formulation and do not raise any additional specific safety concerns. Of note, however, there was one patient (C97-222-23/571) that is listed as having hepatitis, however no additional information is provided. In my review of the LFT line listings, this patient appeared to have normal LFTs. The case report form for this patient should be requested to further evaluate the circumstances surrounding this adverse event and to determine why there were no abnormal LFTs reported for this patient. In addition, the sponsor states that center 8 in study C97-222 should not be relied upon because of gross GCP violations. No additional information is provided regarding the details of these violations. Therefore, the sponsor should also be asked to submit to the HFA MDI formulation IND additional information regarding these violations.

Completed Mometasone HFA Allergic Rhinitis Trials:

Finally, the safety update includes safety results from three studies conducted with the nasal HFA 227 formulation. These three trials were a 2-week safety and efficacy study, a 6-month safety study and an HPA axis study. Similar information to what was submitted for the completed asthma studies was submitted for these three trials. This safety information did not identify any additional concerns regarding the safety of mometasone dpi for asthma.

Conclusions and Comments for the Sponsor:

In summary, the sponsor has submitted a safety update with additional information from their dpi and mdi programs for asthma, as well as from their nasal mdi program for allergic rhinitis. Most of the data is from studies in adults, although some pediatric studies are included as well. Overall, the data do not raise additional safety issues concerning the approvability of mometasone dpi for asthma. The package insert for this drug will be reviewed when the drug is determined to be approvable from the CMC standpoint. Clinically, the NDA remains approvable, however, the following two comments should be conveyed to the sponsor:

1. 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.
2. Submit additional information to the MF MDI IND concerning the GCP violations that occurred at center number 8 in study C97-222.

Appears This Way  
On Original

MEETING MINUTES

FEB 14 2000

Drug Product: Asmanex (mometasone furoate) Inhalation Powder, 220 mcg  
NDA: 21-067  
Applicant: Schering Corporation

Subject of meeting: CMC Deficiencies

Background Summary:

Schering Corporation submitted a new drug application for mometasone furoate dry powder inhaler on November 30, 1998. Mometasone furoate was originally developed and approved as a nasal spray (Nasonex Nasal Spray, NDA 20-762). In the first 10-month PDUFA review cycle, Schering was issued information request letters on May 4 and September 9, 1999, identifying CMC deficiencies, and an approvable letter on October 1, 1999, also including CMC deficiencies. Subsequently, Schering responded to the deficiencies listed in the October 1, 1999, letter, on December 1, 1999. The Division issued an information request letter on January 24, 2000, which listed remaining CMC deficiencies prior to approval. Schering called the Division and requested a meeting to discuss remaining CMC deficiencies with ONDC review staff in the Division.

FDA Participants: Craig Bertha CMC Reviewer  
David Hilfiker Project Manager  
Guirag Poochikian CMC Team Leader

Schering Participants: Alexander Giaquinto Regulatory Affairs  
David Mazzo Manufacturing and Quality Assurance

Prior to the meeting, Schering submitted via facsimile (see attachment 1) a list of specific items, taken from the January 24, 2000, letter, for discussion. These items were addressed in order. The comment, as written in the January 24 letter, is given in *italics*, followed by a summary of the discussion.

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

Schering stated that endotoxin testing is already performed on the final product, and bioburden is included in-process. Microbiologists at Schering do not know how to apply limits that are recommended for injectables to a dry powder inhaler.

FDA stated that clinicians within the Division support endotoxin testing for inhalation powders and/or [ ] lactose. FDA requested that Schering examine clinical trial batches and submit the data. The data will be compared to data submitted for other products to determine if the proposed specifications are appropriate. If the testing and specification for lactose is [ ] Schering will also have to validate the [ ] procedure. Endotoxin assay (and the specification) can occur

Schering stated that they do not currently have an explanation for the [ ] that is seen over time, but that clinical trials were conducted with a similar [ ] in [ ] over the duration of the trials. Schering stated that they will not be able to identify and correct the problem prior to the June action deadline for this NDA, and will commit to address this comment but do not wish it to delay approval. FDA stated that specifications [ ] can be problematic because of the regulatory need to be consistent with the standards applied to competitors' products. FDA stated that this [ ] will require input from the review team in terms of its clinical ramifications, and no commitments can be made on [ ] at this time. FDA further stated that Schering can propose specifications based on the current data, but the specification [ ] would be a review issue as far as its acceptability.

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]*

FDA clarified that the request is for patient complaints that were logged during clinical trials. Schering stated that they had no knowledge of counter complaints, but that patients may not have been paying much attention to the counter mechanism. Schering agreed to provide whatever data is available.

31. *Provide [ ] and emitted dose content uniformity 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 [ ] package is removed.*

FDA clarified that testing should occur around the proposed expiry date (e.g., if expiry is proposed to be 18 months, test at month 16 or 17). Schering was concerned that stability testing on end-of-shelf-life samples will not be completed in time for the June action deadline. FDA stated that this data is required prior to approval.

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

Schering clarified that research is ongoing to improve the [ ] efficiency of the drug product device, to investigate the potential for eliminating the [ ] the product. However, they want FDA to consider the data that is currently submitted for the [ ] drug product, and they will consider submitting a supplemental application

after approval for the improved device. FDA agreed to continue to review the product based on the current data [ ] but asked Schering to provide a brief summary of the proposed changes. Schering agreed to provide a brief summary.

#### OTHER DISCUSSION

Schering representatives brought to the meeting further items for discussion (see attachment 2).

1. The first item refers to comment 11 of the January 24, 2000, information request letter. Comment 11 reads as follows:

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

Subpart 11d reads as follows:

- d. Provide detailed dimensional drawings (with tolerances indicated) for any parts that differ between the [ ] and [ ] devices.*

Schering offered a tutorial session for CMC review staff if the design diagrams that are being prepared in response to subpart 11d are not sufficiently interpretable.

Subpart 11g reads as follows:

- g. Since there are significant differences noted [ ] for drug product [ ] (Kenilworth stability batches) and [ ] (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.*

Schering asked for FDA's opinion on this issue: if there is a statistical difference seen [ ] between the [ ] device, but this difference is not considered clinically meaningful to the clinical review staff, is this comment still an issue? FDA replied that CMC review staff is interested in seeing the complete profile and the comparison in any case. Small but statistical differences [ ] between the [ ] devices are not of concern, but larger

differences between the two [ ] may be of concern from a CMC perspective. Schering also stated that the updated data set that will be provided with the response displays a convergence of the [ ] profile data for the Singapore product as compared to the Kenilworth product.

2. **IND 52,214: mometasone furoate MDI (HFA 227 propellant)**

The second additional item for discussion is in reference to the development of a mometasone furoate metered-dose inhaler utilizing an HFA propellant (HFA 227).

[ ] Schering proposed submission of 3 months of stability data under accelerated and long-term storage conditions in the original NDA for the product fitted with the modified valve, with a commitment to submit updated stability data for 6 months under accelerated and long-term conditions. The existing stability database generated with the product [ ] will be used to supplement the NDA database.

FDA agreed to review the NDA based on 6 months of stability data under accelerated and long-term conditions.

3. **IND 55,108: mometasone furoate nasal MDI**

Schering is developing a mometasone furoate nasal metered dose inhaler for NDA submission. Submission of the NDA was delayed because of [ ] that required qualification toxicology studies prior to NDA submission. Schering will have the data to qualify [ ] and intends to submit the NDA in April 2000. To satisfy the site-specific stability requirement which requires stability data generated on 3 commercial batches from the commercial manufacturing site, Schering wishes to refer to agreements reached at a recent public meeting for discussion of site-specific stability requirements, as presented in the Agency's draft Guidance on drug substance and drug product stability. Schering's interpretation of the agreements are listed in attachment 2 under "NASONEX MDI." Schering proposed that release data would be supplied one month prior to the action deadline for the NDA.

NDA 21-067

February 14, 2000 Meeting Minutes (CMC Deficiencies)

Page 6

FDA commented that they did not recall "agreement" being reached on the required site-specific stability data or the allowance of submission of release data only for site-specific batches 9 months into the review period for a 10-month action deadline. FDA stated that they would have to research the minutes from prior meetings for this product before making any decision on the site-specific stability data that would be required upon application submission.

**POST-MEETING FOLLOW UP NOTES:**

Schering proposed a — stability protocol in a June 17, 1999, submission to the IND. FDA reviewed the proposal and provided comments to Schering via facsimile on July 8, 1999 (see attachment 3). Due to FDA concerns expressed in the July 8 facsimile, FDA believes that the prior comments on site specific stability data, as in the July 8 facsimile, should be upheld.

David Hilfiker  
Project Manager

*DH* 2/25/00

Attachments: (1) 2-8-00 Schering facsimile communication to FDA (2 pages total)  
(2) 2-14-00 Schering addendum to meeting agenda (3 pages total)  
(3) 7-8-99 FDA comments provided to Schering via facsimile (1 page total)

NDA 21-067  
February 14, 2000 Meeting Minutes (CMC Deficiencies)  
Page 7

cc: Original NDA 21-067  
Original INDs 52,214 and 55,108  
HFD-570/Division File  
HFD-570/Hilfiker  
HFD-570/Bertha/2-18-00/2-23-00/2-24-00  
HFD-570/Poochikian/2-18-00/2-24-00

C:\my\_documents\N21067\00-02-14.mtgmin.doc



2000 Galloping Hill Road  
Kenilworth, New Jersey 07033

TELECOPIER TRANSMITTAL SHEET

Please deliver the following 2 pages (including cover page)  
If transmittal is incomplete or illegible, please call: Lynne Boardman at 908-740-5553

DATE	February 08, 2000
TO	David Hilfiker
FAX NUMBER	301-827-1271

FROM	Dr. Alex Gaiquinto
LOCATION	K-6-1
FAX NUMBER	908-740-4131
SUBJECT	Questions for meeting re: Mometasone Furoate Dry Powder Inhaler

**MESSAGE**

Attached are the questions we would like to address to you in advance of our meeting with the division on Monday February 14, 2000. Please call me if you have any questions regarding this matter. My number is 908-740-5770.

Thank you,  
Alexander Giaquinto, Ph.D.

Question 5. Schering had not intended to establish an in-process test or criteria for pyrogens and/or bacterial endotoxins in   lactose.

Questions 6.   does not have a DMF for  . Either Schering must generate a DMF, or get information from   to be included in the NDA.

Question 8.   data for the Singapore stability batches   Kenilworth are not available, since Singapore was not intended to be a site of   testing for the drug product. However, limited research data, generated at the Singapore site for two batches   Kenilworth, can be provided. The data are limited  .

Additionally, the emitted dose delivery testing was only performed for  .

Question 12.

difficult to predict, but would require extensive experimental work just to assign a cause. We cannot predict if the change   could be corrected with the current design and formulation.

Question 28. *In vitro* counter function data are available now for the commercial inhaler, but this   counter was not used in the clinical studies. Thorough patient in-use data on the commercial counter design will not be generated until the counter is tested in our next clinical studies, currently targeted to begin 3Q00.

Question 31. A study to evaluate   data and emitted dose patient use data (25°C)   for product near expiry will be initiated with two batches that have been stored at ambient temperature and humidity for  . Availability of complete study results by June, 2000 is not certain.

Question 32. We do have promising   data for an improved  . However, we do not yet have simulated in-use (25°C,   RH)   data, which relates to   the inhaler.

Additional   studies of these modified components are still ongoing  . The   data using   cannot be supplied before June, 2000. Implementation of   data will require significantly more time  .

## ASMANEX TWISTHALER DPI

The Twisthaler NDA is voluminous, as are subsequent correspondences to the Agency responding to review questions. The objective of our discussion will be to facilitate the completion of a positive review by FDA.

1. We have categorized the latest list of questions into 3 major groups:
  - a) Data available and/or rapidly generated with analysis as requested done or readily completed - responses available in a few weeks.
  - b) Data available and/or easily generated with analysis as requested possible and to be completed - responses available in 1-2 months.
  - c) Data not available, experiments to be designed and conducted and data analysis provided as requested - responses available in 3-6 months. [These are basically the items listed on the list sent earlier.]

Our objective is to reach agreement on those items absolutely necessary for approval. Our proposal is to provide the responses in 3 phases according to our categorization to allow for continued NDA review. Do you agree with this approach?

2. The Twisthaler, its functionality and developmental evolution are not easily understood based solely upon independent review of engineering drawings and performance data. We offer to provide a "tutorial" session to the reviewers in which we would concisely present responses to existing and new questions in a working meeting of duration of your choice. Of course, this would be in addition to complete written documentation. This suggestion is thought to provide a mechanism to avoid further correspondence iterations regarding device design and functionality. [This suggestion is modeled on the former "NDA day" meetings sponsored by the agency with an applicant.] Your feedback on this offer is requested.

3. It is our position that respirable fraction in general is defined as those particles greater than or equal to 2 microns and less than or equal to 8 microns. Increases in the fraction of particles in the less than 2 micron range potentially contributes to increased toxicological effects and increases in the fraction greater than 8 microns potentially contributes to decreased efficacy.

Your position on this "rule of thumb" is sought. In addition, your comments on small changes in [redacted] the respirable range during the development of a DPI are also requested, especially in light of a situation where respirable particle distribution is reproducible within a device version.

ASMANEX MDI

A metered dose inhaler of Asmanex in Propellant 227 is under development. During evaluation of our NDA stability database, we have uncovered a physical incompatibility [redacted] This problem is manifested as

[redacted] 1. This phenomenon becomes more evident with [redacted]

] We have identified several avenues to problem resolution:

- a) [redacted]
- b) [redacted]
- c) [redacted]

Our proposal is to file the NDA identifying the failures on stability due to this [redacted], to completely describe the [redacted] modifications made to correct it, to provide 3 months accelerated and long-term storage data demonstrating product acceptability and to commit to provide 6 months accelerated and long-term data from ongoing studies during the review. Since our existing database is sufficient to demonstrate stability except for [redacted] we would not conduct full testing on the batches with [redacted] unless they were to be used also to satisfy the site specific stability requirement. The existing stability data on batches [redacted] would be used to propose shelf life based upon [redacted] changes of the formulation. Do you agree that this approach is acceptable?

Hilfiker

Memorandum of Telephone Facsimile Correspondence

Date: January 31, 2000

To: Mary Jane Boyle  
Director, U.S. Regulatory Affairs  
Schering Corporation

From: David Hilfiker  
Project Manager

Through: Robin Huff *RAH 1-31-00*  
Pharmacology/Toxicology Team Leader

Subject: Labeling Comments

# of Pages: 4

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

**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 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

cc: ORIG NDA 21-067

HFD-570/DIV FILES

HFD-570/HILFIKER

HFD-570/HUFF

HFD-570/CHUN

HFD-570/SUN

*David Hilfiker* 1/31/00  
\_\_\_\_\_  
David Hilfiker  
Project Manager  
Division of Pulmonary Drug Products

cc: my-documents / N21067 / 99-12-06.fax.doc

Mary Jane:

The following is a two-part presentation of labeling comments for your NDA 21-067 for mometasone furoate.

PRELIMINARY LABELING COMMENTS FOR PENDING NDA 21-067

These preliminary labeling comments are provided in addition to labeling comments provided in the October 1, 1999, action letter for NDA 21-067.

1. In the CLINICAL PHARMACOLOGY section, remove the entire third paragraph that reads,

2. Revise the PRECAUTIONS section, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection as shown below.

1<sup>st</sup> paragraph:

In a 2-year carcinogenicity study in Sprague Dawley rats, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at an inhalation doses — up to 67 mcg/kg (approximately 8 times the maximum recommended daily inhalation dose in adults). In a 19-month carcinogenicity study in Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at — inhalation doses to 160 mcg/kg (approximately times the maximum recommended daily inhalation dose in adults).

3<sup>rd</sup> paragraph:

In reproductive toxicity studies in rats, impairment of fertility — was not produced by subcutaneous doses up to 15 mcg/kg (approximately 6 times the human systemic exposure (AUC) observed following the maximum recommended daily inhalation dose in adults). However, mometasone furoate — caused prolonged gestation, prolonged and difficult labor, reduced offspring survival, and reduced maternal body weight gain — a dose of 15 mcg/kg.

3. Revise the PRECAUTIONS, Pregnancy subsection as follows.

| [ ]  
|

|  
|

J

ADDITIONAL CHANGES REQUESTED TO THE LABELING FOR

[ ] \_\_\_\_\_

J

Contact me at (301) 827-1084 if you have any questions.

David Hilfiker  
Project Manager

Hilfiker

JAN - 4 2000

NDA 21-067

Schering Corporation  
2000 Galloping Hill Road  
Kenilworth, NJ 07033

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

Dear Dr. Lamendola:

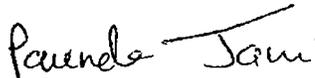
We acknowledge receipt on December 2, 1999, of your December 1, 1999, resubmission to your new drug application (NDA) for mometasone furoate dry powder inhaler.

This resubmission contains additional information submitted in response to our October 1, 1999, action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is June 2, 1999.

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

Sincerely yours,



Parinda Jani  
Acting Chief, Project Management Staff  
Division of Pulmonary and Allergy Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

NDA 21-067

Page 2

cc:

Archival NDA 21-067

HFD-570/Div. Files

HFD-570/Hilfiker

HFD-570/O'Hearn

HFD-570/Himmel

HFD-570/Bertha

HFD-570/Poochikian

HFD-570/Gebert

HFD-570/Wilson

HFD-570/Chen

HFD-570/Uppoor

HFD-570/Chun

HFD-570/Huff

DISTRICT OFFICE

*JH 1/3/00*  
*my 1-4-00.*

Drafted by: HFD-570/Hilfiker/December 14, 1999

Initialed by: HFD-570/Jani

Final: HFD-570/Hilfiker/1-3-00

Filename: c:\my\_documents\N21067\99-12-14.acltr.doc

CLASS 2 RESUBMISSION ACKNOWLEDGEMENT (AC)

(DDR: Update the user fee goal date based on the class of resubmission.)

Dunn

**Memorandum of Telephone Facsimile Correspondence**

Date: 10/8/99  
To: Joseph Lamendola  
VP, Worldwide Regulatory Affairs  
From: Keary L. Dunn  
Regulatory Project Manager  
Subject: NDA 21-067

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

**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 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

  
\_\_\_\_\_  
Keary L. Dunn  
Regulatory Project Manager  
Division of Pulmonary Drug Products



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

MEMORANDUM

DATE: 10/8/99

FROM: Keary L. Dunn *KLD*  
Regulatory Project Manager, DPADP

THRU: Dan O'hearn, M.D., Medical Officer *DOH*  
Martin Himmel, M.D., Deputy Division Director  
Cathie Schumaker, Chief Project Management Staff *CS*  
*10-8-99*

SUBJECT: NDA 21-067 Safety Update request

TO: Joseph Lamendola, Ph.D.  
VP, Worldwide Regulatory Affairs  
Schering Corporation

Reference is made to the telephone conversation on October 7, 1999, between Dr. Lamendola of Schering Corporation and Keary Dunn of this Division regarding the request for all new safety information for mometasone furoate. (Approvable letter of October 1, 1999)

As per 21 CFR 314.50(d)(5)(vi)(b), Dr. Lamendola called to consult the Division regarding the form and content of the requested Safety Update. The major concern was the extent of the safety information needed from mometasone furoate formulations other than the Dry Powder Inhalation formulation (i.e., nasal spray and metered dose inhalation products). Upon discussion with Drs. Himmel, O'Hearn and Cathie Schumaker the Division would like to receive the following safety information.

1. For mometasone furoate DPI, provide all new safety information that was not included in the original NDA submission. The format of this new information is dependent upon the volume of additional exposure information available (see Agency guidance, "The format and content of the Clinical and Statistical Sections of an Application, 7/1988). That guidance states that if the new exposure information is more than 25% of the original information, it should be integrated into the safety database as indicated in the October 1, 1999, approvable letter. The extent and nature of integration of safety data is also dependent on the doses studied, as well as the duration of exposure. The Division would be happy to review alternative proposals that you may wish to submit with regard to the formatting the new safety information.

2. For the approved Nasonex Nasal Spray (NDA 20-762), provide final study reports from any new safety studies conducted since its approval that have not already been submitted. In addition, any new serious adverse events (SAEs) that have not been submitted should also be included in the safety update.
3. For mometasone furoate MDI (IND 52,214), provide final study reports from all new safety studies that have been completed, reports of all new SAEs that have not already been submitted and laboratory data regarding liver function testing from completed studies.

Appears This Way  
On Original

cc.

Original NDA 21-067

Div. file

HFD-570/Ohearn

HFD-570/Dunn

HFD-570/Gebert

HFD-570/Chun

HFD-570/Chen

HFD-570/Bertha

*10/21/99*

**Memorandum of Telephone Facsimile Correspondence**

Date: 10/1/99  
To: Joseph Lamendola, Ph.D.  
Vice President, Worldwide Regulatory Affairs  
From: Keary L. Dunn  
Regulatory Project Manager  
Subject: NDA 21-067

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

**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 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

  
\_\_\_\_\_  
Keary L. Dunn  
Regulatory Project Manager  
Division of Pulmonary Drug Products

907 740 2982  
LSD

5/5/04

We have reviewed the draft package insert, patient instructions for use, and carton/container/pouch labels for NDA 21067. We have the following comments followed by our edits to your draft labeling:

1. The placement of the established and proprietary names on the carton labeling is different than that on the container and pouch label. The Division recommends repositioning the proprietary and established name so that on both labels, the names are configured above the metered dose information (14, 30, 60, and 120 metered dose) as done in the professional sample.
2. Increase the font size of the in-use statement on the cap label to make it commensurate with that of the storage statement.
3. Revise the storage statement to the following on all packaging labels and cartons as per the Stability Guidance: Store in a dry place at 25°C (77°F). [See USP Controlled Room Temperature].
4. The illustrations accompanying the patient instructions for use are not aligned with the instructions. The Division recommends revising the layout so that the illustrations are adjacent to the instructions.
5. In order to identify and distinguish the number of doses per device, clearly color code the backgrounds of the number of inhalations on the cap label as you did for the pouch and carton labels (e.g., indicate the number 60 metered doses in white on dark blue background even on the cap label).
6. The established name is less than half the size of the proprietary name. Additionally, the font type and coloring de-emphasize the prominence of the established name. Revise the label accordingly.
7. For the pouch labels, the product strength, 220mcg, is placed on the label immediately following "Twisthaler" and also above the metered dose content. This information is redundant. We recommend removing the product strength positioned above the metered dose strength.

Division Director's Memorandum

Date: Thursday, September 30, 1999  
NDA: 21-067  
Sponsor: Schering-Plough  
Proprietary Name: Asmanex (mometasone furoate powder for inhalation) 200 mcg,  
400 mcg.

Introduction: This is an original NDA submission for mometasone furoate (MF) in an orally inhaled formulation. Previously, this moiety was approved by this division for nasal allergies in the Nasonex AQ (mometasone furoate) Nasal Spray. This present NDA is ambitious in terms of scope, seeking a broad range of individual populations and dosing regimens.

Chemistry/Manufacturing and Controls: This application as currently submitted has a large number of CMC deficiencies, not the least of which is that the  $\zeta$  changes substantially [ ] for both the 200 and 400 mcg product. Additionally, the in vitro [ ] data suggest some disparity in the delivery of the two dosage strengths if they were used to deliver the same nominal dose (see below). An IR letter was issued to the sponsor based on the initial CMC review in 5/4/99. These issues remain outstanding and the same comments will be replicated in the action letter for this cycle.

Biopharmaceutics: MF is a synthetic corticosteroid that is poorly bioavailable from the oral route, primarily due to high first pass metabolism (being dependant at least in part on CYP3A4). Curiously, unlike fluticasone, which is readily bioavailable via inhalation, it appears that the orally inhaled drug is <1% bioavailable compared to IV administration. There are some signs of systemic activity, particularly at doses exceeding 800 mcg/day (i.e., doses at or higher than the top proposed labeled dose). There is some indication of drug-drug interactions for ketoconazole and some indication of reduced clearance in hepatic patients. These are not of great concern, but should warrant consideration in the product labeling. There are not adequate PK/PD data to relate the 200 mcg and 400 mcg products at the same nominal dose.

Clinical / Statistical: See Dr. O'Hearn's primary review and Dr. Himmel's secondary review memo for details. However, the sponsor has provided adequate clinical evidence to allow for approval of the 400 mcg QD dose, and the 200 mcg BID dose - both in non-oral corticosteroid dependant patients. While efficacy was apparent for 200 mcg QPM, this study was not replicated and was conducted with the 100 mcg product which is not definitively bridged to the 200 mcg product. The 200 mcg QAM dose suffers this same design flaw of being conducted with the 100 mcg product, but also 2 of the three studies submitted failed to convincingly show efficacy and therefore the 200 mcg QAM dose regimen is also not approvable without further support.

A study of 400 and 800 mcg BID for oral-corticosteroid sparing effects showed convincing evidence of the efficacy of 400 mcg BID (unfortunately from the 200 mcg product) and the 800 mcg BID dose (with the 400 mcg product), but no marginal benefit

of the higher dose. Therefore, the 800 mcg BID dose is not being sought, nor should it be included in labeling.

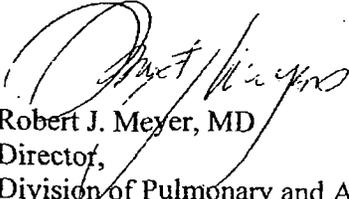
Overall, the product is clinically approvable at a dose of 200 mcg BID or 400 mcg QD for non-oral steroid dependant patients and at a dose of 400 mcg BID for oral corticosteroid effects. However, at the current time, only these doses provided from the 200 mcg product are strongly supported, given the dearth of clinical data (or PK/PD data) to link the 200 and 400 mcg product and given the . . . . . data.

Clinical Auditing/data checking: DSI conducted investigations at 3 study sites, Drs. Craig, Miller and Grossman. All three were routine (not for cause) and the former two resulted in NAI recommendations. While the DSI audit for Grossman did not reveal significant issues with this study, they also conducted 'a for' cause audit of that site for another NDA and found questionable practices that would likely lead to more than a VAI. The implications for this NDA are not clear, since this study's audit was clean with no indication of a systemic problem in the conduct of this NDA's studies.

EERs: One of the EERs was outstanding as of the date of this memo (Singapore site). The finished dosage manufacturer – Schering Kenilworth, NJ received a Warning Letter in response to their inspection of August 18, 1999. There was also a withhold recommendation for the finished dosage release tester – Schering Union, NJ. All other sites were acceptable.

Labeling: The nomenclature committee and the division find the name "Asmanex" acceptable. There will need to be significant revisions to the labeling prior to this product being approved, but given the outstanding clinical and CMC issues, these revisions should be left until the entire application is approvable.

Conclusions: This NDA as submitted and amended cannot be approved, due primarily to CMC considerations – including outstanding unsatisfactory EERs. The clinical data would allow for approval the 200 mcg BID, 400 mcg QD and 400 mcg BID dosage administered via the 200 mcg product. Further data may allow for clinical approval of the 400 mcg product and for a lower once-daily dosing.

  
Robert J. Meyer, MD  
Director,  
Division of Pulmonary and Allergy Drug Products.

*9/30/99*

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee  
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

<b>From:</b> Division of Pulmonary and Allergy Drug Products	<b>HFD-570</b>
<b>Attention:</b> Keary Dunn	<b>Phone:</b> (301) 827-1050
<b>Date:</b> September 29, 1999	
<b>Subject:</b> Request for Assessment of a Trademark for a Proposed New Drug Product	
<b>Proposed Trademark:</b> Asmanex Twisthaler	<b>NDA/ANDA#</b> NDA 21-067
<b>Established name, including dosage form:</b> mometasone furoate inhalation powder	
<b>Other trademarks by the same firm for companion products:</b> Nasonex Nasal Spray	
<b>Indications for Use (may be a summary if proposed statement is lengthy):</b> Asthma	
<b>Initial Comments from the submitter (concerns, observations, etc.):</b>	

Note: Meetings of the Committee are scheduled for the 4<sup>th</sup> Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original NDA 21-067; HFD-570/division file; HFD-570/

Appears This Way  
On Original

Consult #803 (HFD-570)

☐ ☐ mometasone furoate dry powder inhaler

The following look alike/sound alike conflicts were noted: ASMALIX, ASMA, ASMANEPHRIN, and ASMALIX. The Committee felt there is a significant potential for mix-up with the conflicting names. Additionally, the name encodes a medical condition (asthma) and may be in violation of the regulations regarding reminder advertisements. There were no misleading aspects found in the proposed proprietary name.

The proposed established name is not in conformance with USP recommendations for monograph titles. The appropriate established name should be mometasone furoate for inhalation.

The Committee finds both the proposed proprietary and established names unacceptable.

*D. Boring* 7/16/97, Chair  
CDER Labeling and Nomenclature Committee

Div

NDA 21-067

SEP - 9 1999

Schering Corporation  
2000 Galloping Hill Road  
Kenilworth, NJ 07033

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

Dear Dr. Lamendola:

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

We also refer to your submission dated March 30, 1999.

We have completed the review of your submission dated March 30, 1999, and have the following comments and information requests.

1. Include the expiration date on the portion of the device that contains the formulation.
2. 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 [ ] mcg per metered dose).
3. Provide comprehensive stability data obtained in a systematic fashion for drug product with the [ ] proposed [ ]  
These data will be directly compared with data provided for the primary and site specific stability batches [ ]  
[ ] Refer to our earlier comments (16.i of the May 4, 1999, Agency letter) 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 comment 14 of the May 4, 1999, Agency letter that outlined significant differences in [ ] data for the stability samples of product prepared at the Kenilworth site as compared to the Singapore site [ ]

These comments are being provided to you prior to the completion of our review of the application and are in addition to the comments forwarded to you in the May 4, 1999, Agency letter, to give you preliminary notice of issues that have been identified. Per the

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 are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

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

Sincerely

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

NDA 21-067

Page 3

Cc:

Archival NDA 21-067  
HFD-570/Divisional File  
HFD-570/Bertha *CB 9/14/99*  
HFD-570/Dunn  
HFD-570/Poochikian  
HFD-570/O'Hearn  
HFD-570/Gebert  
HFD-570/Chun  
HFD-820/DNDC Division Director  
DISTRICT OFFICE

*Handwritten signature and date 9/14/99*

Drafted by: Dunn/8-17-99  
Initialed by: Schumaker  
Bertha  
Poochikian

*Handwritten signature and date 9/14/99*

*Handwritten signature and date 9/14/99*

F/T by:

Filename:C:\mydocuments\NDAs\N21067.IR.99-8-17.doc

INFORMATION REQUEST (IR)

---

INTEROFFICE MEMORANDUM

---

TO: N21067  
FROM: MARTIN H. HIMMEL, MD - DEPUTY DIRECTOR, HFD-570  
SUBJECT: SECONDARY MEDICAL REVIEW MEMO OF NDA 21067  
DATE: SEPTEMBER 16, 1999  
CC: HFD-570: MEYER, HIMMEL, OHEARN, DUNN

*M. Himmel  
9/16/99*

---

Introduction:

NDA 21-067 was submitted by Schering Corporation for mometasone dpi, a dry powder formulation of mometasone for asthma. The sponsor's proposed indication, as stated in the draft package insert is:

[

In addition, the proposed dosage, as stated in the Dosage and Administration section of the package insert is:

]

The proposed formulation/device of mometasone dpi for marketing will be one that delivers either 200 or 400mcg from the mouthpiece per breath.

This memo will briefly discuss the relevant efficacy, safety and data quality issues that pertain to the approvability of this NDA. For a more extensive discussion of these issues and the data included in the NDA, please see the medical officer review of this NDA written by Dr. Daniel O'Hearn.

Efficacy:

In support of the efficacy of this drug, the sponsor has submitted two placebo controlled trials in patients that were not receiving inhaled (or oral) corticosteroids, three placebo controlled trials in patients already on inhaled corticosteroids and one placebo controlled trial in patients on oral

corticosteroids. All trials were randomized and all had a 12-week double blind treatment period. Change in FEV1 from baseline to endpoint was the primary efficacy endpoint in all the trials except the oral corticosteroid sparing study, which looked at reduction in prednisone use.

The two trials which evaluated efficacy in patients on inhaled bronchodilators were studies C96-186 and C96-136. Study C96-136 evaluated doses of 200 and 400mcg a day delivered as a single dose in the morning. Study C96-186 evaluated the same doses as well as a 200mcg twice-daily dose. Of note, in both trials the 200mcg dose, whether given once or twice daily, were administered using a 100mcg per breath device (which is not one of the to-be-marketed devices). The 400mcg q AM dose was administered using the 200mcg per breath device. Both of these trials demonstrated the statistical superiority of 400mcg q AM vs. placebo. In addition, in trial C96-186, the 200mcg twice-daily dosage was found statistically superior to placebo as well. The 200mcg q AM dose was superior to placebo in study C96-136 but not in study C96-186. Also of note, the 200mcg q AM dose was not superior to placebo on secondary endpoints, such as peak expiratory flow rate (PEFR) in study C96-136.

The three trials conducted in patients already on inhaled corticosteroids were studies C96-168, C96-134 and C96-196. Study C96-196 differed from the other two in that this trial included a two-week open label period in which all patients received 200mcg twice daily of mometasone dpi before the double blind treatment period. The other two trials included a run-in period during which patients were continued on their previous inhaled corticosteroid before double blind therapy. The doses and formulations evaluated in these trials were the following:

Dose	Formulation
Study C96-168	
100mcg twice daily	100mcg
200mcg twice daily	200mcg
Study C96-134	
100mcg twice daily	100mcg
200mcg twice daily	200mcg
400mcg twice daily	400mcg
Study C96-196	
200mcg q AM	100mcg
200mcg q PM	100mcg
400mcg q AM	200mcg
200mcg twice daily	100mcg

All doses studies in these three trials were statistically better than placebo on the primary endpoint except for the 200mcg q AM dose. Also, of note, while the 200 q PM dose was statistically superior to placebo, spirometry in this trial was essentially performed 12 hours after the dose was administered and not 24, as for the AM doses (although the PM dose was statistically superior to placebo on the PM PEFR assessment).

The final trial was the oral steroid sparing study, C96-137. This trial evaluated doses of 400 and 800mcg twice daily vs. placebo using the 200 and 400mcg per inhalation formulations, respectively. As discussed in the medical officer review, serious attempts were made to ensure that patients were on their lowest dose of prednisone before start of double blind therapy. The primary endpoint evaluated in this trial was the percent change from baseline to endpoint in daily prednisone use. Both doses of mometasone dpi were statistically significantly better than placebo on this endpoint, with the 400mcg dose achieving a 46% decrease and the 800mcg dose a 24% decrease. Prednisone use in the placebo arm increased by 164%.

Peak inspiratory flow rates through the mometasone dpi device were evaluated in a number of trials. In study C96-136, six patients with relatively mild asthma (FEV1 of 1.99 - 3.18 liters) generated peak inspiratory flow rates of 53 - 76 liters/minute. In study C96-137, which included patients requiring oral corticosteroids, peak inspiratory flow rates of 60 - 76 liters per minute through the device were seen in the six patients evaluated. Similar inspiratory flow rates were seen in three patients with mild disease in study C96-134.

Overall, the clinical trial database supports the efficacy of the 200mcg twice daily and 400mcg once daily doses as well as the 400 mcg twice-daily dose in patients on oral corticosteroids. The 200mcg twice-daily dose was studied in two trials using the 200mcg per breath formulation (C96-168 and C96-134). However, the 400mcg doses, either once daily or twice daily were only studied using the 200mcg per breath formulation. There is no efficacy data in the NDA on the administration of those doses using the 400mcg per breath nor is there a study which directly compares the efficacy of 400mcg administered either from the 200 or 400mcg per breath formulation. As such, the sponsor should be requested, in the action letter, to conduct a pk/pd study before approval that compares the 400mcg dose from the 200 and 400mcg per breath formulations. This trial should include dose response, possibly the 200mcg dose, to ensure validation of the sensitivity of the study.

**Safety:**

Overall, there is adequate data in the NDA database to support the safety of the proposed doses in asthmatic patients. Concerning long term exposure, approximately 102 patients received 400mcg of drug per day for 1 year and 205 patients received 800-1600mcg per day for 1 year, in 9 month extensions to trials C96-136, C96-135 and C96-137. The database did demonstrate an increased incidence of local adverse events with mometasone that should be included in the label, such as candidiasis, pharyngitis and dysphonia. There were also cases of treatment emergent cataracts noted in study C96-135. In addition, there were reports of elevation of liver function tests in the database, although similar lab reports were seen in the positive control groups and placebo. Concerning the effects of this drug on the hypothalamic-pituitary-adrenal (HPA) axis, this was evaluated in a number of trials. In all trials where Cortrosyn stimulation testing was performed, the assessment was done using a 30-minute infusion of .25mg of Cortrosyn.

In study C96-134, the HPA axis was assessed using a Cortrosyn stimulation test at screening and at the end of 12 weeks (at screening patients were on their individual inhaled corticosteroid). A mean affect on serum cortisol values was not seen, although there were 3 patients in the 200mcg bid arm and one in the 400mcg bid arm that had normal results at screening but were abnormal at follow up. A similar evaluation of Cortrosyn stimulation was performed in study C96-196, however in this trial the assessment was performed at screening (while patients were on inhaled corticosteroids), baseline (after two weeks of mometasone dpi 200mcg bid) and at follow up. Regarding the outlier analysis, the following was seen:

	All Mometasone Treatment Arms	Placebo
SCREENING		
Pre-Cortrosyn < 5mcg/dl	0	
Post Cortrosyn < 18mcg/dl	2	
Difference between pre and post < 7mcg/dl	6	

BASELINE		
Pre-Cortrosyn < 5mcg/dl	2	
Post Cortrosyn < 18mcg/dl	1	
Difference between pre and post < 7mcg/dl	10	
ENDPOINT		
Pre-Cortrosyn < 5mcg/dl	4	1
Post Cortrosyn < 18mcg/dl	1	0
Difference between pre and post < 7mcg/dl	8	1

Regarding the mean changes in cortisol values, the sponsor only presented the data from baseline to follow up and not from screening to follow up. In this presentation of the data, no significant mean differences were seen. However, since all patients had already received mometasone at baseline, the more appropriate presentation of the data would be from screening to follow up. While the outlier data presented above suggests a drug effect, even as early as two weeks after treatment with 200mcg bid, the sponsor should also be asked to present the mean change data from screening to baseline and to follow-up.

Longer-term evaluation of effects on Cortrosyn stimulation was evaluated in trial C96-135. This study, which included patients already receiving inhaled corticosteroids, evaluated doses of 200mcg twice-daily (using the 100mcg formulation), 400mcg once-daily (using the 200mcg formulation) and 800mcg once-daily. Of note, there was no placebo control in this study. However, when individual outlier data was tabulated, there was one in the 400mcg twice daily and four in the 800mcg once daily groups at baseline. At 26 weeks, there were four, six, and four in the 200mcg twice-daily, 400mcg twice-daily and 800mcg daily arms, respectively. At 52 weeks, there were five outliers in each of the mometasone treatment arms, thus suggesting some effect of mometasone on Cortrosyn challenge studies.

The effects of mometasone on the HPA axis were also evaluated in two four-week trials in steroid naïve patients. In study C97-049, 400mcg and 800mcg twice-daily doses were evaluated using the 200 and 400mcg formulations, respectively. The data showed statistically significant differences between the two treatment arms and placebo in plasma cortisol 24 hour AUC at each week of the study with a dose response effect seen. The NDA included a limited presentation of the Cortrosyn challenge data, which was collected at baseline and day 29, and there was a statistically significant effect seen for the high dose. The sponsor should be asked for a more complete presentation of the mean Cortrosyn stimulation data from this trial, as well as a presentation of the individual patients with abnormal results at baseline and follow up. The second four-week trial is study C95-135. This study evaluated doses of 200mcg twice daily and 400, 800 and 1200mcg daily in steroid naïve patients using the 100mcg formulation. Twenty-four hour plasma cortisol levels were collected weekly, however Cortrosyn stimulation assessment was only done at day 29. Mean plasma cortisol levels in this trial did not differ significantly from placebo. Based on C<sub>max</sub> levels, mometasone exposure in the three lower dose groups seems lower than in patients receiving 400mcg bid using the 200mcg formulation. If this trial is to be used to help support the safety of mometasone dpi, the sponsor should be asked to present how exposures to mometasone dpi in this trial compare to the to-be-approved doses using the 200 and 400mcg formulations.

Overall, the plasma cortisol data from trial C97-049, as well as the outlier data on Cortrosyn stimulation testing, suggests an effect of this drug on the HPA axis. These data will ultimately need to be described adequately in the package insert

Data Quality:

Three study sites were audited by the Division of Scientific Investigations (DSI) for this NDA. All three were found to have acceptable data to support the NDA. However, DSI has also indicated to the Division verbally (their report is not complete yet) that they have significant concerns regarding the reliability of data from Dr. Grossman's site, based on a "for cause" audit of other NDAs. As such, they are recommending that Dr. Grossman's data not be relied upon for approval purposes. Therefore, the action letter should request that the two trials that Dr. Grossman participated in be re-analyzed excluding data from Dr. Grossman's center.

Labeling and Nomenclature:

Labeling review has been deferred at this time. A complete review of the package insert will be conducted when the sponsor responds to their action letter.

In previous communications to the Division, the sponsor has proposed the name Asmanex for this drug. This name has been found acceptable by the review team. The draft package insert included in the NDA does not include a proposed name. Following resubmission of the sponsor's response to the action letter, the name Asmanex, or any other proposed name, will need to be evaluated by the Center's nomenclature committee.

Overall Conclusions:

The database in this NDA adequately supports the efficacy of the 200mcg twice daily and 400mcg once daily doses for the treatment of asthma. In addition, the efficacy of the 400mcg twice-daily dose for patients on oral corticosteroids has also been demonstrated. As noted above, this data was generated primarily using the 100 and 200mcg per breath formulations. As such, the sponsor should be requested to conduct a pk/pd study linking the 200mcg and 400mcg formulations at the same nominal dose. Such a trial should also include dose response information to adequately ascertain the sensitivity of the trial. Regarding safety, the database does include adequate long term data as well as overall safety information to support the safety of mometasone dpi at the above listed doses. The sponsor should be asked to further analyze a number the HPA assessments included in the NDA. Based on this, an approvable action letter for this NDA can be sent to the sponsor, from the clinical standpoint, with additional comments and questions to be forwarded to the sponsor as per the medical officer review.

Appears This Way  
On Original

DUNN



U.S. GOVERNMENT MEMORANDUM

DATE: August 30, 1999

TO: Keary L. Dunn, P.M.  
Daniel J. O'Hearn, M.D.

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

*H. W. Ju, M.D. 8/31/99*

SUBJECT: Status of the Inspections of Dr. Grossman

Per our recent conversation, I would like to clarify the results of our investigations of the studies conducted by Dr. Grossman. Please note that there are two separate inspections of Dr. Grossman: one is for his conduct of the study for NDA 21-067, Mometasone (a PDUFA drug), and the other is a For Cause Inspection (FCI) of Dr. Grossman's conduct of studies involving several other drugs.

The results of our inspection of Dr. Grossman's conduct of the studies in support of NDA 21-067, Mometasone are satisfactory, and the data are usable.

However, the results of the FCI raise many questions. Because of these many questions, our inspector is still trying to complete his EIR. Based on the findings described in the Form 483 for this FCI, I believe that the data for these studies are *not* usable. Without the formal EIR, I cannot make a definite conclusion regarding the validity of these studies.

As a result of the latter findings, I would recommend that your statistician not include Dr. Grossman's data for NDA 21-067, Mometasone, in the analysis of the database submitted in support of approval of this drug. In summary, Dr. Grossman's conduct of the latter studies is so questionable as to make his conduct of the Mometasone study suspect.

I am enclosing the results of the Form 483s for the above two inspections. Please bear in mind that my conclusions remain unofficial until I receive and am able to evaluate the completed EIR.

Thanks,

H. W. Ju, M.D.

MEMORANDUM

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

DATE: August 13, 1999

FROM: H. W. JU, M.D.

TO: PROJECT MANAGER: K.Dunn  
MEDICAL OFFICER: D.O'Hearn

SUBJECT: Final Evaluation of Clinical Investigation Inspections

NDA: 21-067  
Sponsor: Schering Corporation  
Drug Product: Mometasone Furoate Inhalation Powder

NAME	CITY	ST	ASSIGN	RECD DATE	ACTN	CLASS	REVIEWER
CRAIG	HERSHEY	PA	05-MAR-99	04-MAY-99	13-MAY-99	NAI	HWJ
GROSSMAN	TUCSON	AZ	05-MAR-99	19-JUL-99	PEND	HWJ ***	
MILLER	N. DARTMOUTH	MA	05-MAR-99	11-MAY-99	19-MAY-99	NAI	HWJ

Statement/Evaluation of the studies and of the acceptability of the data:

Key to Classifications:

NAI = No deviation from regulations - data acceptable

VAI = Minor deviations from regulations - data acceptable

OAI = Significant deviations from regulations - Data unreliable

Data generated by Dr. Craig and Dr. Miller are acceptable to support the approval of the drug.  
Dr. Grossman's EIR is incomplete to form any conclusion at this time.

cc:

HFD-344/Currier

HFD-344/Barton

HFD-344/Huff

*H. W. Ju, M.D.*  
*Aug 13, 1999*

5 Page(s) Withheld



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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

Toyer

NDA 21-067

DATE: February 26, 1999

TO: Director, Division of Scientific Investigations, HFD-340

FROM: John K. Jenkins, M.D. *On Denise Toyer for*  
Director, Division of Pulmonary Drug Products, HFD-570

SUBJECT: Request for Study-Oriented Audits for NDA 21-067,  
mometasone furoate dry powder inhaler

We have identified the following studies as being pivotal to the approval of this application. We recommend that the following sites be audited.

1. STUDY C96-137 Site 04  
Timothy Craig, D.O.  
The Milton S. Hershey Medical Center  
500 University Drive  
P.O. Box 850  
Hershey, Pennsylvania 17033  
Eleven Subjects Enrolled
2. STUDY C96-196 Site 09  
Jay Grossman, M.D.  
Allergy Care Consultants, Ltd.  
3395 North Campbell Avenue  
Tucson, Arizona 85719  
Thirty-two Subjects Enrolled
3. STUDY C96-186 Site 05  
S. David Miller, M.D.  
New England Research Center, Inc.  
49 State Road  
Watuppa Building, North  
Dartmouth, Massachusetts 02747  
Sixteen Subjects Enrolled

The reviewing medical officer for this application is Dr. Daniel O'Hearn, phone 827-1093. The responsible project manager is Dr. Denise Toyer, phone 827-5584.

The ten-month user fee goal date is October 1, 1999. The Division's action goal date is September 15, 1999.

Subject Number	NDA Location	Treatment Visit	FEV <sub>1</sub> from NDA	FEV <sub>1</sub> from DSI
093	Vol. 126, p.2339	Baseline	3.46	
		Week 4 (Day 29)	3.26	
		Week 8 (Day 57)	3.21	
095	Vol. 126, p.2340	Baseline	2.43	
		Week 4 (Day 29)	2.69	
		Week 8 (Day 58)	2.94	
145	Vol. 126, p.2340	Baseline	2.71	
		Week 4 (Day 29)	2.63	
		Week 8 (Day 57)	2.58	
150	Vol. 126, p.2340	Baseline	1.19	
		Week 4 (Day 29)	1.07	
		Week 8 (Day 57)	1.13	
092	Vol. 126, p.2320	Baseline	2.55	
		Week 4 (Day 29)	3.43	
		Week 8 (Day 57)	3.35	
096	Vol. 126, p.2321	Baseline	1.41	
		Week 4 (Day 29)	1.39	
		Week 8 (Day 57)	1.53	
149	Vol. 126, p.2321	Baseline	1.99	
		Week 4 (Day 29)	2.82	
		Week 8 (Day 56)	2.67	
091	Vol. 126, p.2299	Baseline	2.34	
		Week 4 (Day 29)	2.94	
		Week 8 (Day 57)	2.91	
094	Vol. 126, p.2300	Baseline	1.88	
		Week 4 (Day 29)	1.94	
		Week 8 (Day 57)	2.25	
147	Vol. 126, p.2300	Baseline	1.35	
		Week 4 (Day 29)	1.32	
		Week 8 (Day 57)	1.40	
148	Vol. 126, p.2301	Baseline	1.79	
		Week 4 (Day 29)	1.85	
		Week 8 (Day 55)	1.89	

Study C96-137 – Site 04 (Timothy Craig, D.O., The Milton S. Hershey Medical Center, 500 University Drive, P.O. Box 850, Hershey, PA 17033)

Subject Number	NDA Location	Treatment Visit	FEV <sub>1</sub> from NDA	FEV <sub>1</sub> from DSI
042	Vol. 173, p. 2008	Visit 3 - Baseline	1.98	
		Visit 6 - Day 28	1.81	
		Visit 9 - Day 104	1.86	
057	Vol. 173, p.1918	Visit 3 - Baseline	3.46	
		Visit 6 - Day 33	3.11	
		Visit 9 - Day 100	2.38	
338	Vol. 173, p.1919	Visit 3 - Baseline	3.60	
		Visit 6 - Day 30	3.60	
		Visit 9 - Day 100	2.17	
044	Vol. 173, p. 1938	Visit 3 - Baseline	2.11	
		Visit 6 - Day 29	1.76	
		Visit 9 - Day 102	1.86	
058	Vol. 173, p. 1939	Visit 3 - Baseline	1.65	
		Visit 6 - Day 29	1.62	
		Visit 9 - Day 99	1.69	
323	Vol. 173, p. 2010	Visit 3 - Baseline	3.10	
		Visit 6 - Day 29	2.33	
		Visit 9 - Day 96	2.48	
056	Vol. 173, p. 1962	Visit 3 - Baseline	2.93	
		Visit 6 - Day 29	3.43	
		Visit 9 - Day 100	2.92	
324	Vol. 173, p. 1962	Visit 3 - Baseline	2.11	
		Visit 6 - Day 30	2.09	
		Visit 9 - Day 104	2.18	
045	Vol. 173, p. 1981	Visit 3 - Baseline	3.06	
		Visit 6 - Day 29	3.13	
		Visit 9 - Day 103	3.41	
059	Vol. 173, p. 1983	Visit 3 - Baseline	2.58	
		Visit 6 - Day 36	2.66	
		Visit 9 - Day 99	2.74	
336	Vol. 173, p. 1983	Visit 3 - Baseline	2.87	
		Visit 6 - Day 29	2.88	
		Visit 9 - Day 102	2.87	

**Study C96-196 - Site 09 (Jay Grossman, M.D., Allergy Care Consultants, Ltd., 3395 North Campbell Avenue, Tucson, AZ 85719)**

Subject Number	NDA Location	Treatment Visit	FEV <sub>1</sub> from NDA	FEV <sub>1</sub> from DSI
188	Vol. 156, p. 1941	Baseline	2.65	
		Week 4 – Day 29	2.74	
		Week 12	2.39	
196	Vol. 156, p. 1941	Baseline	3.33	
		Week 4 – Day 29	3.20	
		Week 12	3.42	
200	Vol. 156, p. 1942	Baseline	2.57	
		Week 4 – Day 29	3.37	
		Week 12	2.91	
187	Vol. 156, p. 1920	Baseline	2.79	
		Week 4 – Day 29	3.17	
		Week 12	3.46	
194	Vol. 156, p. 1921	Baseline	2.75	
		Week 4 – Day 29	4.83	
		Week 12	5.00	
198	Vol. 156, p. 1921	Baseline	2.55	
		Week 4 – Day 29	2.67	
		Week 12	2.89	
186	Vol. 156, p. 1901	Baseline	2.11	
		Week 4 – Day 29	2.29	
		Week 12	2.22	
195	Vol. 156, p. 1901	Baseline	3.18	
		Week 4 – Day 29	4.03	
		Week 12	3.72	
197	Vol. 156, p. 1902	Baseline	2.12	
		Week 4 – Day 29	2.41	
		Week 12	2.41	
185	Vol. 156, p. 1880	Baseline	2.32	
		Week 4 – Day 29	2.81	
		Week 12	2.90	
199	Vol. 156, p. 1881	Baseline	2.75	
		Week 4 – Day 29	2.99	
		Week 12	3.53	

Study C96-186 – Site 05 (S. David Miller, M.D., New England Research Center, Inc., 49 State Road, Watuppa Building, No. Dartmouth, MA 02747)

NDA 21-067  
Page 5

cc:

Orig.NDA 21-067

HFD-570/Division File

HFD-570/O'Hearn

HFD-570/Toyer

HFD-570/Schumaker

HFD-344/Ju



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

S. David Miller, M.D.  
New England Research Center, Inc.  
49 State Road, Watuppa Bldg.  
No. Dartmouth, Massachusetts, 02747

MAY 19 1999

Dear Dr. Miller:

Between April 13-20, 1999, Ms. Paraluman Leonin, from the Food and Drug Administration (FDA), inspected your conduct of a clinical study (Protocol No. C96-186-05) of the investigational drug mometasone furoate. You conducted this study for Schering Plough Research Institute. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

From our evaluation of the inspection report and of the documents submitted with that report, we conclude that you adhered to the Federal regulations and/or good clinical investigational practices that govern the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Ms. Leonin during the inspection.

Sincerely yours,

Bette L. Barton, Ph.D., M.D.  
Chief  
Good Clinical Practice Branch I, Room 125  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place  
Rockville, Maryland 20855

Page 2 – Jeffrey Herbst, M.D.

CFN:

Field classification: NAI

Headquarters classification:

- 1) NAI
- 2) VAI-no response required
- 3) VAI-response requested

cc:

HFA-224  
HFD-344 Doc. Rm. NDA 21-067  
HFD-570 Review Div. Dir.  
HFD-570/O'Hearn  
HFD-570/Toyer  
HFD-340/R/F  
HFD-344/Chron File  
HFD-344/CIB File #9676  
HFD-344/Ju  
HFR-NWE252/Kraychuk  
HFR-NWE250/Kelley  
HFR-NWE250/Leonin

r/d: rab:5.13.99  
Review Date:GDT/BLB: 5/17/99  
Final Date:SLK: 5/18/99

Note to Review Division Medical Officer

This site was chosen for inspection because it contained the largest number of subjects.

16 subjects were randomized into the study, and 15 of these subjects completed the study. FDA reviewed case report forms and consent forms for all 16 subjects. The inspector noted that data regarding pulmonary function testing were verified by comparison with the raw data.

Data appear acceptable to support drug claims.



DEPARTMENT OF HEALTH & HUMAN SERVICES

N-21067/ Toyer

Food and Drug Administration  
Rockville MD 20857

Timothy J. Craig, D.O., Associate Professor  
The Milton S. Hershey Medical Center/  
Penn State University College of Medicine  
Department of Medicine, P.O. Box 850  
H041, 500 University Drive  
Hershey, PA 17033-0850

MAY 13 1999

Dear Dr. Craig:

Between April 13-15, 1999, Mr. Joseph L. Despina and Ms. Kimberly A. Dux, from the Food and Drug Administration (FDA), inspected your conduct of a clinical study (Protocol No. C96-137-04) of the investigational drug mometasone furoate dry powder. You conducted this study for Schering-Plough Research Institute. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to the Federal regulations and/or good clinical investigational practices that govern the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Mr. Despina and Ms. Dux during the inspection.

Sincerely yours,

Bette L. Barton, Ph.D., M.D.  
Chief  
Good Clinical Practice Branch I, Room 125  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place  
Rockville, Maryland 20855

Page 2 - Timothy Craig, D.O.

CFN:

Field classification: NAI

Headquarters classification:

- 1) NAI
- 2) VAI-no response required
- 3) VAI-response requested

cc:

HFA-224  
HFD-344 Doc. Rm. NDA 21-067  
HFD-570 Review Div. Dir.  
HFD-570/O'Hearn  
HFD-570/Toyer  
HFD-340/R/F  
HFD-344/Chron File  
HFD-344/CIB File #9770  
HFD-344/Ju  
HFR-CE150/Eagan  
HFR-CE150/Rashti  
HFR-CE1505/Despins  
HFR-CE1510/Dux

r/d: rab:5.4.99

Review Date:BLB

Final Date:SLK :AMF5/10/99

Note to Review Division Medical Officer

This site was chosen for inspection because it contained the largest number of subjects.

Data listing tables (FEV and NDA) were compared with original data. No discrepancies were noted.

11 subjects were randomized into the study with the same 11 subjects completing the study. Source documentation of four subjects was compared with information in the CRFs. Informed consent was obtained for all subjects. All adverse events were reported to the sponsor.

Data appears acceptable to support drug claims.

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297  
Expiration Date: November 30, 1996.

# USER FEE COVER SHEET

The reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and reviewing the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Reports Clearance Officer, PHS  
Hubert H. Humphrey Building, Room 721-B  
200 Independence Avenue, S.W.  
Washington, DC 20201  
Attn: PRA

and to:

Office of Management and Budget  
Paperwork Reduction Project (0910-0297)  
Washington, DC 20503

Please DO NOT RETURN this form to either of these addresses.

### See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Schering Corporation  
2000 Galloping Hill Road  
Kenilworth, NJ 07033

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Schering Corporation  
2000 Galloping Hill Road  
Kenilworth, NJ 07033

Attn: Joseph F. Lamendola, Ph.D.

3. TELEPHONE NUMBER (Include Area Code)  
(908) 740-2628

4. PRODUCT NAME  
TRADEMARK J(Mometasone Furoate Inhalation Powder)

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA?  YES  NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER

7. LICENSE NUMBER/NDA NUMBER

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

- A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92  THE APPLICATION IS SUBMITTED UNDER 505(b)(2) (See reverse before checking box.)  
 AN INSULIN PRODUCT SUBMITTED UNDER 506

FOR BIOLOGICAL PRODUCTS ONLY

- WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION  A CRUDE ALLERGENIC EXTRACT PRODUCT  
 BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92  AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION?  YES  NO  
(See reverse if answered YES)

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?  YES  NO  
(See reverse if answered YES)

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE

DATE

for Dr. Lamendola

Vice President  
U.S. Regulatory Affairs

1/28/99



### Memorandum of Facsimile Correspondence

Date: July 1, 1999  
To: Michael Belman, Regulatory Affairs  
FAX: 908-740-2243  
From: Denise Toyer/Keary Dunn, DPDP  
Subject: *Requests for Information for NDA 21-067*

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

**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 the FDA, 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857

Thank you.

NDA 21-067  
Mometasone furoate Dry Powder Inhaler  
Schering Pharmaceuticals

The following comments are being provided to you to help facilitate the clinical pharmacology and biopharmaceutics review of NDA 21-067.

1. The validation report(s) of the assay method(s) used for plasma and urinary cortisol levels was/were not provided in Item six. We recommended that you submit the validation report(s) for our review.
2. The following information should be submitted for our review.
  - a. Protein binding.
  - b. In vivo metabolic pathway(s) of mometasone and the possible metabolites, if available.
  - c. Data to support statement in the PI "In vitro studies have confirmed the primary role of CYP3A4 in the metabolism of this compound.
  - d. In vitro tests for pharmacologic activities of metabolites(s).

Appears This Way  
On Original

Dunn

**Memorandum of Telephone Facsimile Correspondence**

Date: June 30, 1999

To: Mr. Michael Belman  
Regulatory Affairs, Schering Pharmaceuticals  
908-740-2982

From: Dr. Denise P. Toyer  
Project Manager

Subject: NDA 21-067 Questions

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

**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 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

*Denise P. Toyer*

---

Denise P. Toyer  
Project Manager  
Division of Pulmonary Drug Products

EKGs were performed at Screening and at Week 52 for C96-135 in NDA 21-067.

For Subject 174 (MF DPI 400 BID) it is stated for Day 365 "Inferior QT lower in inferior leads" It also says probable old infarction and possible old anterior infarction. Could the sponsor please clarify what is old or changed in this subject's EKG. This listing is on p. 7189, Vol. 22 (4-MONTH SUPPLEMENT.)

For Subject 53 (MF DPI 800 QD) it is not clear what the change at Day 365 was. This listing is on p. 7195. Could the sponsor please clarify.

CC:

HFD-570/Division File  
HFD-570/Dunn  
HFD-570/Original NDA

*Toyer*

**Memorandum of Telephone Facsimile Correspondence**

Date: June 7, 1999  
To: Mr. Michael Belman  
Regulatory Affairs, Schering Corporation  
From: Dr. Denise P. Toyer  
Project Manager  
Subject: Questions for NDA 21-067, Mometasone Furoate DPI

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

**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 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

*Denise P. Toyer*

---

Denise P. Toyer  
Project Manager  
Division of Pulmonary Drug Products

NDA 21-067

Mometasone Furoate Dry Powder Inhaler

Page 2

1. Please provide clarification on the following issues.

**C96-196 in NDA 21-067**

- a For Subject 254, the WBC is listed as 1.98 at Visit 9C on p. 881 in Vol. 1-170 and 5.47 on p. 3497 in Vol. 1-178.
- b For Subject 259, Alkaline Phosphatase is listed as 117 on V9C on p. 932 in Vol. 1-170 but is listed as 82 on p. 3560.
- c For Subject 82, ALT is listed as 106 for V9C on p.818 in Vol. 1-170 but a value of 29 is listed for this individual for V9C on p. 3411.

**C96-186 in NDA 21-067**

- d For Subject 181 from Site 06, Glucose is listed as 152 at Endpoint. In Vol. 1-153, p.716, the glucose at Visit 8F is listed as 152 but in Vol. 1-160, p. 3243, the value is listed as 89 for Visit 8F.
2. Please clarify if the "N" values in section 14.3.6 for the tabulated data on mean values for blood pressure, heart and respiratory rate are correct. These values appear low (e.g., in comparison to the "N" values listed on page 1158).

NDA 21067  
HFD-570 DIV FILE  
HFD-58 TOYER

**Memorandum of Telephone Facsimile Correspondence**

Date: May 4, 1999  
To: Mr. Ravi Chivukula  
Manager, WRA CMC  
From: Dr. Denise P. Toyer  
Project Manager  
Subject: Information request for NDA 21-067

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

**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 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

*Denise P. Toyer*

---

Denise P. Toyer  
Project Manager  
Division of Pulmonary Drug Products

8 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 21-067

MAY - 4 1999

Schering Corporation  
2000 Galloping Hill Road  
Kenilworth, New Jersey 07033

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

Dear Dr. Lamendola:

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

We also refer to your submissions dated January 28, and February 5, 9, and 26, and March 9, 1999.

We have completed our review of the chemistry, manufacturing, and controls section of your submission and have the following comments and information requests.

The following comments pertain to the drug substance.

1. Provide confirmation that [ ]
2. Provide the specifications, storage conditions, and associated retest period for the anhydrous mometasone furoate reference standard.
3. The acceptance criteria for recurring unidentified related compounds [ ] should be tightened to less than [ ]
4. There should be a quantitative and validated test and appropriate specifications for [ ] the drug substance at release and for retest or recertification [ ]
5. 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.

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

6. 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.
7. The stability data presented for the [ ] drug substance indicated that the [ ] for most batches was about [ ] with a range from [ ]  
Based on these data the acceptance limit should be tightened.
8. Tighten the acceptance criteria range for the [ ] determined in [ ] to reflect the data.
9. The detected individual impurities are less than [ ] in batches prepared with the [ ] process for commercial production, therefore the specification for total related substances in the drug substance should be tightened to reflect these data (e.g., not more than [ ])
10. Container labels for the drug substance should clearly state that the compound should be protected from light.

The following comments pertain to the drug product.

11. The following comments pertain to lactose.
  - a. Provide confirmation that the only source of lactose anhydrous NF will be [ ]
  - b. The anhydrous lactose used at both drug product manufacturing sites should be obtained from the same supplier and should be the same grade.
  - c. 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.
  - d. 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.

- e. 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.
- f. Specify a test with acceptance criteria for the [ ] to assure the proper [ ]
- g. The following comments pertain to the assay and impurities determinations and method [ ] for the anhydrous lactose.
- (1) 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.
  - (2) Provide an explanation for the apparent increase in variability of the assay results when comparing the data for the [ ] versus the [ ]. Include revisions in the method if warranted.
  - (3) Depending on the responses to the above two requests, the assay acceptance limit currently proposed of [ ] may need to be tightened.
- h. For greater assurance of the reproducibility of the physical characteristics of the [ ] a lower limit for the [ ] should be proposed that is reflective of the data for [ ] used in the clinical and primary stability batches of drug product [ ]
- i. In order to complete the evaluation of [ ] method used for [ ] provide a correlation with the actual [ ]  
Revise the specifications to indicate the correlated [ ]
- j. For the method used for determination of [ ] indicate what [ ] testing or calibration is performed to assure accuracy of the [ ]
- k. Tighten the acceptance criteria for [ ] lactose to reflect the data provided (volume 2.3, 4B23.4, p. 12). For example.
- At least [ ]
  - Median [ ]

- l. Identify the sites of [ ] the equipment, and the detailed [ ] parameters [ ] for the [ ] 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.
- m. 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.

12. The following comments pertain to the drug product manufacturing.
  - a. Include an assay of the [ ] [ ] the in-process tests performed during the manufacture of the drug product. Propose associated acceptance criteria.
  - b. For release sampling, we recommend that [ ] [ ] be monitored for inhalers from the beginning, middle, and end of a batch.
  - c. For the primary stability batches of drug product stored [ ] at 25°C/60%RH and those drug product batches stored [ ] at 25°C, [ ] RH, 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 [ ] [ ]

13. The following comments pertain to the specifications and test methods for the drug product.
  - a. The description test [ ] [ ] acceptance limits allow the color of the formulation agglomerates to range from white to off-white, therefore, include a quantitative test for color with appropriate acceptance criteria for release and stability testing.

- b. Additional comments on the [ ] specification for the drug product may be forthcoming depending on the results of the investigation of the trends and substantial differences between batches [ ] at 25°C/ [ ] as outlined below in comment 16.i. [ ]
- c. We recommend that the [ ] for degradant assay method [ ] contain [ ] in addition to [ ] and mometasone furoate.
- d. Provide an explanation for the observation that the precision of replicate injections of the Mometasone Furoate Limit of Quantitation Solution [ ] 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 system suitability RSD limits for replicate injections of this solution for the methods.
- 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.
- f. Revise the method [ ] for examination of the powder agglomerates to include photomicrographs of both acceptable and unacceptable agglomerates (e.g., as in the validation report in volume 2.7, 4B8.3, pp. 490, 493, 496, and 499).
- g. Revise the method [ ] for microscopic examination of the dispersed agglomerates to include representative photomicrographs of the dispersed agglomerates, as well as the [ ] lactose and the [ ] anhydrous 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 *dispersed* agglomerates that are being examined.
- h. The [ ] data collected from the first 20 inhalations (method [ ] 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 [ ]

- i. Revise the specification and test [ ] in the drug product formulation ( [ ] to include examination with acceptance limits [ ]
- j. Revise all acceptance criteria for the emitted and metered dose content uniformity for the drug product to clarify that the  $\pm 15\%$  range for the mean applies to both stages of testing (i.e., the mean of the first stage can not be outside of this range).
- k. Include detailed drawings and descriptions of all custom or non-commercial equipment in the methods [ ] to allow Agency laboratories to perform and assess these.
- l. Provide data for multiple inhalers that address the repeatability and reproducibility of the entire method ( [ ]

]

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

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

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

- o. The shelf-life specifications for both strengths of the product for the average emitted unit dose should be controlled *separately* for the beginning and the end inhalations to  $\pm 15\%$  of the label claimed delivery.
14. The following comments pertain to stability and release data collected for the drug product.
  - a. Account for the [ ] for the primary stability batches of drug product prepared in Singapore as compared to drug product batches prepared in Kenilworth.
  - b. From the release data provided for clinical and primary stability batches it was noted that the [ ] for batches prepared in Singapore was [ ] from drug product prepared at the Kenilworth site. This difference should be accounted for and rectified.
  - 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 [ ] in dosing after the first quarter on stability at 25°C/60%RH whereas Singapore product [ ] in dosing for this period. Additionally, the metered doses for the Kenilworth batches are [ ] 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.
  - d. Based on the release and stability data presented for the Kenilworth and Singapore product, it is noted that there are distinct differences between the 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 and measures should be taken to determine the cause and the appropriate corrective actions should be taken.

- 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.

- 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 [ ] will be representative of drug product that would have resulted from [ ] using the total agglomerate batch.

15. 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 the [ ] 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.

- b. As the acceptance specifications for [ ] list only [ ] it is not clear what supplier [ ] 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 [ ] 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 ( ) need to be supported by relevant performance and stability data.

- 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 15.b.).
- d. Drug master files ( ) were reviewed and found to be inadequate to support your application and the holders have been notified of the deficiencies.
- 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.
- f. There appears to be a difference in the material/number ( ) for the ( ) 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.
- g. There should be a test of the flow resistance of the assembled device. Acceptance criteria should be included in the appropriate specification sheets.
- 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.
- i. Provide a ( ) test for the ( )
- j. Provide the acceptance specifications for both the ( ) ( )
- k. As requested at the September 14, 1998, pre-NDA meeting, long-term and, specifically, accelerated stability data should be provided for drug product packaged in ( ) as well as ( ) so that the comparability can be assessed. Additionally, provide data to demonstrate comparable physicochemical properties, thickness, functionality, etc. Also indicate what types ( ) were used for the clinical and primary stability batches of drug product in the application.
- l. Based on the package description ( ) (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 the [ ] 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 15.j. and 15.k. above.

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

n. 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).

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

[ ]

NMT [ ]  
NMT

NMT  
NMT

NMT  
NMT

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

a. The [ ] in the average emitted dose observed after activation from non-upright positions, particularly at 90° from vertical, for later inhalations from both strengths, are not considered to be insignificant [ ] 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 24.b.

- b. Provide the results of the [ ] testing performed as per the protocol listed in volume 2.5, 4B7.3, p. 46.
- 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).
- 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).
- e. Provide the duration of the flow or the total volume collected for each flow rate for the studies of the effect of the flow rate on the emitted dose [ ] (volume 2.5, 4B7.3, pp. 54-57).
- 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.
- g. Provide the emitted dose [ ] data for New Jersey and [ ] and [ ] took place so that these data can be compared to the data provided (volume 2.5, 4B7.3, pp. 58-59).
- 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).
- 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.
  - (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 lower initial amounts [ ] than the remaining batches, do not display the [ ] seen for the remaining batches in the first month of storage. The difference in the amount [ ] seen initially and the difference in rate [ ] seen over time should be investigated, explained and corrected.
  - (2) For the [ ] two of the 400 mcg strength product batches [ ] former of these [ ] Likewise,

Losses of this magnitude are not acceptable and corrective action will need to be undertaken.

- j. Comments on the [ ] will be withheld pending the appropriate modifications to the specifications and the results of the above mentioned investigation.
- 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 [ ] and [ ] data available for these batches stored within their unopened [ ] under conditions of 25°C, [ ] H.

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

- a. Comments on the proposed 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.
- 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 [ ]
- c. The placement of only one batch out of [ ] batches of drug product on stability from each production site is not acceptable and the number of stability batches should be increased substantially for such a large number of production batches.
- 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).
- e. As per comment 14.e., modify the protocol to indicate that the [ ] [ ] testing [ ] should be performed through unit life (i.e., over the labeled number of inhalations).

- 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.
  - (2) Batch size.
  - (3) Source of container and closure
  - (4) Specifications, (i.e., test parameters, method numbers and acceptance criteria).
  - (5) Storage orientation.
  - (6) Statistical analysis approach and designation of parameters examined.
  - (7) Format of the stability data to be reported.
  - (8) Proposed expiration dating period.

The following preliminary comments refer to the labels and labeling provided in volume 2.1, section 2. We may provide additional comments when the proposed to-be-marketed (i.e., full mock-ups) labels are submitted.

18. The trademark and the established name of the product should always include the metered dose for both strengths for all labels and labeling.
19. The device should bear a place for recording the date that the was opened and a corresponding statement instructing the patient to discard the product "X many days from the date of opening". The PATIENT INSTRUCTIONS FOR USE should be revised accordingly.
20. 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.
21. 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.
22. 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.
  - b. The lactose used in the formulation should be described as anhydrous.

- 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).
23. The HOW SUPPLIED section of the labeling should be revised as follows.
  - a. The fill weight of the various presentations should be included.
  - 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").
  - c. The [ ] 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/75%RH.
24. 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.
  - 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)]."
  - c. The warning "Do not breath out through the inhaler" should be strengthened and written in bold in the patient instructions.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the 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 are subject to change as the review of your application is finalized. In

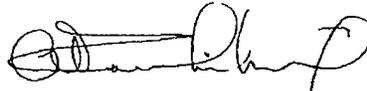
NDA 21-067

Page 15

addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Dr. Denise Toyer, Project Manager, at (301) 827-5584.

Sincerely,



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

NDA 21-067

Page 16

cc:

Archival NDA 21-067

HFD-570/Division. Files

HFD-570/Bertha/4-28-99 *CB 5/4/99*

HFD-570/O'Hearn

HFD-570/Chen

HFD-570/Gebert

HFD-570/Chun

HFD-570/Toyer *5-3-99 DP. Toyer*

HFD-820/DNDC Division Director (only for CMC related issues)

DISTRICT OFFICE

Drafted by: Toyer/April 14, 1999

Initialed by: Schumaker/4-26-99

Poochikian/4-29-99

final: Toyer/4-30-99

filename: c:/mydocuments/ongoing/n21067.99-04-30

INFORMATION REQUEST (IR)

MESSAGE CONFIRMATION

10/21/98 10:22  
ID=PULMONARY DIV FDA

BOX	GROUP

TIME	DISTANT STATION	PAGES	RESULT	EPROP PAGES	S. CODE
08:18	08:17 91908740000	011/011	OK		0000

Memorandum of Telephone Facsimile Correspondence

Date: 10/21/98

To: Mr. Michael Belman  
Schering-Plough Pharmaceuticals

From: Dr. Denise P. Toyer  
Project Manager

Subject: Minutes for Meeting

Reference is made to the September 14, 1998, meeting held between representatives of your company and members of this division. 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 301-827-5584.

**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 5600 Fishers Lane, HFD-570, DDPD, Rockville, MD 20857.

Thank you.

*Denise P. Toyer*  
 \_\_\_\_\_  
 Denise P. Toyer

**Minutes of Industry Meeting**

**Date:** September 14, 1998  
**Time:** 3:00 p.m. to 4:00 p.m.  
**Place:** Conference Room "B"  
**IND:** IND 46,216  
**Sponsor:** Schering Plough Pharmaceuticals  
**Drug:** Mometasone Dry Powder Inhaler  
**Meeting Type:** PreNDA  
**IMTS #:** 2974

**FDA Attendees:**

Dr. Craig Bertha	Chemistry Reviewer
Dr. Misoon Chun	Pharmacology and Toxicology Reviewer
Mr. Keary Dunn	Project Manager
Dr. John Jenkins	Division Director
Dr. Robert Meyer	Medical Team Leader (Medical Reviewer)
Dr. Guirag Poochikian	Chemistry Team Leader
Dr. Hilary Sheevers	Pharmacology and Toxicology Team Leader
Dr. Denise Toyer	Project Manager
Dr. Ramana Upoor	Clinical Pharmacology and Biopharmaceutics Team Leader
Dr. Steve Wilson	Biometrics Team Leader

**Schering-Plough Attendees:**

Dr. Melton Affrime	Vice President, Clinical Research, Clinical Pharmacology
Mr. Michael Belman	Manager, Regulatory Affairs
Ms. Tracy Blazovic	Associate Director, Worldwide Regulatory Affairs
Dr. Mitch Cayen	Senior Director, Drug Metabolism and Pharmacokinetics
Dr. Imtiaz Chaudry	Vice President, Pharmaceutical Sciences
Mr. Ravi Chivukula	Manager, Worldwide Regulatory Affairs CMC
Dr. Francis M. Cuss	Vice President, Biological Research, Allergy and Immunology
Dr. Judy Harrison	Director of Clinical Research, Allergy
Dr. Joseph Lamendola	Vice President, Regulatory Affairs
Dr. Eugene McGonigle	Vice President, Pharmaceutical Analytical Chemistry, R&D
Dr. Heribert Staudinger	Vice President, Clinical Research, Allergy, CNS
Ms. Lucy Schneyer	Manager, BioStatistics
Dr. Elmer Mirro	Senior Director, Pathology

### BACKGROUND

Schering Pharmaceuticals plans to submit a new drug application for mometasone furoate dry powder inhaler during the 4<sup>th</sup> quarter of this calendar year. Schering requested this preNDA meeting to discuss this submission. Reference background package dated August 17, 1998.

### INTRODUCTION

The Division discussed the content and timing required to assure that the maximal benefit is derived from preNDA meetings. To provide substantial benefits to both the Division and the applicant the preNDA meeting should be scheduled from six to twelve months prior to the planned submission of the application. When the preNDA meeting is held in close proximity to the submission of the application, the benefits are minimal. If the applicant has substantially completed the preparation of the submission, the Division's recommendations may not have an impact upon the submission. Schering noted that their End-of-Phase 2 meeting was delayed due to the compilation of data and thereby affected the timing of this meeting. They agreed with the Division that the content and timing of future End-of-Phase 2 and preNDA meetings should be consistent with Division guidance documents.

The Division noted that the intent of the preNDA meeting is to discuss formatting and the proposed submission. The review of specific data is not the objective of the preNDA meeting. We noted that the background package for this meeting focused on specific data. The Division will discuss the issues identified in this package by Schering and provide overall formatting comments.

### CLINICAL/STATISTICS

Schering requested the Division's comments on two issues under this section. A brief synopsis of these two issues is described below.

1. Schering believes their clinical program supports the dosing recommendations listed below. They provided a rationale for this assumption.

Previous Therapy	Recommended Dosing
Steroid Naïve	(
Inhaled Steroids	)
Oral Steroids	)

**Division Response:** Although Schering's rationale for the proposed dosing recommendations appears adequate, a definitive answer cannot be given at this time. The Division must review the data provided in the NDA prior to determining the appropriate dosing recommendation, however, it appears that Schering has developed sufficient data to address these proposed recommendations.

- Schering has reviewed the data for C96-196 and eventually plans to submit an efficacy supplement to support labeling for a starting dose of 200 mcg QD PM for both inhaled steroid dependent and steroid naïve patients. They propose performing one additional trial to be submitted in the efficacy supplement. They propose that the data from C96-196 and the proposed trial would be sufficient for approval of this once daily, lower dose regimen. This dosing regimen could then be applied to the steroid naïve patients with mild persistent asthma without further study.

**Division Response:** Without reviewing the existing data and without knowing the outcomes of the proposed study, it is difficult to predict whether or not Schering's assumption is correct. However, we recommend that Schering design a trial that will include both corticosteroid-naïve patients and inhaled corticosteroid dependent patients. This type of study could provide sufficient data to support Schering's proposed reduced lower starting dose.

The following comments refer to the format of the proposed new drug application.

- In addition to the information supplied in the Representative Data Displays, Demography, Table 7, the Division recommends that the ages of the study participants be listed in groups (i.e., 5-11, 12-16, and >50). When a table is split among several pages the headings should be repeated (i.e., number of patients).
- The Division recommends that data presented on page 75, Figure 2, include changes over the course of the disease followed by endpoint representation. While Schering should include explanatory reports concerning

drop-outs from the study and can graphically refer to the diminishing numbers of patients in each data point, the Division feels that there is useful information in reviewing the data over the course of the study, as well as at endpoint.

5. The representation of the cortisol data should include not only the mean response and summary statistics, but should also include, in the same table, the number of patients with abnormal results by any of the cortisol response metrics.

The Division will accept the submission of the long-term safety data (i.e., 200 patients with one year of treatment exposure) with the four-month safety update. We strongly encourage Schering to provide these data as early as possible. However, we remind Schering that due to the FDAMA timing constraints that will be instituted on October 1, 1998, we expect all future new drug application submissions to be complete and contain all of the requisite data upon submission. The Division plans to manage all NDAs received after October 1, 1998, on a ten-month review cycle, however the PDUFA reauthorization provides for ten-month reviews at a target of only 30 percent of NDAs for FY 1999.

6. The Division warns that any submissions received after the filing date may impact upon whether the application receives a ten-month versus a twelve-month review during the transition to the fully implemented ten-month review cycle.

Schering informed the Division that they are willing to work with us to help facilitate a ten-month review cycle for this application. Schering encouraged the Division to notify them of any additional information or data required. The Division indicated that if the application is "user-friendly" this will assist the reviewers in conducting their review.

7. The Division indicated that, having the main study reports including tables, the integrated summary of safety, and the integrated summary of efficacy in MS Word format (i.e., CDROM or diskettes) would be helpful for the reviewers.

**CHEMISTRY, MANUFACTURING AND CONTROLS**

The comments regarding the timing and content of the background package were reiterated as they relate to the CMC section. There were no questions listed in the CMC section of the package therefore the Division can only assume that previous meetings and communications have been successful and that all outstanding issues have been adequately addressed. However, the Division provided the following NDA formatting comments.

8. All future background packages for all types of meetings should be paginated.
9. The NDA should contain a cross-reference table listing all batches and any associated container and closure changes made for these (e.g., biobatch, primary stability, clinical, production, etc.).
10. The table of contents for the entire chemistry section should be included in the front of each CMC jacket.
11. We recommend that the drug product (DP) stability data be submitted in the Excel format.

**Post-meeting addendum:** The following column headings would assist the reviewer: batch, storage conditions, month, wrapped/unwrapped, inverted/upright, if applicable, data, etc.

12. The following comments pertain to the discussions on the August 10, 1998, proposal for a change in the [ ] [ ] Schering should provide the long-term and, in particular, the accelerated stability data with the new [ ] [ ] in the NDA so that comparability with the old [ ] can be determined.
13. The assigned CFN (central file number) assigned to each site should be provided to assist the reviewer with the inspection request.

Although Schering did not list any specific questions in the background package, the following additional comments were provided by the CMC reviewer.

**Drug Substance**

14. Drug substance [ ] below [ ] should be controlled by both an upper and lower limit on the

amount. (Listed in the background package as CMC item  
for discussion: [ ] Profile Below [ ]

### Drug Product

#### 15. Drug Substance [ ] in Formulation

From the photos of the microscopic examination of the DP formulation at 40X, 80X, and 200X, it appears that 40x is an adequate magnification to use for examination of the [ ] agglomerates [ ]

[ ] (Listed in the background package as CMC item for discussion: Item for Discussion: Microscopic Examination of Powder [ ]

However, Schering was reminded, as previously discussed in the last meeting, that in order to examine the changes in the drug substance for the DP formulation with time, we believe a higher magnification may be needed (Schering may also need to look at [ ]).

From the pictures provided this does seem to be the case.

#### 16. Lactose Quantitative Color Test

Our problem with the use of the compendial color determination for the lactose is that the absorbance @ [ ] may be too high based on the data (specifications based on data for lactose used in clinical and stability batches). Schering should provide some data to allow us to associate the color of a solution with absorbance of [ ] with some known color standards [ ]

[ ] (Listed in the background package as CMC item for discussion: Excipient Testing, Lactose Monohydrate NF)

#### 17. Lactose [ ] lactose content.

Schering was asked to provide actual data in the NDA for both the lactose used in the clinical and primary stability batches. The acceptance criteria can then be evaluated [ ]

[ ] The validation data for these methods should also be included.

18. Lactose Microbial Limits

In terms of the microbial limits for the lactose it appears inconsistent that the total aerobic plate count and total yeast and mold count for the incoming Lactose Monohydrate NF were set [

] when the limits for the DP are [

]. Schering should address this in the application.

19. Lactose [ ] Test Parameters

[ ] lactose should be included in the test parameters. Depending on the method [

] lactose may be necessary.

We recommend that you include comparative data for all lactose parameters [

] in the application.

Schering indicated that they will include comparative data for all parameters [

] lactose in the application along with justifications (supported by data) for not doing all of the tests routinely on the [ ] material.

20. [ ] Testing for [ ]

Schering proposed an - approach for examination of [ ] [ ] but it does not appear [

]. We recommended that Schering reconsider the methodology. [

]

## 21. [ ] for DP

The package indicates that the [ ] data in the NDA will be provided in terms of the [ ] drug substance found on [ ]

[ ]. No comments on the selection of groupings are appropriate at this time. However, we can inform you that the specification limits proposed appear quite broad, [ ]

the 200 and 400 µg product, respectively. This potential to receive doses that vary by this much in the [ ] range is worrisome. For the 400 µg strength product: [ ]

[ ] (Listed in the background package as CMC item for discussion: [ ] Preliminary Data and Specifications)

22. Production batch stability protocols should be revised to include testing of the [ ] product for [ ] of proposed expiry period after storage at [ ] for annual batches (as discussed in the 4/27/98 meeting). (Listed in the background package as CMC Item for Discussion: Stability Protocol.)

Schering indicated that they were under the impression that they could test for 6 months at [ ] for annual batches of [ ] product. The Division indicated that testing of [ ] product for 6 months at [ ] would be acceptable for an 18-month expiry, however, for longer proposed expiry periods the Division would need higher humidity conditions for [ ] of the proposed expiry.

23. The section on [ ] should be removed. Any changes that occur should be supported by data from the approved stability protocol in its entirety (long term and accelerated data).

24. Proposed Scheme for Additional Requirements for Stability Testing [ ]

If the [ ] product shows significant change by 6 months at [ ] it must be tested at [ ] for [ ] and dose content uniformity for [ ] of the proposed expiry period.

For the initial determination of the "in-use" period [ ] storage for [ ] product intended to

be [ ] for marketing), one batch (each strength) may not be enough to be representative of the typical batch. We recommend that more than one batch be tested. (Listed in the background package as CMC Item for Discussion: Stability at [ ] Proposal.)

Schering stated that they thought that they were required to only place one [ ] ([ ] [ ]) batch under conditions of [ ] to see when a failure occurs. However, Schering will place more batches under these conditions and asked if the lack of multiple batch data in the NDA would be a filing issue. Schering was informed that this would depend on the data generated as of this date. Schering proposed submitting whatever data they have on this one batch stored [ ] at [ ] so that we can make a decision on whether this is a filability issue or not.

25. Schering clarified that the trade and sample products will have identical fills. The [ ] will be different. (Listed in the background package as CMC Item for Discussion: Trade and Sample Sizes.)
26. The Division requested a mock-up of the device prior to making any comments on the device markings. (Listed in the background package as CMC Item for Discussion: ID of Device.)
27. The NDA will include long term and accelerated data on several batches from the Kenilworth facility using an adequate stability protocol. Based on this information the Division agreed with Schering's proposal to submit at least three months of site specific drug product stability data for the Singapore site at the time of submission. The six- and nine-month data should be provided as soon as it is available.

#### PHARMACOLOGY AND TOXICOLOGY

There are no regulatory issues to discuss for this section and the preclinical development for the reformulation appears to be satisfactory. However, the Division provided the following suggestions which assist with the review of the pharmacology and toxicology section.

28. The summary tables for the reports should be modified or revised to include the "**% changes**" from the baseline or the "**incidence**" should be expressed in **quantal basis** (i.e., 1/5) rather than just indicating that the observations were noted in M or F.

29. The preclinical studies conducted for the bridging information (2-14 days and 1-3 months studies and other) should be summarized in a study synopsis format similar to the clinical studies format rather than a narrative format.
30. The Division would prefer the summary for the pharmacology and toxicology section in the WORD format on a separate floppy disk. If possible, the individual animal line listings should be provided as data sets (SAS transport file, version 5) as described in the draft guidance document.

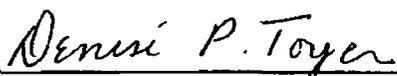
#### CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

31. The data submitted and the conversations with the Division appear to support Schering's proposed limited pharmacokinetic program. The data recently submitted have not been reviewed at this time, however if the process is acceptable then Schering's approach to address this issue appears to be reasonable. The sponsor should submit the detailed data in the NDA and if we agree with their interpretation, then this limited PK program is acceptable. The sponsor should also include their higher dose PK/PD studies in the Human Pharmacokinetics and Bioavailability section of the NDA. They should also summarize information on assay validation, mometasone metabolism and protein binding in the NDA.
32. The Division would prefer the summary reports for the clinical pharmacology and biopharmaceutics section in the WORD format.

#### STATISTICS

33. Please provide the program codes (used to generate results and tables), annotated CRFs (containing the names of the variables) and complete descriptions of derived variables.

In addition, please note, with rationale, any between-study variation in the methodologies use to analyze these data.

  
Denise Toyer, R.Ph., Pharm.D.  
Project Manager

IND 46,216

Page 11

cc:

Orig. IND

HFD-570/Division File

HFD-570/Bertha/10-4-98/10-13-98

HFD-570/Chun/10-9-98

HFD-570/Jenkins

HFD-570/Meyer/9-30-98

HFD-570/Poochikian/10-4-98/10-13-98

HFD-570/Sun

HFD-570/Toyer

HFD-570/Uppoor/9-30-98/10-9-98

HFD-570/Wilson/10-5-98/10-19-98

Initialed by: Schumaker/9-28-98

c:\mydocuments\ongoing\I46216.98-09-14.min

Div File

RECORD OF TELEPHONE CONVERSATION

IND: 46,216 DATE: 10/9/98  
SPONSOR: Schering Pharmaceuticals  
DRUG: mometasone furoate Dry Powder Inhaler  
INITIATED BY: APPLICANT X FDA  
NAMES AND TITLES OF PERSONS WITH WHOM CONVERSATION WAS HELD:  
FDA: Dr. Misoon Chun and Dr. Denise Toyer  
SPONSOR: Mr. Michael Belman

---

**BACKGROUND**

Recommendations on the format and contents of the pharmacology and toxicology section were made by the Division during the September 14, 1998, preNDA meeting. Schering requested clarification on several of the recommendations.

**TELECON**

The suggestions and recommendations made by the Division for the pharmacology and toxicology section were not requirements. The Division does not consider Schering's inability to provide the data in the format requested a filing issue. The Division indicated that if Schering's concern is timing, as it relates to the various data formats requested, we are willing to discuss a post-submission time frame for submission of the data in the recommended format.

Schering will contact the Division in approximately one week to further discuss this issue if further clarification is needed.

Denise P. Toyer  
Denise Toyer  
Project Manager

cc:  
Orig. IND  
HFD-570/Division File  
HFD-570/Chun/10-13-98  
HFD-570/Toyer  
Initialed by: Schumaker/10-13-98

c:\mydocuments\ongoing\I46216.98-10-09

Toyer

**Minutes of Industry Meeting**

**Date:** April 27, 1998  
**Time:** 1:00 p.m. to 2:30 p.m.  
**Place:** Conference Room "A"  
**IND:** IND 46,216  
**Sponsor:** Schering Plough Pharmaceuticals  
**Drug:** Mometasone Dry Powder Inhaler  
**Meeting Type:** Chemistry  
**IMTS #:** 2557

**FDA Attendees:**

Craig Bertha, Ph.D. Chemistry Reviewer  
Robert Meyer, M.D. Medical Team Leader  
Linda Ng, Ph.D. Chemistry Reviewer  
Guirag Poochikian, Ph.D. Chemistry Team Leader  
Denise Toyer, Pharm.D. Project Manager

**Schering-Plough Attendees:**

Dr. Imtiaz Chaudry Vice President, Pharmaceutical Sciences  
Mr. Ravi Chivukula Manager, Technical Support, Worldwide  
Regulatory Affairs  
Dr. Eugene McGonigle Vice President, Pharmaceutical  
Analytical Chemistry, R&D  
Dr. Michael Mitchell Presidential Fellow, Chemical  
Development  
Dr. Nicholas Pelliccione Senior Director, Technical Support,  
Worldwide Regulatory Affairs  
Dr. Van Reif Associate Director, Pharmaceutical  
Analytical Chemistry, R&D  
Ms. Lois Singer Director, Pharmaceutical Package  
Development  
Mr. Bruce Wyka Associate Director, Pharmaceutical  
Analytical Chemistry, R&D  
Dr. Tsong-Toh Yang Senior Principal Scientist,  
Pharmaceutical Dosage Form Development

**BACKGROUND**

A chemistry, manufacturing and controls End-of-Phase 2 meeting was held on February 10, 1997. Schering requested this meeting to follow-up on some issues which were outstanding at the end of the February 10, 1997 meeting. See the background package dated March 23, 1998.

Schering provided an overview of the drug development program since their last meeting with the Division. They indicated that they plan to submit the NDA in either November or December 1998, with data for the 200 and 400 µg doses only. Data for the drug substance will come from Schering's Ireland and Singapore sites. Data for the drug product will come from the Kenilworth and Singapore sites.

Schering noted that they conducted the clinical studies with the [ ] process but now use an [ ] process. The only change in the [ ] process is that the reagents have changed.

**DRUG SUBSTANCE**

1. In terms of the potential [ ] in the drug substance, if your new method shows that [ ] is not present for multiple batches, a routine specification would not be needed (as proposed in the April 16, 1998, facsimile). Include the data in the NDA.

**Response:** Schering stated that they do not know the detection limit of the [ ] determining method as of yet and that is why they have given a conservative estimate of ~ ppm as the limit of [ ]

2. Since mometasone is known to be photosensitive, Schering should include data demonstrating the absence [ ] and [ ] (N20-762, see last page) in the drug substance prepared from the [ ] process as compared to the approved process.

**Response:** Schering stated that the [ ] were unique to the [ ] of the drug substance [ ] and that they did not occur with the [ ] The Division asked that this data be documented in the NDA.

3. As proposed, the current DS [ ] cut-offs will allow any profile under [ ] to be accepted. There should be more cut-offs below [ ] to help define the profile of [ ] in this range since at least [ ] are in this [ ] range (note that medians are typically about [ ]). The Division stated that also providing a specification for the median may be helpful in controlling the profile.

**Response:** Schering will send in a proposal at a later time for us to comment on that would include additional cutoffs to control the drug substance [ ]

4. It was also noted that the [ ] profile for the batches of drug substance prepared by the [ ] process in Ireland was shifted to [ ] (avg. median size for two batches is [ ]) relative to the Union, New Jersey, batches (avg. median of [ ] batches is [ ]). Where was the [ ] done and were there differences in the processes [ ] at the two sites that may account for this shift?

**Response:** Schering confirmed that this was the case and they had also noted this. They stated that [ ] [ ] at the two sites (Avondale, Ireland, and Singapore) were made by different manufacturers and that they would be adjusting the [ ] parameters so that the [ ] profiles of the [ ] drug substance would be as similar as possible for the two sites.

5. Where will the drug substance be manufactured [ ] [ ] Details about the [ ] process should be presented in the NDA.

**Response:** The Division elaborated on this point and asked that detailed Standard Operating Procedures (SOPs) be included in the application that would document the details of [ ] procedure at each site.

6. The Division recommended conducting a test [ ] for [ ] of the drug substance.

**Response:** Schering indicated that the [ ] test would confirm [ ] the drug substance. The Division indicated that the data from this test should be included to demonstrate that the [ ] method will be able to [ ] The Division also inquired as to the sensitivity level of the test [ ]

7. Have studies been done to determine whether [ ] under conditions of higher humidity? If these studies have been conducted, what were the results?

**Response:** Schering indicated that these studies have been conducted. The results indicate that exposure of the

humidity does not result [ ] Schering agreed to provide these data in the development section of the NDA.

8. Are there [ ] of the drug substance?

**Response:** There is no evidence of any [ ] The studies which support this conclusion will be included in the development section of the NDA.

9. The impurities specifications appear to be broad relative to the data. For example, the [ ] process batches have total impurities of up to only [ ] and the limit is set at no more than [ ]. Although levels for product on stability have not been reviewed, the point is that impurities specifications should be reflective of the data.

**Response:** Schering acknowledged comment nine.

10. The Division noted that [ ] emitted dose data. What are the flow rate and volume for the DPI emitted dose data?

**Response:** Schering indicated that the flow rate is 60 ml/min for a duration of [ ].

### Drug Product

The following comments were provided to Schering during the meeting but were not discussed in detail.

11. If possible, the microscopic evaluation of the drug product powder formulation should include a qualitative examination of the drug substance [ ] If changes can successfully be induced and identified at 40X in lieu of 100x, then 40x magnification may be acceptable.
12. How many samples, for each study number, are used to generate the data [ ] The Division expects a complete profile to be submitted instead of [ ].
13. The Division asked Schering to explain what [ ] mean. The Division may recommend [ ] specification, depending on the explanation.

14. The [ ] is not mentioned in the listed [ ] study for the [ ] comparison (i.e., pp 46, 48, and 50).
15. The [ ] listed on page 52 may not be appropriate but will be evaluated when the data are submitted. The Division feels it is premature to concur with these [ ] until we are able to look at the [ ] Preliminary, we feel [ ] would be adequate.

**Drug Product**

16. Since [ ] packaging is used [ ] routine testing on the annual stability batches should include storage and testing for [ ] of the expiry period at [ ]

**Response:** Schering acknowledged the requirement for the annual [ ] (routine postmarket stability) batches. Schering stated that [ ]

[ ] product. They discontinued the studies on the [ ] product after [ ] developed.

The Division indicated that Schering's patient use period study, which is currently conducted at [ ] to determine the length of time the [ ] product, should be done at a minimum of [ ] Schering agreed to take some [ ] product stored at [ ] that is currently on stability (early points presumably), remove the [ ] and store at [ ] to repeat the patient use period study with our required higher humidity.

17. The Division requires specifications for control of key physicochemical characteristics of lactose for use in the formulation of an inhalation drug product in addition to those listed in the National Formulary.

**Response:** Schering is not familiar with these specifications and would like a copy. The Division agreed to provide the additional specifications as soon as possible.

The following comments were provided to Schering during the meeting but were not discussed in detail.

*is this a  
RTF issue**they feel they  
have agreed*

18. In terms of the stability data for the Singapore drug product, the Division indicated that we require [ ] of stability data for drug product batches prepared at the Singapore site at the time of submission. The Division indicated that they may be willing to discuss Schering's proposal of [ ] data at the time of submission and updated data [ ] as soon as it becomes available.
19. The following data from DPI Characterization Studies should be included in the development section of the NDA.
- The data that characterizes the DPI in terms of dose build-up/flow resistance (including the data discussed on the flow generated by healthy patients and patients with varying degrees of obstructed lung function). The Division asked at what point during the inspiration does the dose leave the device. Schering noted that the dose leaves the device within one second and that this occurs probably less than a half second after the start of the inspiration.
  - The data that characterizes the performance of DPI (metered and emitted dose, [ ] under various dosing orientations and handling situations, (e.g., after dropping, shaking, etc.)). Schering should also outline the necessity for particular handling by the patient (e.g., tapping, etc.) that would be necessary to ensure reproducible dose content uniformity [ ]
  - Since multiple strengths are proposed (100, 200, and 400 µg), data characterizing the in vitro dose proportionality (emitted dose, content uniformity, and [ ] between the multiple strengths of the DPI should be included.
  - We recommend that devices used in clinical studies be sent for testing of pertinent performance parameters and physical attributes after use (e.g., emitted dose, [ ] microbial limits). The Division noted that this type of data is particularly important for the 100 µg pediatric product since children are more likely to breath into the device. Breathing into the device may introduce moisture into the formulation reservoir and ultimately change performance [ ]
  - Results of the studies on the effect of moisture equilibration of the DPI at various high and low humidity conditions on pertinent parameters, i.e.,

- f. Since there was some slight photolability of mometasone furoate monohydrate noted in the Nasonex immediate container, photostability should be evaluated. The Division is unsure how much light can pass through the device components or the color of these. Schering indicated that they planned to undertake the normal ICH photostability studies for the product.
  - g. Data on the studies that characterize the optimum and minimum fill weight for the DPI.
  - h. Uniformity of emitted dose intra-device should be submitted.
19. DMF's for composition of the components of the DPI should be submitted. Schering should provide a commitment not to change any source of the raw materials of the components.
20. A statistical analysis which includes the  $C$   
J. would be useful.

*Denise P. Toyer*

Denise P. Toyer, R.Ph., Pharm.D.  
Project Manager

**Post Meeting Note:**

The following information was faxed to Schering on May 7, 1998.

Specifications in addition to those in the National Formulary for control of key physicochemical characteristics of lactose for use in the formulation of an inhalation drug product:

- a. [
- b. ]
- c. ]
- d. Quantitative color and clarity
- e. Assay
- f. Impurities and degradants
- g. Solvents (if applicable)
- h. Water content
- i. Microbial limits (total aerobic count, total mold and yeast, absence of pathogens)
- j. Specific and quantitative protein content
- k. Pyrogens, and/or bacterial endotoxins tests

IND 46,216

Page 8

cc: Original IND 46,216  
HFD-570/Division File  
HFD-570/Poochikian/8-10/98  
HFD-570/Bertha/8-6-98  
HFD-570/Meyer  
HFD-570/Toyer  
HFD-570/Ng/8-10-98

c:\mydocuments\ongoing\I46216.98-04-27

### Meeting Attendees

**Date:** April 3, 1998  
**Location:** Conference Room 10B45  
**Time:** 2:00 to 2:30 p.m.  
**Sponsor:** Schering Pharmaceuticals  
**Meeting Type:** End-of-Phase 2  
**IND(s):** 46,216  
**IMTS:** 2535

#### FDA

Dr. Misoon Chun  
Dr. Bradley Gillespie  
Dr. Robert Meyer  
Dr. Hilary Sheevers  
Ms. Denise Toyer

#### Schering

Ms. Michael Belman  
Dr. Joseph Lamendola  
Dr. Mel Brannan  
Dr. Francis Cuss  
Dr. Elmer Mirro  
Dr. Keith Nolop  
Ms. Lucy Schneyer

#### Background

Schering requested an End-of-Phase 2 meeting to discuss the proposed doses for the impending Phase 3 clinical trials. See the background packages dated January 29, and March 23, 1998. An End-of-Phase 2 CMC meeting was held on February 10, 1997. A follow-up CMC meeting will be held April 27, 1998 to resolve and discuss other CMC issues.

#### Pharmacology and Toxicology

The proposed bridging toxicology program for mometasone furoate lactose containing DPI formulation can be found on pages eight and nine of the Pharmacology/Toxicology section of the January 29, 1998, submission.

**Discussion/Conclusion:** The Division indicated that the sponsor's approach appears to be acceptable. The required studies have been completed or are currently ongoing.

#### Clinical Pharmacology and Biopharmaceutics

A summary of the clinical pharmacology studies that have been conducted can be found on page 5 of Human/PK bioavailability section of the January 29, 1998, submission.

**Discussion/Conclusion:** The Division noted that the sponsor received a biopharmaceutics waiver for Nasonex because an assay of adequate sensitivity was not available. We will require that Schering demonstrate that they cannot quantify plasma mometasone concentrations after use of the DPI before we grant a waiver for demonstrating bioavailability. Once the sponsor has completed their planned single-dose absolute bioavailability study they should contact the Clinical Pharmacology and Biopharmaceutics reviewer for further discussion.

### Clinical

A brief overview of the Phase 2/3 clinical program can be found on pages one and two of the clinical section of the January 29, 1998, submission.

#### **Discussion/Conclusion:**

- A review of the data summaries submitted indicates that the proposed studies should provide adequate data for review in support of the indications the sponsor is requesting.
- The sponsor's decision not to submit [ study with the submission of the NDA is acceptable. ]
- The Division noted that the development program does not contain a topical-effects study. Although this is not required, any specific claims of a topical-effect labeling would have to be supported by such a study.
- The Division asked if Schering planned to include the 800 mcg/day (single dose) in their development program. Schering indicated that this dosing arm was included in the safety studies to offer a broader range of doses for safety evaluation only. Schering's current development program does not include the 800 mcg/day (single dose) dose.
- The Division asked about Schering's pediatric plans for this product. In light of the recent FDAMA implications on pediatric exclusivity Schering would like further clarification on the impact discussions regarding the pediatric program would have upon their request for exclusivity.
- The Division reminded Schering that we consider asthma a similar disease in adults and children. They would be able to extrapolate some adult efficacy data to children. The sponsor would be required to identify appropriate doses in children. Schering noted that their goal is to find an effective dose with minimal systemic effects. The Division reminded Schering that

they could extrapolate local safety based on adults, and pediatric short-term data but we would require long-term systemic safety data in children. Although a growth study is not required at NDA filing it would be desirable to have a growth study.

- Schering asked what would be required to obtain an [ ] for this product. The Division noted that if multiple secondary endpoints, which are captured in the patient diaries, show [ ] which is separated from placebo and is statistically maintained thereafter in the study, then the Division would approve labeling with an onset consistent with these data.

Action Items

1. The Division will further investigate Schering's request for further guidance on pediatric exclusivity under FDAMA.
2. Schering will contact the Clinical Pharmacology and Biopharmaceutics reviewer as soon as the single-dose absolute bioavailability study has been completed.

*Denise P. Toyer*

---

Denise P. Toyer, R.Ph.  
Project Manager

cc:

Original IND 46,216  
HFD-570/Division File  
HFD-570/Gillespie/4-22-98  
HFD-570/Meyer/4-24-98  
HFD-570/Bertha  
HFD-570/Chun  
HFD-570/Gebert  
HFD-570/Jenkins  
HFD-570/Ng  
HFD-570/Poochikian  
HFD-570/Sheevers  
HFD-570/Wilson  
Initialed by: Schumaker/4-20-98  
cc:\MyDocuments\ongoing\I46216.min

Memorandum of Telephone Facsimile Correspondence

Date: 01/16/98  
To: Joseph Lamendola, Ph.D.  
Vice President  
U.S. Regulatory Affairs  
Thru: Cathie Schumaker (Schumaker)  
Chief, Project Management Staff  
From: Denise P. Toyer, R.Ph.  
Project Manager  
Subject: IND 46,216 Trademark Review

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

**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 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

*Denise P. Toyer*  
Denise P. Toyer  
Project Manager  
Division of Pulmonary Drug Products

46,216  
Mometasone furoate Dry Powder Inhaler  
Schering-Plough Corporation

The Labeling and Nomenclature Committee has reviewed your request for the proposed Trademark [ (mometasone furoate dry powder inhaler). ]

X The following look alike/sound alike conflicts were noted by the committee: Asmalix, Asma, and Asmanephrin. The committee felt there is significant potential for mix-up with these conflicting names. Additionally, the name encodes a medical condition (asthma) and may be in violation of the regulations regarding reminder advertisements.

This information is provided as guidance for your selection of a trademark. We acknowledge that Asmalix and Asmanephrin may also be in violation of the regulation regarding reminder advertisements.

Per our conversation on January 16, 1998, the procedure for filing a grievance in response to this review is as follows.

1. Submit the grievance to the Division of Pulmonary Drug Products (DPDP) for review and response.
2. If you do not agree with DPDP's response, you may submit the grievance to the Office of the Director (ODE II), attention Dr. Bilstad, for review and response.
3. If you do not agree with DPDP and ODE II's response, you may submit the grievance to the Center, attention Dr. Lumpkin, for review and response.

*not final?*

Please note that the trademark review will be finalized at the time of approval of the NDA.

If you have any further questions please contact Ms. Denise Toyer, Project Manager, at 301-827-5584.

cc:

Original IND 46,216  
HFD-570/Division File  
HFD-570/Toyer

47 Page(s) Withheld

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

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(4) Draft Labeling

TO (Division/Office): HFD 530 Dan Boring Labeling and Nomenclature Committee

FROM: HFD-570 (Division of Pulmonary Drug Products)  
Denise P. Toyer

May 9, 1997	IND NO.: 46,216	NDA NO.:	TYPE OF DOCUMENT: Trademark Review	DATE OF DOCUMENT: May 6, 1997
NAME OF DRUG: [ ]	PRIORITY CONSIDERATION: Standard	CLASSIFICATION OF DRUG: 3S	DESIRED COMPLETION DATE: 8/1/97	

NAME OF FIRM: Schering Corporation

REASON FOR REQUEST

I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER                         |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                                |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                                     |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                           |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                                    |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):<br>Trademark Review |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER:	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER:

III. BIOPHARMACEUTICS

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

IV. DRUG EXPERIENCE

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
-----------------------------------	--------------------------------------

COMMENTS/SPECIAL INSTRUCTIONS: Please evaluate the proposed name and make recommendations.  
 (mometasone furoate dry powder inhaler, xxx mcg). The sponsor is currently conducting Phase 2/3 trials for the treatment of moderate asthma.

cc: Original IND 46,216  
HFD-570/Div. Files  
HFD-570/Toyer  
HFD-570/Schumaker

SIGNATURE OF REQUESTER: <i>Denise P. Toyer</i>	METHOD OF DELIVERY (Check one): <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

MAY 16 1997  
DK

**REQUEST FOR TRADEMARK REVIEW**

**TO:** Dan Boring, Chair, (HFD-530)  
Labeling and Nomenclature Committee  
Corporate Building, Room N461

**FROM:** Denise P. Toyer, (HFD-570)  
Division of Pulmonary Drug Products HFD-570

**DATE:** May 14, 1997

**SUBJECT:** Request for assessment of the proposed name

**Proposed Trademark:** [ J  
**IND #** 46,216

**Established name, including dosage form:** mometasone faired dry powder inhaler, xxx mcg

**Other trademarks by the same firm for comparison products:**  
N/A

**Indications for use (may be a summary if proposed statement is lengthy):**

An inhaled corticosteroid used as maintenance therapy for asthma patients.

**Initial comments from the submitter: (concerns, observations, etc.)**

**NOTE:** Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Dec. 1990

IND 46,216  
Page 2

cc:

Orig. IND# 46,216  
HFD-570/Division File  
HFD-570/Ng  
HFD-570/Toyer

F/T by: Toyer/5-14-97

N:\IND\46216\PM\97-05-15.CON

## Minutes of Industry Meeting

**Date:** February 10, 1997  
**Time:** 1:00 p.m. to 2:30 p.m.  
**Place:** Conference Room "O"  
**IND:** IND 46,216  
**Sponsor:** Schering Plough Pharmaceuticals  
**Drug:** Mometasone Dry Powder Inhaler  
**Meeting Type:** Chemistry  
**IMTS #:** 893

### FDA Attendees:

Craig Bertha, Ph.D.	Chemistry Reviewer
Linda Ng, Ph.D.	Chemistry Reviewer
Guirag Poochikian, Ph.D.	Chemistry Team Leader
Denise Toyer, R.Ph.	Project Manager

### Schering-Plough Attendees:

Dr. Thomas Ambrosio	Developmental Fellow, Pharmaceutical Package Development
Dr. Imtiaz Chaudry	Vice President, Pharmaceutical Sciences
Mr. Ravi Chivukula	Manager, Technical Support, Worldwide Regulatory Affairs
Dr. Francis M. Cuss	Vice President, Biological Research-Allergy and Immunology
Dr. Tobias Massa	Senior Director, Worldwide Technical Support, Worldwide Regulatory Affairs
Dr. Eugene McGonigle	Vice President, PACRD
Dr. Michael Mitchell	Presidential Fellow, Chemical Development
Ms. Lois Singer	Senior Associate Director, Pharmaceutical Package Development
Mr. Bruce Wyka	Associate Director, PACRD

### Background

Schering is currently developing mometasone furoate monohydrate to be used in a dry powder inhaler. They wanted to discuss several aspects of the manufacturing, packaging and control operations as well as their plans for synthesis of the drug substance. See background package dated November 27, 1996 for further information related to the meeting.

### Objectives

The objective of this meeting is to determine if the proposed CMC plan for mometasone furoate is acceptable to the division.

Numerous slides were presented (copies attached), by Schering, during the meeting. Due to time restraints, the reviewers could not comment on each slide. Therefore, the Division's recommendations are only for the "points for discussion" which are presented below.

1. Tests and acceptance criteria for the selection and qualification of materials of construction for the powder inhaler, i.e., U.S.P. Biological, U.S.P. Physicochemical as well as [ ] of drug contacting components using an aqueous medium:

All physical and chemical tests were done as specified in the U.S.P. No [ ] have been identified at the present time.

Recommendation: There are no assurances that the [ ] didn't change anything. Schering must set some type of acceptance criteria for the [ ] Choose a solvent [ ] and determine what the specifications are. Every [ ] should be tested at the present time. At a later date, a less frequent testing schedule may be set up.

2. Criteria for qualifying alternate sources of component materials and/or vendors in the event of non-availability of current specified [ ]

Recommendation: Any change in component materials which come in contact with the patient or the powder cannot be reported in the annual report. These are considered critical changes and must be reported according to prior approved supplements with appropriate supporting data.

3. Acceptability of tests and specifications for quality control of individual components and [ ] sourced from the device [ ] This will include testing to be done by the vendor and Schering in addition to plans for periodic confirmatory testing by Schering:

The vendor will conduct quality assurance testing on all [ ] Schering has rechecked all [ ] received from vendor in the initial three batches. Schering will set up a schedule and only periodically recheck the vendor's test results.

Recommendation: Clearly indicate who will evaluate the

(Schering or an outside laboratory).

4. **Concurrence on the adequacy of criteria to demonstrate that the performance of DPI's from [ ] production [ ] is similar to the units from the production grade [ ] which are being used in the clinical trials:**

Schering used the [ ] as its benchmarks to ensure that they were within the current limits of an approved drug. Data regarding the [ ] came from published literature. To determine the effect on flow rate Schering used the commercial product Pulmicort. They anticipate using [ ] which will produce [ ] but are not sure at the present time how many component pieces the final [ ] will produce. Regardless of the quantity of component pieces [ ] produced, Schering will ensure the equivalency and use the same component specifications initially used in the production grade [ ]

**Recommendation:** None.

5. **Tests to demonstrate the ruggedness of the DPI device under conditions of simulated patient use:**

Schering will test every strength device to determine the effects of use and misuse by patients. Priming studies will also be done.

**Recommendation:** Although 4L is the U.S.P. recommendation, the Division recommends 2L as a volume to be tested. 3L is the maximum that should be used. A true description of performance will be placed in the description section of the labeling (e.g. the device will deliver "x" amount at "y" liter/minutes for "z" seconds).

6. **Bioburden/Microbial control and specifications for the device components and finished product:**

All testing, controls and specifications are conducted in accordance with information presented at recent DIA meeting.

Recommendation: None.

7. **Criteria to demonstrate the need, or lack of need, for a [ ] package:**

The initial unit was studied at 3 months and found to have some problems. Modifications were made to address the problems. No new studies have been conducted to determine if the modifications were acceptable. Schering anticipates studying storage conditions at [ ] for [ ]

Recommendation: [ ] RH for [ ] is acceptable as long as no trends are identified.

8. **Acceptability of our release and stability testing programs with a focus on storage position, temperature and humidity conditions:**

Schering is not using the [ ] because they found problems with it. They are using [ ] Can Schering submit an outlier test protocol to meet the [ ] Is there a limit on the outliers?

Recommendation: The Division recommends using 4 seconds at 30 liters per minute instead of [ ] Using [ ] will make it difficult to create a good [ ] profile of the product. Although [ ] is cumbersome, it could provide a better profile [ ] than the [ ] The Division will not require both methods.

[ ] methods for [ ] should be capable of profiling the whole dose including profiles [ ]

1. Develop more data and submit for further review. An appropriate outlier program is acceptable but a cap on the outlier has to be provided.

9. **Physical-chemical tests to demonstrate equivalence of the [ ] drug substance manufacturing process:**

Testing including purity profiles should be demonstrated and submitted. Currently there is a discussion within the agency regarding the 1.0% level for impurities listed in the ICH guidelines. The division is leaning towards [ ] for inhalation products. At the present time this is only a discussion and as

IND 46,216

Page 5

soon as a final decision has been determined the sponsors will be notified.

Schering was asked to evaluate the presence of [ ] in the drug substance. Schering agreed, and if no [ ] are observed based on a validated sensitive method, the test may be left out of the acceptance testing program.

**Recommendation:** Data to support proposed specification should be submitted to the Division for comments.

*Denise P. Toyer*

---

Denise P. Toyer  
Project Manager

ATTACHMENTS

IND 46,216  
Page 6

cc:

Division File

Orig. IND 46,216

HFD-570/Poochikian/3-12-97/3-13-97

HFD-570/Ng/3-12-97/3-13-97

HFD-570/Bertha/3-12-97

HFD-570/Toyer

HFD-570/Meyer

HFD-570/Whitehurst

R/D: TOYERD/2-14-97

F/T: TOYERD/3-14-97

N:\IND\46216\PM\97-02-10.min

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-067	Efficacy Supplement Type SE-	Supplement Number
Drug: Asmanex Twisthaler		Applicant: Schering
RPM: Lori Garcia	HFD-570	Phone # 301-827-1050
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
<ul style="list-style-type: none"> <li>• Review priority</li> </ul>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<ul style="list-style-type: none"> <li>• Chem class (NDAs only)</li> </ul>		3
<ul style="list-style-type: none"> <li>• Other (e.g., orphan, OTC)</li> </ul>		
❖ User Fee Goal Dates		31-Mar-2005
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
<ul style="list-style-type: none"> <li>• User Fee</li> </ul>		<input checked="" type="checkbox"/> Paid
<ul style="list-style-type: none"> <li>• User Fee waiver</li> </ul>		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
<ul style="list-style-type: none"> <li>• User Fee exception</li> </ul>		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP</li> </ul>		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• Exception for review (Center Director's memo)</li> </ul>		
<ul style="list-style-type: none"> <li>• OC clearance for approval</li> </ul>		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
<ul style="list-style-type: none"> <li>• Information: Verify that form FDA-3542a was submitted.</li> </ul>		<input type="checkbox"/> Verified **Not submitted
<ul style="list-style-type: none"> <li>• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.</li> </ul>		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).</li> </ul>		<input type="checkbox"/> Verified

● Exclusivity (approvals only)	
● Exclusivity summary	-Mar-2005
● Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	( ) Yes, Application # _____ (x) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	
<b>General Information</b>	
❖ Actions	
● Proposed action	(x) AP ( ) TA ( ) AE ( ) NA
● Previous actions (specify type and date for each action taken)	5/17/04(AE); 12/4/00(AE); 3/14/00(AE); 10/1/99(AE)
● Status of advertising (approvals only)	(x) Materials requested in AP letter ( ) Reviewed for Subpart H
● Public communications	
● Press Office notified of action (approval only)	( ) Yes ( ) Not applicable
● Indicate what types (if any) of information dissemination are anticipated	(x) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
● Division's proposed labeling (only if generated after latest applicant submission of labeling)	09-Mar-2005
● Most recent applicant-proposed labeling	15-Nov-2004
● Original applicant-proposed labeling	30-Nov-1998
● Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	2/18/05(DDMAC); 12/17/04(DMETS); 4/4/04(DMETS)
● Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
● Division proposed (only if generated after latest applicant submission)	
● Applicant proposed	15-Nov-2004
● Reviews	
● Post-marketing commitments	
● Agency request for post-marketing commitments	PREA(peds studies in 4-11yo)
● Documentation of discussions and/or agreements relating to post-marketing commitments	-Mar-2005(AP letter)
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	3/9/05; 1/28/05; 12/3/04; 9/3/04; 5/5/04
❖ Memoranda and Telecons	7/7/04
❖ Minutes of Meetings	
● EOP2 meeting (indicate date)	4/3/98
● Pre-NDA meeting (indicate date)	9/14/98
● Pre-Approval Safety Conference (indicate date; approvals only)	
● Other	

❖ Advisory Committee Meeting	N/A
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
<b>Summary Application Review</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	30-Mar-2005
<b>Clinical Information</b>	
❖ Clinical review(s) (indicate date for each review)	5/5/04; 9/5/00; 2/28/00; 9/16/99
● Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	1/31/05; 5/5/04
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
● Pediatric Page(separate page for each indication addressing status of all age groups)	12/1/00
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	4/26/04; 3/30/04; 9/14/99
❖ Biopharmaceutical review(s) (indicate date for each review)	3/4/04; 9/22/99; 1/7/99
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	9/16/99 (clinical review)
• Bioequivalence studies	
<b>CMC Information</b>	
❖ CMC review(s) (indicate date for each review)	12/22/04; 11/16/04; 5/6/04; 11/29/00; 7/26/00; 12/13/99; 12/6/99; 4/9/99
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	4/9/99
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: 17-Nov-2004 (x) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (x) Requested* Agreement #5 in AP letter ( ) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	4/28/04; 8/27/99; 3/23/99; 1/3/99
❖ Nonclinical inspection review summary	
● Statistical review(s) of carcinogenicity studies (indicate date for each review)	
❖ CAC/ECAC report	

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>21-067</u>	
Drug <u>Asmanex Twisthaler</u>	Applicant <u>Schering Corporation</u>
RPM <u>Hilfiker</u>	Phone <u>7-1084</u>
<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Reference listed drug _____	
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rolling Review
Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P	
Pivotal IND(s) <u>46,216</u>	
Application classifications: Chem Class _____ Other (e.g., orphan, OTC) _____	PDUFA Goal Dates: Primary <u>12-5-00</u> Secondary <u>same</u>

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

**GENERAL INFORMATION:**

- ◆ User Fee Information:
  - User Fee Paid
  - User Fee Waiver (attach waiver notification letter)
  - User Fee Exemption
  
- ◆ Action Letter.....  AP  AE  NA
  
- ◆ Labeling & Labels
  - FDA revised labeling and reviews..... Comments in letter
  - Original proposed labeling (package insert, patient package insert) ..... As of 10-17-00
  - Other labeling in class (most recent 3) or class labeling..... \_\_\_\_\_
  - Has DDMAC reviewed the labeling? .....  Yes (include review)  No
  - Immediate container and carton labels ..... As of 11-8-00
  - Nomenclature review ..... ✓
  
- ◆ Application Integrity Policy (AIP)  Applicant is on the AIP. This application  is  is not on the AIP.
  - Exception for review (Center Director's memo)..... \_\_\_\_\_
  - OC Clearance for approval..... \_\_\_\_\_

- ◆ Status of advertising (if AP action)  Reviewed (for Subpart H – attach review)  Materials requested in AP letter
- ◆ Post-marketing Commitments
  - Agency request for Phase 4 Commitments.....
  - Copy of Applicant's commitments .....
- ◆ Was Press Office notified of action (for approval action only)?.....  Yes  No
  - Copy of Press Release or Talk Paper.....
- ◆ Patent
  - Information [505(b)(1)] ..... yes
  - Patent Certification [505(b)(2)].....
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....
- ◆ Exclusivity Summary .....
- ◆ Debarment Statement ..... yes
- ◆ Financial Disclosure
  - No disclosable information ..... ✓
  - Disclosable information – indicate where review is located .....
- ◆ Correspondence/Memoranda/Faxes ..... Yes\*
- ◆ Minutes of Meetings ..... Yes\*
  - Date of EOP2 Meeting 4-3-98
  - Date of pre NDA Meeting 9-14-98
  - Date of pre-AP Safety Conference \_\_\_\_\_
- ◆ Advisory Committee Meeting ..... N/A
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....
- ◆ Federal Register Notices, DESI documents ..... N/A

**CLINICAL INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

- ◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... Pending
- ◆ Clinical review(s) and memoranda ..... Yes\*

- ◆ Safety Update review(s) ..... None this cycle
- ◆ Pediatric Information
  - Waiver/partial waiver (Indicate location of rationale for waiver)  Deferred Pediatric Page..... ✓
  - Pediatric Exclusivity requested?  Denied  Granted  Not Applicable
- ◆ Statistical review(s) and memoranda ..... None this cycle
- ◆ Biopharmaceutical review(s) and memoranda ..... None this cycle
- ◆ Abuse Liability review(s) ..... N/A  
 Recommendation for scheduling .....
- ◆ Microbiology (efficacy) review(s) and memoranda ..... N/A
- ◆ DSI Audits ..... NAI
  - Clinical studies  bioequivalence studies .....

**CMC INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

- ◆ CMC review(s) and memoranda ..... Yes\*
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability ..... Pending
- ◆ DMF review(s) ..... Yes\*
- ◆ Environmental Assessment review/FONSI/Categorical exemption ..... exemption
- ◆ Micro (validation of sterilization) review(s) and memoranda ..... N/A
- ◆ Facilities Inspection (include EES report)  
 Date completed 11-30-00 .....  Acceptable  Not Acceptable
- ◆ Methods Validation .....  Completed  Not Completed

**PRECLINICAL PHARM/TOX INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

- ◆ Pharm/Tox review(s) and memoranda ..... Labeling only
- ◆ Memo from DSI regarding GLP inspection (if any) ..... N/A

- 
- ◆ Statistical review(s) of carcinogenicity studies ..... N/A
  - ◆ CAC/ECAC report ..... N/A

Appears This Way  
On Original

