CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-067

Chemistry Review(s)

NDA 21-067

Asmanex® Twisthaler®

Schering Corporation

Craig M. Bertha, Ph.D.
Division of New Drug Chemistry II
Office of New Drug Chemistry

Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 21-067

2. REVIEW #: 8

3. REVIEW DATE: 21-DEC-2004

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	30-NOV-1998
Amendment (BZ, replacement volumes)	28-JAN-1999
Amendment (BC)	05-FEB-1999
Amendment (BC, devices and parts)	09-FEB-1999
Amendment (BC, marked devices)	26-FEB-1999
Amendment (BZ, DS impurities spec.)	09-MAR-1999
Amendment (BC)	30-MAR-1999
Amendment (AC)	30-JUN-1999
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Amendment (BC, marked devices)	17-SEP-1000
Amendment (BC, response comment 13m)	01-OCT-1999
Amendment (AZ, 01-OCT-1999 AE response)	01-DEC-1999
Amendment (BC, response comment 11c,d)	17-FEB-2000
Amendment (BC, response comment 6)	10-MAY-2000
Amendment (AZ, 14-MAR-2000 AE response)	02-JUN-2000
Amendment (AZ, 10-AUG-2000 DR response)	17-OCT-2000
Amendment (BC, stability update)	18-OCT-2000
Amendment (AZ, 04-DEC-2000 AE response)	14-NOV2003
Amendment (BC, [ ] data)	03-DEC-2003
Amendment (BC, corrected stability data in SAS)	10-DEC-2003
Amendment (BL, labeling)	14-FEB-2004
Amendment (BL, updated labeling)	12-APR-2004
Amendment (BL, updated labeling)	10-MAY-2004
Amendment (BL, updated labeling)	13-MAY-2004
Amendment (BL, updated labeling)	14-MAY-2004
Amendment (BZ, incomp. response to 17-MAY-2004 AE)	29-JUN-2004
Amendment (BC, new [ ] acceptance criteria proposal)	29-JUN-2004
Amendment (AZ, completes response to 17-MAY-2004 AE letter and responds to 03-SEP-2004 DR)	28-SEP-2004

Chemistry Review Data Sheet

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (BL)	15-NOV-2004
Amendment (BC, response to 03-DEC-2004 DR letter)	14-DEC-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Schering Corporation
Address:	2000 Galloping Hill Road, Kenilworth, NJ 07033
Representative:	Mr. Isidoro Perez, President Worldwide Regulatory Affairs
Telephone:	908-740-4290

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Asmanex® Twisthaler® 220 mcg
b) Non-Proprietary Name (USAN): Mometasone Furoate inhalation powder
c) Code Name/# (ONDC only): SCH 32088
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Section 505(b)(1) of the FD&C Act

10. PHARMACOL. CATEGORY: Anti-inflammatory glucocorticosteroid for prophylactic maintenance treatment of Asthma

11. DOSAGE FORM: Inhalation Powder

12. STRENGTH/POTENCY: 220 mcg metered mometasone furoate/actuation, 200 mcg emitted /actuation

13. ROUTE OF ADMINISTRATION: Inhalation

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

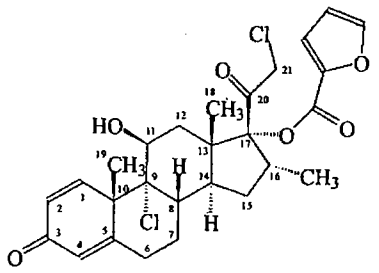
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Systematic Name (USAN) : 9 Pregna-1,4-diene-3,20-dione, 9,21-dichloro-17-((2-furanylcarbonyl)oxy)-11-hydroxy-16-methyl-, (11beta, 16alpha)



Mometasone Furoate

Molecular Formula: $C_{27}H_{30}Cl_2O_6$
Molecular Weight: 521.443

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
٢	Type II	٢		3	adequate	1/22/99 5/26/00 3/19/04	See p. 4 of CR#1 See p. 7 CR#3 See pp. 8, 14 CR#5
	Type I			3	adequate	1/25/99 9/8/99 2/10/00 8/10/00	See p. 86 of CR#1 See p. 66 of CR#2 See p. 43 of CR#3 See p 10 of CR#4
	Type III				withdrawn[3]		See p. 87 of CR#1
	Type III			1	adequate	2/4/99 9/2/99 2/3/00 4/11/00 3/1/04 7/30/04	See p. 85 of CR#1 See p. 67 of CR#2 See p. 44 of CR#3 See p. 14 of CR#5 See p. 27 of CR#6
ل	Type III		ل	3	adequate	1/26/99 9/25/00 3/19/04	See p. 85 of CR#1 See p. 67 of CR#2 See p. 44 of CR#3

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
							See p. 34 of CR#4 See p. 14 of CR#5
[	Type III	[	[	3	**not reviewed**[2]		See p. 86 of CR#1
	Type III			3	**adequate**	2/3/99 2/22/00	See p. 85 of CR#1 See p. 67 of CR#2
	Type III			3	**adequate**	1/26/99 3/10/00 9/28/00	See p. 85 of CR#1 See p. 67 of CR#2 See p. 44 of CR#3 See p. 34 of CR#4
	Type IV			3	**adequate**	1/27/99 9/25/00	See p. 85 of CR#1 See p. 67 of CR#2 See p. 15 of addendum CR#2 See p. 44 of CR#3 See p. 34 of CR#4
	Type IV			3	**adequate**	1/27/99 9/25/00	See p. 85 of CR#1 See p. 67 of CR#2 See p. 44 of CR#3 See p. 35 of CR#4
	Type IV			3	**adequate**	4/13/00 9/25/00	See. p. 45 of CR#3 See p. 35 of CR#4
	Type I			3	**adequate**	10/18/99 6/16/00	See p. 90 of CR#1 See p. 75 of CR#2 See p. 51 of CR#3
	Type III			3	**adequate**	1/28/99 8/31/99 3/30/04	See p. 85 of CR#1 See p. 67 of CR#2 See p. 14 of CR#5
				3	**adequate**	8/31/99	See p. 75 of CR#2 (to support DMF [redacted]
	Type III			3	**withdrawn**	8/31/99 5/2/00	See p. 89 of CR#1 See p. 75 of CR#2 See p. 50 of CR#3 See p. 37 of CR#4
]	Type III	]	]	3	**adequate**	9/8/99 2/2/00 4/26/00 3/31/04	See p. 90 of CR#1 See p. 74 of CR#2 See p. 50 of CR#3 See p. 14 of CR#5

[1]DMF [ ] was withdrawn and applicant not seeking approval for alternate [ ] (see response to comment 15.c on p. 67 of CR#2).
[2]Schering did not use [ ] supplier from the vendor list (see response to comment 15.e on p. 68 of CR#2).

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
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4 – Sufficient information in application
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6 – DMF not available
7 – Other (explain under "Comments")

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

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	[redacted]	
IND		[redacted]
IND	46,216	Mometasone Furoate Inhalation Powder
NDA	19-543	Elocon (Mometasone Furoate) Ointment (approved 30-Apr-87)[2]
NDA	19-625	Elocon (Mometasone Furoate) Emulsion, Cream (approved 06-May-87)[2]
NDA	19-796	Elocon (Mometasone Furoate) Lotion (approved 30-Mar-89)[2]
NDA	20-762	Nasonex (Mometasone Furoate)[3] Nasal Spray (approved 01-Oct-97)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	COMMENTS
Biometrics	Not sufficient to establish shelf life based on the stability data with two lots of Kenilworth manufactured product.	05-MAR-2004	See p. 109 of CR#1. See response to comments 13.m and 17.a on pp. 40 and 93 of CR#2, respectively. See p. 64 in CR#3. See p.45 in CR#4. See p. 14 of CR#5 and p. 13 of CR#6. See p. 20 of CR#7 (18 month expiry acceptable).
EER	Acceptable	17-NOV-2004	
Pharm/Tox	02-FEB-1999	Acceptable, 23-MAR-1999	Impurities Consult (DS/DP), see response to comment 3 and note on p. 33 of CR#2.
Biopharm	Not forwarded	Not needed	
LNC	Asmanex® forwarded under IND 46,216 PM sent consult to OPDRA on Asmanex® Twisthaler® again on 14-JAN-2004	Initially Unacceptable Acceptable	LNC recommends against Asmanex®. LNC and OPDRA accepts Asmanex® Twisthaler®
Methods Validation	Not forwarded.		Will be forwarded once drug product specifications finalized and updated MV packages submitted by firm. See agreement 5 in the draft letter of agreements.
Clinical	22-MAR-1999 19-OCT-1999	Consults were FYI only for MO	Consult requesting consideration of *in vitro* dose proportionality differences between strengths and — flow rate dependency. Follow up to above consult which provides — data versus flow rate at constant volume in terms of the actual amount of MF collected.
EA	Firm requests categorical exclusion under 21 CFR 25.31(b).	Not needed.	See p. 111 of CR#1.
Microbiology	Not forwarded.	Not needed.	See comments on pp. 28, 61 of CR#1.

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-067

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval

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

Several agreements are in place for this application. They are listed below.

1. Schering agrees to submit a prior approval supplement containing all pertinent supportive documentation for [ ] of Singapore as a manufacturing site for the drug product.
2. Schering also agrees to re-evaluate the [ ] acceptance criteria after one year of commercial experience.
3. Schering agrees to re-evaluate the specifications for resistance to flow-by pressure drop after one year of commercial production experience (see p. 26 of CR#5).
4. Schering agrees to 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., [ ] deposition. They agree to a projected completion date of no more than twelve (12) months.
5. Schering agrees to 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.

II. Summary of Chemistry Assessment

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

Drug Substance

The drug substance (DS) mometasone furoate (both anhydrous and monohydrate)

is a light sensitive compound and is used as the anhydrate in several approved commercial drug products (ointments, creams and nasal spray). DMF [ ]from [ ] is referenced for the [ ] used to prepare the DS. This file was found to be adequate in a review dated 23-APR-2003. Some minor changes in the specifications of the reagents were noted in the latest amendment to the DMF (20-AUG-2003) which was reviewed (19-MAR-2004) and found to be adequate. The monohydrate form of the drug substance is manufactured by Schering Plough in Singapore for the Asmanex Twisthaler drug product (DP). The previously included DS manufacturing site in Avondale, Ireland has been removed from the application.

Drug Product

The drug product is a device-metered inhalation powder (dry powder inhaler or DPI). The device [ ] containing the formulation (mometasone furoate and anhydrous lactose i[ ]The cap, which includes [ ] is sealed to the device [ ] when not in use. Opening of the cap for the device, by turning counter-clockwise, exposes a white colored plastic mouth-piece, loads the dose and advances the counter.

The drug product was previously manufactured in Kenilworth, NJ and Singapore. Drug product quality control operations are also performed at the Union facility in NJ. The applicant has withdrawn Singapore as a second drug product manufacturing site. Some differences and inconsistencies were noted in the [ ] of the drug product from the Kenilworth and Singapore sites in several earlier reviews.

The application originally proposed two strengths of the product [ ] mcg/actuation) but the higher strength has been withdrawn. The 220 mcg strength is proposed to be supplied as 14, 30, 60 and 120 actuation/inhaler versions. The target fills for each are the *same* regardless of the number of label claim actuations. The label claim number of actuations is controlled by the device lock-out set-point.

Expiry: 18 months was found to be supported by the currently available data (see p. 20 of CR#7).

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

The drug product is used for oral inhalation of the mometasone furoate, a glucocorticosteroid, in an anhydrous lactose-based formulation, for the maintenance treatment of asthma. The drug product includes components that protect the formulation from moisture [ ] and patients are advised not to exhale

into the inhaler. The drug product is currently proposed to be produced in one strength (220 mcg is the metered dose) of mometasone furoate and is labeled for 30, 60, or 120 doses of mometasone furoate at 200mcg/actuation emitted from the mouthpiece (there is also a 14 count professional sample). The proposed maximum daily recommended dose is 400 micrograms (emitted dose from 2 inhalations). Patients are asked to store the drug product in a dry place at controlled room temperature, [ ] and discard the inhaler 45 days after opening the foil pouch or when dose counter reads "00", whichever comes first. No cleaning instructions are proposed.

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D., CMC Reviewer
HFD-570/820

C. CC Block

cc:
Orig. NDA 21-067
HFD-570/Division File
HFD-570/CBertha
HFD-570/RLostritto
HFD-570/LGarcia

R/D Init. by RLostritto:_____

Filename and Location: c:\data\mydocuments\reviews etc\NDA\21067\Review 6\04-12-14_rev.doc

17 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/

Craig Bertha
12/21/04 08:01:50 AM
CHEMIST

Richard Lostritto
12/22/04 04:10:33 PM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Memorandum

DATE: December 10, 2004.

TO: Division File System

FROM: Prasad Peri, Ph.D, HFD 570

SUBJECT: Asmanex (mometasone furoate) Twisthaler NDA 21-067.

Labeling Review of submission dated May 10, 2004, May 13, 2004 and May 14, 2004.

Note that my chemistry review 5 dated May 5, 2004, included several CMC based comments for the package insert (PI), patient instructions for use (PIFU), the carton/container/pouch labels for NDA 21067.

1. 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).

2. 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.

3. For the pouch labels, the product strength, 220 mcg, 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.

4. The placement of the established and proprietary names on the carton labeling is different than that on the container and pouch label. The Agency 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.

5. Increase the font size of the in-use statement on the cap label to make it commensurate with that of the storage statement.

6. Revise the storage statement to the following on all packaging labels and cartons as per the Draft Stability Guidance: Store in a dry place at 25°C (77°F). [See USP Controlled Room Temperature].

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

The applicant sent in responses (dated May 10, 2004, and May 13, 2004) to the labeling/ PI/PIFU comments communicated to them in a fax dated May 5, 2004.

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

/s/

Prasad Peri
12/10/04 12:04:44 PM
CHEMIST

Richard Lostritto
12/13/04 03:34:39 PM
CHEMIST

NDA 21-067

Asmanex® Twisthaler®

Schering Corporation

Craig M. Bertha, Ph.D.
Division of New Drug Chemistry II
Office of New Drug Chemistry

Division of Pulmonary and Allergy Drug Products

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4. REVIEWER: Craig M. Bertha, Ph.D.

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Telephone:	908 740 4290

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Asmanex® Twisthaler® 220 mcg
b) Non-Proprietary Name (USAN): Mometasone Furoate inhalation powder
c) Code Name/# (ONDC only): SCH 32088
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Section 505(b)(1) of the FD&C Act

10. PHARMACOL. CATEGORY: Anti-inflammatory glucocorticosteroid for prophylactic maintenance treatment of Asthma

11. DOSAGE FORM: Inhalation Powder (code 800)

12. STRENGTH/POTENCY: 220 mcg metered mometasone furoate/actuation, 200 mcg emitted /actuation

13. ROUTE OF ADMINISTRATION: Inhalation

14. Rx/OTC DISPENSED: _X__Rx ___OTC

Chemistry Review Data Sheet

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

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

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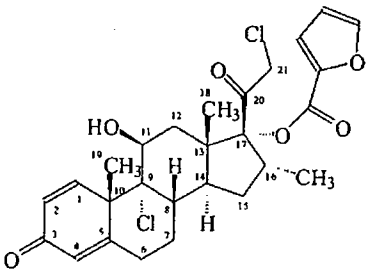

Mometasone Furoate

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[ ]	Type I			3	adequate	1/25/99 9/8/99 2/10/00 8/10/00	See p. 86 of CR#1 See p. 66 of CR#2 See p. 43 of CR#3 See p 10 of CR#4
[ ]	Type III			7	withdrawn[3]		See p. 87 of CR#1
[ ]	Type III			1	adequate	2/4/99 9/2/99 2/3/00 4/11/00 3/1/04	See p. 85 of CR#1 See p. 67 of CR#2 See p. 44 of CR#3 See p. 14 of CR#5 See p. 27 of CR#6

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DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
						7/30/04	
	Type III			3	adequate	1/26/99 9/25/00 3/19/04	See p. 85 of CR#1 See p. 67 of CR#2 See p. 44 of CR#3 See p. 34 of CR#4 See p. 14 of CR#5
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[1]DMF [redacted] was withdrawn and applicant not seeking approval for [redacted]
(see response to comment 15.c on p. 67 of CR#2)
[2]Schering did not use the [redacted] in clinical or stability batches and has deleted this material and the supplier from the vendor list (see response to comment 15.e on p. 68 of CR#2).

[1] Action codes for DMF Table:
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CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	COMMENTS
Biometrics	Not sufficient to establish shelf life based on the stability data with two lots of Kenilworth manufactured product.	3/5/04	See p. 109 of CR#1. See response to comments 13.m and 17.a on pp. 40 and 93 of CR#2, respectively. See p. 64 in CR#3. See p.45 in CR#4. See p. 14 of CR#5 and p. 13 of CR#6. See p. 13 of this review.
EER	Withhold recommended by the office of compliance. Indicates validation failure.	3/12/04	**All sites submitted to OC by chemist in the EES on 07-OCT-2004. The overall recommendation is PENDING. See the response to comment 1 below on p. 12.**
Pharm/Tox	2/2/99	Acceptable, 3/23/99	Impurities Consult (DS/DP), see response to comment 3 and note on p. 33 of CR#2.
Biopharm	Not forwarded	Not needed	
LNC	Asmanex® forwarded under IND 46,216 PM sent consult to OPDRA on Asmanex® Twisthaler® again on 01/14/04	Initially Unacceptable **Acceptable**	LNC recommends against Asmanex®. **LNC and OPDRA accepts Asmanex Twisthaler**
Methods Validation	Not forwarded.		Will be forwarded once drug product specifications finalized and updated MV packages submitted by firm. See response to comment 5 below in this review on p. 22.
Clinical	3/22/99 10/19/99	Consults were FYI only for MO	Consult requesting consideration of *in vitro* dose proportionality differences between strengths and flow rate dependency. Follow up to above consult which provides data versus flow rate at constant volume in terms of the actual amount of MF collected.
EA	Firm requests categorical	Not needed.	See p. 111 of CR#1.

Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	COMMENTS
	exclusion under 21 CFR 25.31(b).		
Microbiology	Not forwarded.	Not needed.	See comments on pp. 28, 61 of CR#1.

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-067

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable. *It is requested that the PM forward the comments in the draft DR letter to the applicant as soon as feasible.*

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

Several agreements are in place for this application. They are listed below.

1. Schering agrees to submit a prior approval supplement containing all pertinent supportive documentation for [ ] of Singapore as a manufacturing site for the drug product.
2. Schering also agrees to re-evaluate the [ ] acceptance criteria after one year of commercial experience. See response to comment 4c below.
3. Schering agrees to re-evaluate the specifications for resistance to flow-by pressure drop after one year of commercial production experience (see p. 26 of CR#5).

II. Summary of Chemistry Assessment

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

Drug Substance

The drug substance (DS) mometasone furoate is a light sensitive compound and is used in several approved commercial drug products (ointments, creams and nasal spray). DMF [ ] from [ ] is referenced for the [ ] used to prepare the DS. This file was found to be adequate in a review dated 23-APR-2003. Some minor changes in the specifications of the reagents were noted in the latest amendment to the DMF (20-AUG-2003) which was reviewed (19-MAR-2004) and found to be adequate. The final drug substance is manufactured by Schering Plough in Singapore. The previously included DS manufacturing site in Avondale, Ireland has been removed from the application.

Drug Product

The drug product is a device-metered inhalation powder (dry powder inhaler or DPI). The device [ ] containing the formulation (mometasone furoate and anhydrous lactose [ ]). The cap, which includes [ ] is sealed to the device [ ] [ ] when not in use. Opening of the cap for the device, by turning counter-clockwise, exposes a white colored plastic mouth-piece, loads the dose and advances the counter.

The drug product was previously manufactured in Kenilworth, NJ and Singapore. Drug product quality control operations are also performed at the Union facility in NJ. The applicant has withdrawn Singapore as a second drug product manufacturing site. Some differences and inconsistencies were noted in the [ ] of the drug product from the Kenilworth and Singapore sites in several earlier reviews. This is addressed further in the review of the stability data provided in response to comment 2 below.

The application originally proposed two strengths of the product [ ] mcg/actuation) but the higher strength has been withdrawn. The 220 mcg strength is proposed to be supplied as 14, 30, 60 and 120 actuation/inhaler versions. The target fills for each are the *same* regardless of the number of label claim actuations. The label claim number of actuations is controlled by the device lock-out set-point.

Expiry: 18 months was found to be supported by the currently available data.

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

The drug product is used for oral inhalation of the mometasone furoate, a glucocorticosteroid, in an anhydrous lactose-based formulation, for the maintenance treatment of asthma. The drug product includes components that protect the formulation from moisture [ ] [ ] and patients are advised not to exhale into the inhaler. The drug product is currently proposed to be produced in one strength (220 mcg is the metered dose) of mometasone furoate and is labeled for 30, 60, or 120 doses of mometasone furoate at 200mcg/actuation emitted from the mouthpiece (there is also a 14 count professional sample). The proposed maximum daily recommended dose is 400 micrograms (2 inhalations). Patients are asked to store the drug product in a dry place at controlled room temperature, [ ]) and discard the inhaler 45 days after opening the foil pouch or when dose counter reads "00", whichever comes first. No cleaning instructions are proposed.

C. Basis for Approvability or Not-Approval Recommendation

The inadequacy of the sites of manufacture and testing for the drug product and the [ ] acceptance criteria to be applied to the annual stability batches (shelf-life specification) are the remaining critical issues to be resolved.

The Office of Compliance states in their Establishment Status Report that the Kenilworth and Union sites are under *withhold* status for failing validation. Inspection of the Union and Kenilworth sites have been assigned as of 13-OCT-2004. The inspections are pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D., CMC Reviewer
HFD-570/820

C. CC Block

cc:
Orig. NDA 21-067
HFD-570/Division File
HFD-570/CBertha
HFD-570/RLostritto
HFD-570/LGarcia

R/D Init. by RLostritto:_____

Filename and Location: c:\data\mydocuments\reviews etc\NDA\21067\Review 6\04-09-28.rev.doc

21 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/

Craig Bertha
11/8/04 01:39:23 PM
CHEMIST

See finalized TOC and other minor edits.

Richard Lostritto
11/16/04 04:13:00 PM
CHEMIST

NDA 21-067

Asmanex® Twisthaler®

Schering Corporation

Craig M. Bertha, Ph.D.
Division of New Drug Chemistry II
Office of New Drug Chemistry

Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 21-067

2. REVIEW #: 6

3. REVIEW DATE: 05-AUG-2004

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	30-NOV-1998
Amendment (BZ, replacement volumes)	28-JAN-1999
Amendment (BC)	05-FEB-1999
Amendment (BC, devices and parts)	09-FEB-1999
Amendment (BC, marked devices)	26-FEB-1999
Amendment (BZ, DS impurities spec.)	09-MAR-1999
Amendment (BC)	30-MAR-1999
Amendment (AC)	30-JUN-1999
Amendment (BC, stability update)	23-AUG-1999
Amendment (BC, marked devices)	17-SEP-1000
Amendment (BC, response comment 13m)	01-OCT-1999
Amendment (AZ, 01-OCT-1999 AE response)	01-DEC-1999
Amendment (BC, response comment 11c,d)	17-FEB-2000
Amendment (BC, response comment 6)	10-MAY-2000
Amendment (AZ, 14-MAR-2000 AE response)	02-JUN-2000
Amendment (AZ, 10-AUG-2000 DR response)	17-OCT-2000
Amendment (BC, stability update)	18-OCT-2000
Amendment (AZ, 04-DEC-2000 AE response)	14-NOV2003
Amendment (BC, individual data)	03-DEC-2003
Amendment (BC, corrected stability data in SAS)	10-DEC-2003
Amendment (BL, labeling)	14-FEB-2004
Amendment (BL, updated labeling)	12-APR-2004
Amendment (BL, updated labeling)	10-MAY-2004
Amendment (BL, updated labeling)	13-MAY-2004
Amendment (BL, updated labeling)	14-MAY-2004

6. SUBMISSION(S) BEING REVIEWED:

Chemistry Review Data Sheet

Submission(s) Reviewed	Document Date
Amendment (BZ, incomplete response to 17-MAY-2004 AE letter)	29-JUN-2004
Amendment (BC, new acceptance criteria proposal)	29-JUN-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Schering Corporation
Address:	2000 Galloping Hill Road, Kenilworth, NJ 07033
Representative:	Mr. Isidoro Perez, President Worldwide Regulatory Affairs
Telephone:	908 740 4290

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Asmanex® Twisthaler® 220 mcg
b) Non-Proprietary Name (USAN): Mometasone Furoate inhalation powder
c) Code Name/# (ONDC only): SCH 32088
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Section 505(b)(1) of the FD&C Act

10. PHARMACOL. CATEGORY: Anti-inflammatory glucocorticoid for prophylactic maintenance treatment of Asthma

11. DOSAGE FORM: Inhalation Powder (code 800)

12. STRENGTH/POTENCY: 220 mcg metered mometasone furoate/actuation, 200 mcg emitted /actuation

13. ROUTE OF ADMINISTRATION: Inhalation

14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

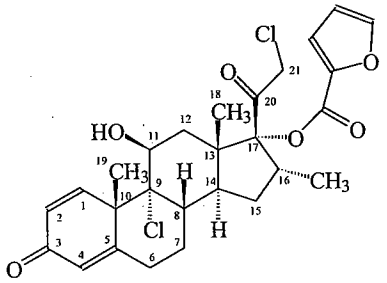
Chemistry Review Data Sheet

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Systematic Name (USAN) : 9 Pregna-1,4-diene-3,20-dione, 9,21-dichloro-17-((2-furanylcarbonyl)oxy)-11-hydroxy-16-methyl-, (11beta, 16alpha)



Mometasone Furoate

Molecular Formula: $C_{27}H_{30}Cl_2O_6$

Molecular Weight: 521.443

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[ ]	Type II	[ ]	[ ]	3	**adequate**	1/22/99 5/26/00 3/19/04	See p. 4 of CR#1 See p. 7 CR#3 See pp. 8, 14 CR#5
[ ]	Type I			3	**adequate**	1/25/99 9/8/99 2/10/00 8/10/00	See p. 86 of CR#1 See p. 66 of CR#2 See p. 43 of CR#3 See p 10 of CR#4
[ ]	Type III			7	**withdrawn**[1]		See p. 87 of CR#1
[ ]	Type III			1	**adequate**	2/4/99 9/2/99 2/3/00 4/11/00 3/1/04 7/30/04	See p. 85 of CR#1 See p. 67 of CR#2 See p. 44 of CR#3 See p. 14 of CR#5 See p. 26 of CR#6

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[	Type III	[	[	3	**adequate**	1/26/99 9/25/00 3/19/04	See p. 85 of CR#1 See p. 67 of CR#2 See p. 44 of CR#3 See p. 34 of CR#4 See p. 14 of CR#5
	Type III			3	**not reviewed**[2]		See p. 86 of CR#1
	Type III			3	**adequate**	2/3/99 2/22/00	See p. 85 of CR#1 See p. 67 of CR#2
	Type III			3	**adequate**	1/26/99 3/10/00 9/28/00	See p. 85 of CR#1 See p. 67 of CR#2 See p. 44 of CR#3 See p. 34 of CR#4
	Type IV			3	**adequate**	1/27/99 9/25/00	See p. 85 of CR#1 See p. 67 of CR#2 See p. 15 of addendum CR#2 See p. 44 of CR#3 See p. 34 of CR#4
	Type IV			3	**adequate**	1/27/99 9/25/00	See p. 85 of CR#1 See p. 67 of CR#2 See p. 44 of CR#3 See p. 35 of CR#4
	Type IV			3	**adequate**	4/13/00 9/25/00	See. p. 45 of CR#3 See p. 35 of CR#4
	Type I			3	**adequate**	10/18/99 6/16/00	See p. 90 of CR#1 See p. 75 of CR#2 See p. 51 of CR#3
	Type III			3	**adequate**	1/28/99 8/31/99 3/30/04	See p. 85 of CR#1 See p. 67 of CR#2 See p. 14 of CR#5
				3	**adequate**	8/31/99	See p. 75 of CR#2 (to support DMF [redacted])
	Type III			3	**withdrawn**	8/31/99 5/2/00	See p. 89 of CR#1 See p. 75 of CR#2 See p. 50 of CR#3 See p. 37 of CR#4
]	Type III	]	]	3	**adequate**	9/8/99 2/2/00 4/26/00 3/31/04	See p. 90 of CR#1 See p. 74 of CR#2 See p. 50 of CR#3 See p. 14 of CR#5

[1]DMF [ ] was withdrawn and applicant not seeking approval [ ]]
(see response to comment 15.c on p. 67 of CR#2).
[2]Schering did not use the [ ] in clinical or stability batches and has deleted this material and the supplier from the vendor list (see response to comment 15.e on p. 68 of CR#2).

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	[redacted]	
IND		[redacted]
IND	46,216	Mometasone Furoate Inhalation Powder
NDA	19-543	Elocon (Mometasone Furoate) Ointment (approved 30-Apr-87)[2]
NDA	19-625	Elocon (Mometasone Furoate) Emulsion, Cream (approved 06-May-87)[2]
NDA	19-796	Elocon (Mometasone Furoate) Lotion (approved 30-Mar-89)[2]
NDA	20-762	Nasonex (Mometasone Furoate)[3] Nasal Spray (approved 01-Oct-97)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	COMMENTS
Biometrics	Not sufficient to establish shelf life based on the stability data with two lots of Kenilworth manufactured product.	3/5/04	See p. 109 of CR#1. See response to comments 13.m and 17.a on pp. 40 and 93 of CR#2, respectively. See p. 64 in CR#3. See p.45 in CR#4. See p. 14 of CR#5 and p. 12 of CR#6.
EER	Withhold recommended by the office of compliance. Indicates validation failure.	3/12/04	**Kenilworth and Union, NJ sites will have a PAI readiness dated of 30-SEP-2004 according to the 29-JUN-2004, amendment.**
Pharm/Tox	2/2/99	Acceptable, 3/23/99	Impurities Consult (DS/DP), see response to comment 3 and note on p. 33 of CR#2.
Biopharm	Not forwarded	Not needed	
LNC	Asmanex® forwarded under IND 46,216 PM sent consult to OPDRA on Asmanex® Twisthaler® again on 01/14/04	Initially Unacceptable **Acceptable**	LNC recommends against Asmanex®. **LNC and OPDRA accepts Asmanex Twisthaler**
Methods Validation	Not forwarded.		Will be forwarded once drug product specifications finalized and updated MV packages submitted by firm. See comment 5 in the attached draft letter.
Clinical	3/22/99 10/19/99	Consults were FYI only for MO	Consult requesting consideration of *in vitro* dose proportionality differences between strengths and flow rate dependency. Follow up to above consult which provides data versus flow rate at constant volume in terms of the actual amount of MF collected.
EA	Firm requests categorical exclusion under 21 CFR 25.31(b).	Not needed.	See p. 111 of CR#1.

Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	COMMENTS
Microbiology	Not forwarded.	Not needed.	See comments on pp. 28, 61 of CR#1.

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-067

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable. *It is requested that the PM forward the comments in the draft letter to the applicant as soon as feasible.*

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

Several agreements are in place for this application. They are listed below.

1. Schering agrees to submit a prior approval supplement containing all pertinent supportive documentation for [ ] of Singapore as a manufacturing site following the final approval of the drug product specifications.
2. Schering also agrees to re-evaluate the [ ] acceptance criteria after one year of commercial experience. See more elaborate comment in the draft letter below.
3. Schering agrees to re-evaluate the specifications for resistance to flow-by pressure drop after one year of commercial production experience.

II. Summary of Chemistry Assessments

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

Drug Substance

The drug substance (DS) mometasone furoate is a light sensitive compound and is used in several approved commercial drug products (ointments, creams and nasal spray). DMF[ ] from [ ] is referenced for [ ] used to prepare the DS. This file was found to be adequate in a review dated 23-APR-2003. Some minor changes in the specifications of the reagents were noted in the latest amendment to the DMF (20-AUG-2003) which was reviewed (19-MAR-2004) and found to be adequate. The final drug substance is manufactured by Schering Plough in Singapore. The previously included DS manufacturing site in Avondale, Ireland has been removed from the application.

Drug Product

The drug product is a device-metered inhalation powder (dry powder inhaler or DPI). The device [ ] containing the formulation (mometasone furoate and anhydrous lactose [ ]. The cap [ ] is sealed to the device [ ] when not in use. Opening of the cap for the device, by turning counter-clockwise, exposes a white colored plastic mouth-piece. The closure of the cap (turning clockwise) loads the next dose into the dosing hole of the dosing plate and advances the counter.

The drug product was previously manufactured in Kenilworth, NJ and Singapore. Drug product quality control operations are also performed at the Union facility in NJ. The applicant has withdrawn Singapore as a second drug product manufacturing site. Differences and inconsistencies were noted in the quality [ ] of the drug product from the Kenilworth and Singapore sites in several earlier reviews. These differences could not be satisfactorily addressed and were approvability issues.

The application originally proposed two strengths of the product [ ] mcg/actuation) but the higher strength has been withdrawn. The 220 mcg strength is proposed to be supplied as 14, 30, 60 and 120 actuation/inhaler versions. The target fills for each are the same regardless of the number of label claim actuations. The label claim number of actuations is controlled by the device lock-out set-point.

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

The drug product is used for oral inhalation of the mometasone furoate in an anhydrous lactose-based formulation, for the maintenance treatment of asthma. The drug product includes components that protect the formulation from moisture [ ] and patients are advised not to exhale into the inhaler. The drug product is currently proposed to be produced in one strength (220 mcg is the metered dose) of mometasone furoate and is labeled for 30, 60, or 120 doses of mometasone furoate at 200mcg/actuation emitted from the mouthpiece. The proposed maximum daily recommended dose is 400 micrograms (2 inhalations). Patients are asked to store the drug product in a dry place at controlled room temperature, [ ] and discard the inhaler 45 days after opening the foil pouch or when dose counter reads "00", whichever comes first. No cleaning instructions are proposed.

C. Basis for Approvability or Not-Approval Recommendation

The adequacy of the sites of manufacture and testing for the drug product and the expiration dating period for the product are the remaining critical issues resulting from this review. A consult had been forwarded by Dr. Peri to biometrics during the CR#5 cycle for evaluating the proposed shelf life of [ ] The biometrics staff was of the opinion that there was insufficient stability data to evaluate the shelf life. Dr. Peri noted that this information would be discussed/forwarded to the applicant in the next (the current) review cycle. As such, see the IR letter request comment on p. 12 below. The GMP problems at the Kenilworth manufacturing site may be the reason why the applicant has not provided updated stability data since 2000.

The Office of Compliance states in their Establishment Status Report that the Kenilworth and Union sites are under *withhold* status for failing validation. The applicant claims that the "PAI readiness date" for the Kenilworth and Union, NJ sites to be 30-SEP-2004. As such, the 29-JUN-2004, amendment was not considered a complete response to the last AE letter of 17-MAY-2004.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D., CMC Reviewer
HFD-570/820

C. CC Block

cc:
Orig. NDA 21-067
HFD-570/Division File
HFD-570/CBertha
HFD-570/RLostritto
HFD-570/LGarcia
HFD-570/SBarnes

R/D Init. by RLostritto:_____

Filename and Location: c:\data\mydocuments\reviews etc\NDA\21067\Review 6\04-06-29.rev.doc

16 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/

Craig Bertha
8/25/04 06:16:28 AM
CHEMIST

Richard Lostritto
8/25/04 04:28:48 PM
CHEMIST

The Agency acknowledges your agreement to do the following:

11. Submit a prior approval supplement containing all pertinent supportive documentation for [ ] of Singapore as a manufacturing site following the final approval of the drug product specifications.

12. Re-evaluate the [ ] acceptance criteria after one year of commercial experience.

13. Re-evaluate the specifications for resistance to flow by pressure drop after one year of commercial production experience.

Prasad Peri
Division of New Drug Chemistry II
Office of New Drug Chemistry

Division of Pulmonary and Allergy Drug Products

We need to ~~inc~~ include these comments in the approval letter.

Table of Contents

Chemistry Review Data Sheet

1. NDA: 21-067

2. REVIEW #: 5

3. REVIEW DATE: May 5, 2004

4. REVIEWER: Prasad Peri, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	Nov. 30, 1998
Chemistry Review # 1 (Dr. Craig Bertha)	Mar. 23, 1999
Addendum to Chemistry Review # 1 (Dr. Craig Bertha)	Aug. 23, 1999
Chemistry Review # 2 (Dr. Craig Bertha)	Dec. 1, 1999
Addendum to Chemistry Review # 2 (Dr. Craig Bertha)	Dec. 8, 1999
Chemistry Review # 3 (Dr. Craig Bertha)	July 18, 2000
Chemistry Review # 4 (Dr. Craig Bertha)	Nov. 29, 2000

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (AZ) Responses to Agency letter dated Dec. 4, 2000	Nov. 14, 2003
Amendment (BC) Individual ⌈ ⌋ data in hard copy and SAS Transport Format	Dec. 3, 2003
Amendment (BC) Corrected Stability data in SAS Transport Format	Dec. 10, 2003
Amendment (BL) Labeling provided	Feb. 14, 2004
Amendment (BL) Updated labeling provided	Apr. 12, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Schering Corporation
Address:	2000 Galloping Hill Road, Kenilworth, NJ 07033
Representative:	Mr. Isidoro Perez, President Worldwide Regulatory Affairs
Telephone:	908 740 4290

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Asmanex® Twisthaler® 220 mcg
b) Non-Proprietary Name (USAN): Mometasone Furoate inhalation powder
c) Code Name/# (ONDC only): SCH 32088
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Section 505(b)(1) of the FD&C Act

10. PHARMACOL. CATEGORY: Anti-inflammatory glucocorticoid for prophylactic maintenance treatment of Asthma

11. DOSAGE FORM: Inhalation Powder (code 800)

12. STRENGTH/POTENCY: 220 µg metered mometasone furoate/actuation, 200 µg emitted /actuation

13. ROUTE OF ADMINISTRATION: Inhalation

14. Rx/OTC DISPENSED: _X__Rx ___OTC

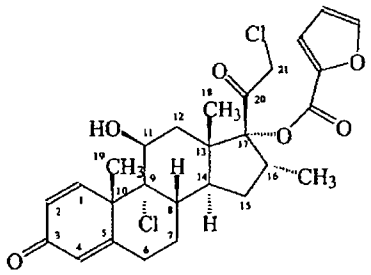
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Systematic Name (USAN) : 9 Pregna-1,4-diene-3,20-dione, 9,21-dichloro-17-((2-furanylcarbonyl)oxy)-11-hydroxy-16-methyl-, (11beta,16alpha)

Chemistry Review Data Sheet



Mometasone Furoate

Molecular Formula: $C_{27}H_{30}Cl_2O_6$

Molecular Weight: 521.443

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
٢	Type II	٢	٢	3	**Adequate**	1/22/99 5/26/00 3/19/04	See p. 4 of CR#1 See p. 7 CR#3 See p 14 CR5
	Type I			3	**adequate**	1/25/99 9/8/99 2/10/00 8/10/00	See p. 86 of CR#1 See p. 66 of CR#2 See p. 43 of CR#3 See p 10 of CR#4
	Type III			7	**withdrawn[1]**		See p. 87 of CR#1
	Type III			1	**Inadequate (multiple changes in specifications of components)**	2/4/99 9/2/99 2/3/00 4/11/00 3/1/04	See p. 85 of CR#1 See p. 67 of CR#2 See p. 44 of CR#3 **See p. 14 of CR#5**
	Type III			3	**adequate**	1/26/99 9/25/00	See p. 85 of CR#1 See p. 67 of CR#2 See p. 44 of CR#3 See p. of CR#4
	Type III			3	**not reviewed[2]**		See p. 86 of CR#1
	Type III			3	**adequate**	2/3/99 2/22/00	See p. 85 of CR#1 See p. 67 of CR#2
	Type III			3	**adequate**	1/26/99 3/10/00 9/28/00	See p. 85 of CR#1 See p. 67 of CR#2 See p. 44 of CR#3 See p. of CR#4
٦	Type IV	٦	٦	3	**adequate**	1/27/99	See p. 85 of CR#1 See p. 67 of CR#2 See p. 15 of addendum CR#2

Chemistry Review Data Sheet

						9/25/00	See p. 44 of CR#3 See p. 34 of CR#4
[	Type IV	[		3	**adequate**	1/27/99 9/25/00	See p. 85 of CR#1 See p. 67 of CR#2 See p. 44 of CR#3 See p. of CR#4
	Type IV			3	**adequate**	4/13/00 9/25/00	See. p. 45 of CR#3 See p. 35 of CR#4
	Type I			3	**adequate**	10/18/99 6/16/00	See p. 90 of CR#1 See p. 75 of CR#2 See p. 51 of CR#3
	Type III			3	**adequate**	1/28/99 8/31/99	See p. 85 of CR#1 See p. 67 of CR#2
				3	**adequate**	8/31/99	See p. 75 of CR#2 (to support DMF [redacted]
	Type III			3	**withdrawn**	8/31/99 5/2/00	See p. 89 of CR#1 See p. 75 of CR#2 See p. 50 of CR#3 See p. of CR#4
]	Type III			3	**adequate**	9/8/99 2/2/00 4/26/00	See p. 90 of CR#1 See p. 74 of CR#2 See p. 50 of CR#3

[1]DMF [ ] was withdrawn and applicant not seeking approval [ ] (see response to comment 15.c on p. 67 of CR#2).

[2]Schering did not use the [ ] in clinical or stability batches and has deleted this material and the supplier from the vendor list (see response to comment 15.e on p. 68 of CR#2).

DMF [redacted] was updated to state the change of ownership and minor modification to an excipient documentation purposes.
DMF [redacted] No revisions since last review.
DMF [redacted] No revisions since last review.
DMF [redacted] was last reviewed by Dr. Bertha. Information was provided in the Application and evaluated in Chemistry Review 3.
DMF [redacted] was last reviewed by Dr. Peri in review dated March 31, 2004.
DMF [redacted] was last reviewed by Dr. Peri in review dated March 30, 2004.
DMF [redacted] was last reviewed by Dr. Peri in review dated March 19, 2004.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	[	
IND		]
IND	46,216	Mometasone Furoate Inhalation Powder
NDA	19-543	Elocon (Mometasone Furoate) Ointment (approved 30-Apr-87)[2]

NDA	19-625	Elocon (Mometasone Furoate) Emulsion, Cream (approved 06-May-87)[2]
NDA	19-796	Elocon (Mometasone Furoate) Lotion (approved 30-Mar-89)[2]
NDA	20-762	Nasonex (Mometasone Furoate)[3] Nasal Spray (approved 01-Oct-97)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not sufficient to establish shelf life based on the stability data with two lots of Kenilworth manufactured product.	3/5/04	See p. 109 of CR#1. See response to comments 13.m and 17.a on pp. 40 and 93 of CR#2, respectively. See p. 64 in CR#3. See p. in CR#4.
EER	Withhold recommended by the office of compliance. Indicates validation failure.	3/12/04	**Kenilworth site not ready for inspection.**
Pharm/Tox	2/2/99	Acceptable, 3/23/99	Impurities Consult (DS/DP), see response to comment 3 and note on p. 33 of CR#2.
Biopharm	Not forwarded	Not needed	
LNC	Asmanex® forwarded under IND 46,216 PM sent consult to OPDRA on Asmanex® Twisthaler® again on 01/14/04	Initially Unacceptable **Acceptable**	LNC recommends against Asmanex®. **LNC and OPDRA accepts Asmanex Twisthaler**
Methods Validation	Not forwarded.		Will be forwarded once drug product specifications finalized and updated MV packages submitted by firm.
Clinical	3/22/99 10/19/99	Consults were FYI only for MO	Consult requesting consideration of *in vitro* dose proportionality differences between strengths and - flow rate dependency. Follow up to above consult which provides - data versus flow rate at constant volume in terms of the actual amount of MF collected.
EA	Firm requests categorical exclusion under 21 CFR 25.31(b).	Not needed.	See p. 111 of CR#1.
Microbiology	Not forwarded.	Not needed.	See comments on pp. 28, 61 of CR#1.

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-067

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is approvable. Refer to deficiencies listed at the end of the review (pages 75-77) for comments to be sent to the applicant.

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

Several agreements are in place for this application. They are listed below.

1. Schering agrees to submit a prior approval supplement containing all pertinent supportive documentation for [ ] of Singapore as a manufacturing site following the final approval of the drug product specifications.
2. Schering also agrees to reevaluate the [ ] acceptance criteria after one year of commercial experience.
3. Schering agrees to re-evaluate the specifications for resistance to flow by pressure drop after one year of commercial production experience.

II. Summary of Chemistry Assessments

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

Drug Substance

1. The drug substance is a well known compound that is already approved in several commercial drug products (ointments, creams and nasal spray).
2. It is a light sensitive compound.
3. DMF [ ] for [ ] the drug substance [ ] was found to be adequate in a review dated April 23, 2003. Some minor changes in the specifications of the reagents are noted in the latest amendment to the DMF (dated Aug. 20, 2003). The DMF was reviewed (review date March 19, 2004) for these changes and found to be adequate.
4. The final drug substance is manufactured by Schering Plough in Singapore. Previously listed Ireland site has been removed for the manufacture of the drug substance.

Drug Product

1. The drug product is a tubular shaped dry powder inhaler (DPI) device [ ] containing the formulation (mometasone furoate and anhydrous lactose [ ]. Once the cap for the device is opened (by twisting anticlockwise) a white colored plastic mouth-piece is exposed which the patient places in their mouth and breathes in to get the medication. The patient closes the cap (twisting the cap clockwise) which triggers the device to meter the next dose into the delivery chamber [ ] The clockwise twisting action of the cap while closing the device also triggers the device counter to count down the number of remaining doses.
2. The drug product was previously manufactured in Kenilworth, NJ and Singapore. Drug product quality control operations are also performed at the Union facility in NJ. The applicant is now withdrawing Singapore as the drug product manufacturing site. **Differences and inconsistencies were noted in the quality [ ] of the drug product from the Kenilworth and Singapore sites in several earlier reviews.** These differences could not be satisfactorily addressed and were the major approval issues.
3. **The Office of Compliance in their Establishment Status Report state that the Kenilworth and Union sites are under withhold status for failing validation. It is not clear when they will be ready for inspection.**
4. The 220 µg strength is proposed to be supplied as 14, 30, 60 and 120 actuation/inhaler versions. The target fills for each are the same regardless of the number of label claim actuations. The label claim number of actuations is controlled by the device lock-out set-point.
5. For the acceptance criteria [ ] Schering accepted the Agency's previous recommendation for the range and mean for Group 1, however for Groups 2, 3, and 4, they propose to re-center them (that is, shift the mean but maintain the same range about the mean). Schering proposes to test 6 devices and take the average values of the stage groups.
6. For emitted dose content uniformity (DCU) Schering proposes to test ~devices for stage I and ~ additional for stage II. If any actuation from a device is out of the acceptable range, they plan to test 3 additional doses from the same device which have to meet the acceptance criteria. Since there are several one time out of specification results for the DCU, I am proposing a cap on the actual value beyond which a batch should be rejected [ ]
7. A consult has been forwarded to biometrics for evaluating the proposed shelf life [ ] The biometrics staff recommended that there is insufficient stability data to evaluate the shelf life. Hence their recommendation is that data is not sufficient for estimating the shelf life of the product. This comment will be discussed/forwarded to the applicant in the next review cycle.
8. Several updates have been provided to analytical methods used for release and stability testing on the drug product. Schering introduced tighter controls on temperature and humidity requirements for test [ ]
9. Several labeling comments have been proposed and will be forwarded to the applicant.

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

The patients are advised not to blow into the inhaler. The drug product is to be inhaled orally. The applicant does not describe the use of a spacer between the mouthpiece of the device and the patient's mouth. The drug product is produced in one strength of mometasone furoate and is labeled for 30, 60, or 120 doses of mometasone furoate at 200µg/actuation through the device. The proposed maximum daily recommended dose is 400 micrograms (2 inhalations). Patients are asked to store the drug product in a dry place at controlled room temperature, [redacted] and discard the inhaler 45 days after opening the foil pouch or when dose counter reads "00", whichever comes first. No cleaning instructions are provided

C. Basis for Approvability or Not-Approval Recommendation

Several deficiencies are listed at the end of the review (page 74 onwards). These are clarifications and certain agreements to acceptance criteria for dose content uniformity that the applicant has to provide.

It is also noted that the office of compliance could not complete their inspection of the site due to the site not being ready for inspection.

Hence based on the **firm's lack of readiness for the Preapproval Inspection (PAI)** and several agreements needed from the applicant regarding acceptance criteria, the application is approvable from a CMC standpoint.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Prasad Peri/May 4, 2004
Rik Lostritto/ May 4, 2004
Lorie Garcia/ May 4, 2004

C. CC Block

70 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/

Prasad Peri
5/5/04 05:20:21 PM
CHEMIST

Richard Lostritto
5/6/04 02:54:53 PM
CHEMIST

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

NDA #: 21-067 **CHEM. REVIEW #**4 **REVIEW DATE:** 11/29/00

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	11/30/98	12/1/98	12/5/98
BZ (replacement volumes)	1/28/99	1/29/99	1/29/99
BC	2/5/99	2/8/99	2/9/99
BC (devices and parts)	2/9/99	2/10/99	2/12/99
BC (marked devices)	2/26/99	3/1/99	3/4/99
BZ (DS impurities spec)	3/9/99	3/10/99	3/10/99
BC	3/30/99	3/31/99	3/31/99
AC	6/30/99	6/30/99	7/6/99
BC (stability update)	8/23/99	8/24/99	9/1/99
BC (marked devices)	9/17/99	9/20/99	9/21/99
BC (response com 13.m)	10/1/99	10/4/99	10/12/99
AZ (10/1/99 AE response)	12/1/99	12/2/99	12/2/99
BC (response com 11.c,d)	2/17/00	2/18/00	2/22/00
BC (response com 6)	5/10/00	5/15/00	5/16/00
AZ (3/14/00 AE response)**	6/2/00	6/5/00	6/9/00
AZ (8/10/00 DR response)*	10/17/00	10/18/00	10/23/00
BC (stability update)*	10/18/00	10/20/00	10/24/00

*Subject of this review. **Only labels and labeling reviewed from this amendment in CR#4.

NAME & ADDRESS OF APPLICANT: Schering Corporation
Galloping Hill Road
Kenilworth, N.J. 07033

DRUG PRODUCT NAME:

Proprietary:	Asmanex® Twisthaler® 220 mcg
Nonproprietary:	mometasone furoate inhalation powder
USAN:	mometasone furoate
Code Name/#:	SCH 32088
Chem.Type/Ther.Class:	3S

PHARMACOL. CATEGORY/INDICATION: Anti-inflammatory glucocorticoid for the prophylactic maintenance treatment of asthma

DOSAGE FORM: inhalation powder

DOSE: 200 mcg two or four times daily

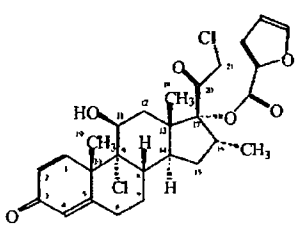
STRENGTH: 220 mcg metered mometasone furoate/actuation (200 mcg emitted/act, formulation emitted/act); See remark 4&13 regarding # of inhalations/unit on p. 7&9, respectively

ROUTE OF ADMINISTRATION: inhalation

DISPENSED: _X_ Rx ___ OTC

SPECIAL PRODUCTS: ___ Yes _X_ No

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



9,21-Dichloro-17-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methylpregna-1,4-diene-3,20-dione

Molecular Formula: $C_{27}H_{30}Cl_2O_6$
Molecular Weight: 521.443

Appears This Way
On Original

SUPPORTING DOCUMENTS:

Drug Master Files:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1 and 2 review
[	[	[	adequate	1/22/99 5/26/00	See p. 4 of CR#1 See p. 7 of CR#3
			adequate	1/25/99 9/8/99 2/10/00 8/10/00	See p. 86 of CR#1 See p. 66 of CR#2 See p. 43 of CR#3 See p. 10 of CR#4
			withdrawn[1]		See p. 87 of CR#1
			adequate	2/4/99 9/2/99 2/3/00 4/11/00	See p. 85 of CR#1 See p. 67 of CR#2 See p. 44 of CR#3
			adequate	1/26/99 9/25/00	See p. 85 of CR#1 See p. 67 of CR#2 See p. 44 of CR#3 See p. 34 of CR#4
			not reviewed[2]		See p. 86 of CR#1
			adequate	2/3/99 2/22/00	See p. 85 of CR#1 See p. 67 of CR#2
			adequate	1/26/99 3/10/00 9/28/00	See p. 85 of CR#1 See p. 67 of CR#2 See p. 44 of CR#3 See p. 34 of CR#4
			adequate	1/27/99 9/25/00	See p. 85 of CR#1 See p. 67 of CR#2 See p. 15 of addendum CR#2 See p. 44 of CR#3 See p. 34 of CR#4
			adequate	1/27/99 9/25/00	See p. 85 of CR#1 See p. 67 of CR#2 See p. 44 of CR#3 See p. 34 of CR#4
			adequate	4/13/00 9/25/00	See. p. 45 of CR#3 See p. 35 of CR#4
			adequate	10/18/99 6/16/00	See p. 90 of CR#1 See p. 75 of CR#2 See p. 51 of CR#3
			adequate	1/28/99 8/31/99	See p. 85 of CR#1 See p. 67 of CR#2
			adequate	8/31/99	See p. 75 of CR#2 (to support DMF [redacted]
			withdrawn	 8/31/99 5/2/00	See p. 89 of CR#1 See p. 75 of CR#2 See p. 50 of CR#3 See p. 37 of CR#4
]	]	]	adequate	9/8/99 2/2/00 4/26/00	See p. 90 of CR#1 See p. 74 of CR#2 See p. 50 of CR#3

[1]DMF [ ] was withdrawn and applicant not seeking approval [ ] (see response to comment 15.c on p. 67 of CR#2).

[2]Schering did not use [ ] in clinical or stability batches and has deleted this material and the supplier from the vendor list (see response to comment 15.e on p. 68 of CR#2).

RELATED DOCUMENTS:[1]

IND [ ]

IND [ ]
IND 46,216 Mometasone Furoate Inhalation Powder
NDA 19-543 Elocon (Mometasone Furoate) Ointment (approved 30-Apr-87)[2]
NDA 19-625 Elocon (Mometasone Furoate) Emulsion, Cream (approved 06-May-87)[2]
NDA 19-796 Elocon (Mometasone Furoate) Lotion (approved 30-Mar-89)[2]
NDA 20-762 Nasonex (Mometasone Furoate)[3] Nasal Spray (approved 01-Oct-97)

[1]All Schering products. [2]These products are for topical dermatological application; [3]Monohydrate form of DS.

CONSULTS:

Consult	Date Forwarded	Status	Comments
EER	2/2/99	4/18/00	Acceptable OC recommendation, however Kenilworth, NJ site still listed as OAI alert.
Microbiology	Not forwarded.	Not needed.	See comments on pp. 28, 61 of CR#1.
Biometrics (Stability)	11/8/00	Pending	See p. 109 of CR#1. See response to comments 13.m and 17.a on pp. 40 and 93 of CR#2, respectively. See p. 64 in CR#3. See p. 45 in CR#4.
Pharmacology	2/2/99	Acceptable, 3/23/99	Impurities Consult (DS/DP), see response to comment 3 and note on p. 33 of CR#2.
Methods Validation	Not forwarded.		Will be forwarded once drug product specifications finalized and updated MV packages submitted by firm.
Environmental Assessment	Firm requests categorical exclusion under 21 CFR 25.31(b).	Not needed.	See p. 111 of CR#1.
Clinical	3/22/99 10/19/99	Consults were FYI only for MO	Consult requesting consideration of *in vitro* dose proportionality differences between strengths and — flow rate dependency. Follow up to above consult which provides — data versus flow rate at constant volume in terms of the actual amount of MF collected.
Labeling & Nomenclature	Asmanex® forwarded under IND 46,216 PM sent consult to OPDRA on Asmanex® Twisthaler® 10/00	Unacceptable Pending	LNC recommends against Asmanex®.

REMARKS/COMMENTS: See review notes.

CONCLUSIONS & RECOMMENDATIONS: In terms of Chemistry, Manufacturing and Controls information, the application is **approvable (AE) pending a satisfactory decision regarding the EER, the biometrics consult, the OPDRA consult regarding the trademark, and resolution by the applicant of the deficiencies in the attached draft letter. The comments and commitments contained in the attached letter should also be communicated to the applicant.**

cc:
Orig. NDA 21-067
HFD-570/Division File
HFD-570/CBertha/11/29/00
HFD-570/DHilfiker
HFD-570/GPoochikian
HFD-570/LGilbert-McClain
R/D Init. by GPoochikian:_____
filename: 00-10-18.rev.doc

_____
Craig M. Bertha, Ph.D.
Review Chemist

82 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Hilfiker

JUL 26 2000

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

NDA #: 21-067	CHEM. REVIEW #3	REVIEW DATE: 7/18/00	
SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	11/30/98	12/1/98	12/5/98
BZ (replacement volumes)	1/28/99	1/29/99	1/29/99
BC	2/5/99	2/8/99	2/9/99
BC (devices and parts)	2/9/99	2/10/99	2/12/99
BC (marked devices)	2/26/99	3/1/99	3/4/99
BZ (DS impurities spec)	3/9/99	3/10/99	3/10/99
BC	3/30/99	3/31/99	3/31/99
AC	6/30/99	6/30/99	7/6/99
BC (stability update)	8/23/99	8/24/99	9/1/99
BC (marked devices)	9/17/99	9/20/99	9/21/99
BC (response com 13.m)	10/1/99	10/4/99	10/12/99
AZ (10/1/99 AE response)	12/1/99	12/2/99	12/2/99
BC (response com 11.c,d)*	2/17/00	2/18/00	2/22/00
BC (response com 6)*	5/11/00	5/12/00	5/16/00
AZ (3/14/00 AE response)*	6/2/00	6/5/00	6/9/00

*Subject of this review.

NAME & ADDRESS OF APPLICANT: Schering Corporation
Galloping Hill Road
Kenilworth, N.J. 07033

DRUG PRODUCT NAME:

Proprietary:	Asmanex® Twisthaler® 220 mcg
Nonproprietary:	mometasone furoate inhalation powder
USAN:	mometasone furoate
Code Name/#:	SCH 32088
Chem.Type/Ther.Class:	3S

PHARMACOL. CATEGORY/INDICATION: Anti-inflammatory glucocorticoid for the prophylactic maintenance treatment of asthma

DOSAGE FORM: inhalation powder

DOSE: 200 mcg two or four times daily

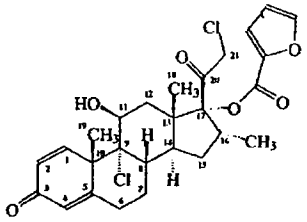
STRENGTH: 220 mcg metered mometasone furoate/actuation (200 mcg emitted/act, formulation emitted/act); See remark 4&13 regarding # of inhalations/unit on p. 5&7, respectively

ROUTE OF ADMINISTRATION: inhalation

DISPENSED: _X_ Rx ___ OTC

SPECIAL PRODUCTS: ___ Yes _X_ No

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



Mometasone Furoate

9,21-Dichloro-17-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methylpregna-1,4-diene-3,20-dione

Molecular Formula: $C_{27}H_{30}Cl_2O_6$
Molecular Weight: 521.443

SUPPORTING DOCUMENTS:

Drug Master Files:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1 and 2 review
[redacted]			adequate	1/22/99	See p. 4 of CR#1 See p. of CR#3
			inadequate	1/25/99 9/8/99 2/10/00	See p. 86 of CR#1 See p. 66of CR#2 See p. 43 of CR#3
			withdrawn[1]		See p. 87 of CR#1
			adequate	2/4/99 9/2/99 2/3/00 4/11/00	See p. 85 of CR#1 See p. 67of CR#2 See p. 44 of CR#3
			inadequate	1/26/99	See p. 85 of CR#1 See p. 67of CR#2 See p. 44 of CR#3
			not reviewed[2]		See p. 86 of CR#1
			adequate	2/3/99 2/22/00	See p. 85 of CR#1 See p. 67of CR#2 See p. of CR#3
			inadequate	1/26/99 3/10/00	See p. 85 of CR#1 See p. 67of CR#2 See p. 44 of CR#3
			inadequate	1/27/99	See p. 85 of CR#1 See p. 67of CR#2 See p. 15 of addendum CR#2 See p. 44 of CR#3
			inadequate	1/27/99	See p. 85 of CR#1 See p. 67of CR#2 See p. 44 of CR#3
			inadequate	4/13/00	See. p. 45 of CR#3
			adequate	10/18/99 6/16/00	See p. 90 of CR#1 See p. 75of CR#2 See p. 51 of CR#3
			adequate	1/28/99 8/31/99	See p. 85 of CR#1 See p. 67of CR#2
			adequate	8/31/99	See p. 75of CR#2 (to support DMF [redacted]
			inadequate	 8/31/99 5/2/00	See p. 89 of CR#1 See p. 75 of CR#2 See p. 50 of CR#3
			adequate	9/8/99 2/2/00 4/26/00	See p. 90 of CR#1 See p. 74of CR#2 See p. 50 of CR#3

[1]DMF was withdrawn and applicant not seeking approval (see response to comment 15.c on p. 67 of CR#2).

[2]Schering did not use in clinical or stability batches and has deleted this material and the supplier from the vendor list (see response to comment 15.e on p. 68 of CR#2).

RELATED DOCUMENTS:[1]

IND [redacted]
IND [redacted]
IND 46,216 Mometasone Furoate Inhalation Powder
NDA 19-543 Elocon (Mometasone Furoate) Ointment (approved 30-Apr-87)[2]
NDA 19-625 Elocon (Mometasone Furoate) Emulsion, Cream (approved 06-May-87)[2]
NDA 19-796 Elocon (Mometasone Furoate) Lotion (approved 30-Mar-89)[2]
NDA 20-762 Nasonex (Mometasone Furoate)[3] Nasal Spray (approved 01-Oct-97)

[1]All Schering products. [2]These products are for topical dermatological application; [3]Monohydrate form of DS.

CONSULTS:

Consult	Date Forwarded	Status	Comments
EER	2/2/99	4/18/00	Acceptable OC recommendation
Microbiology	Not forwarded.	Not needed.	See comments on pp. 28, 61 of CR#1.
Biometrics (Stability)	Not forwarded.		See p. 109 of CR#1. See response to comments 13.m and 17.a on pp. 40 and 93 of CR#2, respectively. See p. 64 in CR#3.
Pharmacology	2/2/99	Final, 3/23/99	Impurities Consult (DS/DP), see response to comment 3 and note on p. 33 of CR#2.
Methods Validation	Not forwarded.		Will be forwarded once updated MV packages submitted by firm.
Environmental Assessment	Firm requests categorical exclusion under 21 CFR 25.31(b).	Not needed.	See p. 111 of CR#1.
Clinical	3/22/99 10/19/99	Consults were FYI only for MO	Consult requesting consideration of *in vitro* dose proportionality differences between strengths and flow rate dependency. Follow up to above consult which provides data versus flow rate at constant volume in terms of the actual amount of MF collected.
Labeling & Nomenclature	Asmanex® forwarded under IND 46,216 Requested PM to send consult on Twisthaler® 9/99	Final Pending	LNC recommends against Asmanex®

REMARKS/COMMENTS: See review notes.

CONCLUSIONS & RECOMMENDATIONS: In terms of Chemistry, Manufacturing and Controls information, the application is considered **not approvable (NA).** The deficiency comments in the attached letter should be forwarded to the applicant.

cc:
Orig. NDA 21-067
HFD-570/Division File
HFD-570/CBertha/7/18/00
HFD-570/DHilfiker
HFD-570/GPoochikian
HFD-570/LGilbert-McClain
R/D Init. by GPoochikian: 7/24/00
filename: 00-06-02.rev.doc

Craig M. Bertha, Ph.D.
Review Chemist

89 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

Hilfiker

DEC 13 1999

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

NDA #: 21-067 **ADDENDUM TO CHEM. REVIEW #2** **REVIEW DATE:** 12/8/99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	11/30/98	12/1/98	12/5/98
BZ (replacement volumes)	1/28/99	1/29/99	1/29/99
BC	2/5/99	2/8/99	2/9/99
BC (devices and parts)	2/9/99	2/10/99	2/12/99
BC (marked devices)	2/26/99	3/1/99	3/4/99
BZ (DS impurities spec)	3/9/99	3/10/99	3/10/99
BC	3/30/99	3/31/99	3/31/99
AC	6/30/99	6/30/99	7/6/99
BC (stability update)	8/23/99	8/24/99	9/1/99
BC (marked devices)	9/17/99	9/20/99	9/21/99
BC (comment 13.m rev.)	10/1/99	10/4/99	10/12/99
AZ* (AE letter response)	12/1/99	12/2/99	12/2/99

*Subject of this review.

NAME & ADDRESS OF APPLICANT: Schering Corporation
Galloping Hill Road
Kenilworth, N.J.
07033

DRUG PRODUCT NAME:

Proprietary:	Asmanex® Twisthaler® 220 mcg
Nonproprietary:	mometasone furoate inhalation powder
USAN:	mometasone furoate
Code Name/#:	SCH 32088
Chem.Type/Ther.Class:	3S

PHARMACOL. CATEGORY/INDICATION: Anti-inflammatory glucocorticoid for the prophylactic maintenance treatment of asthma

DOSAGE FORM: inhalation powder

DOSE: 200 mcg two or four times daily

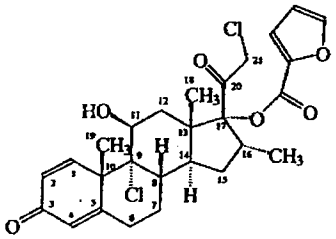
STRENGTH: 220 mcg metered mometasone furoate/actuation (200 mcg emitted/[ ] mg formulation emitted/act); See remark 5 regarding # of inhalations/unit on p. 4 and remark 13 regarding dropping the [ ] strength on p. 6.

ROUTE OF ADMINISTRATION: inhalation

DISPENSED: _X_ Rx ___ OTC

SPECIAL PRODUCTS: ___ Yes _X_ No

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



Mometasone Furoate

9,21-Dichloro-17-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methylpregna-1,4-diene-3,20-dione

Molecular Formula: $C_{27}H_{30}Cl_2O_6$
Molecular Weight: 521.443

SUPPORTING DOCUMENTS:

Drug Master Files:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1 and 2 review
[redacted]			adequate	1/22/99	See p. 4 of CR#1
			inadequate inadequate	1/25/99 9/8/99	See p. 86 of CR#1 See p. 66of CR#2
			withdrawn[1]		See p. 87 of CR#1
			inadequate inadequate	2/4/99 9/2/99	See p. 85 of CR#1 See p. 67of CR#2
			inadequate	1/26/99	See p. 85 of CR#1 See p. 67of CR#2
			not reviewed[2]		See p. 86 of CR#1
			inadequate	2/3/99	See p. 85 of CR#1 See p. 67of CR#2
			inadequate	1/26/99	See p. 85 of CR#1 See p. 67of CR#2
			inadequate	1/27/99	See p. 85 of CR#1 See p. 67of CR#2 See p. 15 of addendum CR#2
			inadequate	1/27/99	See p. 85 of CR#1 See p. 67of CR#2
			inadequate	10/18/99	See p. 90 of CR#1 See p. 75of CR#2
			inadequate adequate	1/28/99 8/31/99	See p. 85 of CR#1 See p. 67of CR#2
			adequate	8/31/99	See p. 75of CR#2 (to support DMF [redacted])
			inadequate inadequate	8/31/99	See p. 89 of CR#1 See p. 75 of CR#2
			inadequate inadequate	9/8/99	See p. 90 of CR#1 See p. 74of CR#2

[1]DMF [redacted] was withdrawn and applicant not seeking approval [redacted] (see response to comment 15.c on p. 67 of CR#2).

[2]Schering did not use [redacted] in clinical or stability batches and has deleted this material and the supplier from the vendor list (see response to comment 15.e on p. 68 of CR#2).

RELATED DOCUMENTS:[1]

IND [redacted]
IND [redacted]
IND 46,216 Mometasone Furoate Inhalation Powder
NDA 19-543 Elocon (Mometasone Furoate) Ointment (approved 30-Apr-87)[2]
NDA 19-625 Elocon (Mometasone Furoate) Emulsion, Cream (approved 06-May-87)[2]
NDA 19-796 Elocon (Mometasone Furoate) Lotion (approved 30-Mar-89)[2]
NDA 20-762 Nasonex (Mometasone Furoate)[3] Nasal Spray (approved 01-Oct-97)

[1]All Schering products. [2]These products are for topical dermatological application; [3]Monohydrate form of drug substance.

CONSULTS:

Consult	Date Forwarded	Status	Comments
EER	2/2/99	Pending	
Microbiology	Not forwarded.	Not needed.	See comments on pp. 28, 61 of CR#1.
Biometrics (Stability)	Not forwarded.		See p. 109 of CR#1. See response to comments 13.m and 17.a on pp. 40 and 93 of CR#2, respectively.
Pharmacology	2/2/99	Final, 3/23/99	Impurities Consult (DS/DP), see response to comment 3 and note on p. 33 of CR#2.
Methods Validation	Not forwarded.		Specifications and methods should be revised prior to analysis by Agency labs.
Environmental Assessment	Firm requests categorical exclusion under 21 CFR 25.31(b).	Not needed.	See p. 111 of CR#1.
Clinical	3/22/99 10/19/99	Pending Pending	Consult requesting consideration of *in vitro* dose proportionality differences between strengths and ~ flow rate dependency. Follow up to above consult which provides ~ data versus flow rate at constant volume in terms of the actual amount of MF collected.
Labeling & Nomenclature	Asmanex® forwarded under IND 46,216 Requested PM to send consult on Twisthaler® 9/99	Final Pending	LNC recommends against Asmanex®

REMARKS/COMMENTS: See review notes.

CONCLUSIONS & RECOMMENDATIONS: In terms of Chemistry, Manufacturing and Controls information, the application is considered **not approvable.** The deficiency comments in the attached letter should be forwarded to the applicant. Note that these comments supercede those included in the draft letter of CR#2.

cc:
Orig. NDA 21-067
HFD-570/Division File
HFD-570/CBertha/12/8/99
HFD-570/DHilfiker
HFD-570/GPoochikian
HFD-570/DO'Hearn
R/D Init. by GPoochikian: 12/13/99
filename: 99-12-01.rev.doc

Craig M. Bertha, Ph.D.
Review Chemist

Dunn

DEC - 6 1999

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

NDA #: 21-067	CHEM. REVIEW #2	REVIEW DATE: 12/1/99	
SUBMISSION TYPE	**DOCUMENT DATE**	**CDER DATE**	**ASSIGNED DATE**
ORIGINAL	11/30/98	12/1/98	12/5/98
BZ (replacement volumes)	1/28/99	1/29/99	1/29/99
BC	2/5/99	2/8/99	2/9/99
BC (devices and parts)	2/9/99	2/10/99	2/12/99
BC (marked devices)	2/26/99	3/1/99	3/4/99
BZ (DS impurities spec)	3/9/99	3/10/99	3/10/99
BC	3/30/99	3/31/99	3/31/99
AC*	6/30/99	6/30/99	7/6/99
BC* (stability update)	8/23/99	8/24/99	9/1/99
BC* (marked devices)	9/17/99	9/20/99	9/21/99
BC* (comment 13.m rev.)	10/1/99	10/4/99	10/12/99

*Subjects of this review.

NAME & ADDRESS OF APPLICANT: Schering Corporation
Galloping Hill Road
Kenilworth, N.J.
07033

DRUG PRODUCT NAME:

Proprietary:	Asmanex® Twisthaler® 220 mcg o. [ ]
Nonproprietary:	mometasone furoate inhalation powder
USAN:	mometasone furoate
Code Name/#:	SCH 32088
Chem.Type/Ther.Class:	3S

PHARMACOL. CATEGORY/INDICATION: Anti-inflammatory glucocorticoid for the prophylactic maintenance treatment of asthma

DOSAGE FORM: inhalation powder

DOSE: 200 mcg once or twice daily or 400 mcg once daily

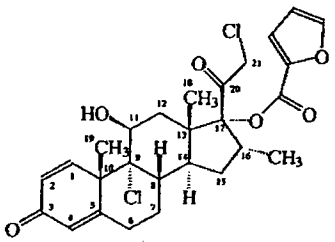
STRENGTHS: 220 mcg metered mometasone furoate/actuation (200 mcg emitted/act, formulation/act); metered/act (400 mcg emitted/act, formulation/act).
See remark 5 regarding # of inhalations/unit on p. 4.

ROUTE OF ADMINISTRATION: inhalation

DISPENSED: _X_ Rx ___ OTC

SPECIAL PRODUCTS: ___ Yes _X_ No

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



Mometasone Furoate

9,21-Dichloro-17-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methylpregna-1,4-diene-3,20-dione

Molecular Formula: $C_{27}H_{30}Cl_2O_6$
Molecular Weight: 521.443

SUPPORTING DOCUMENTS:

Drug Master Files:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1 and 2 review
[	[	[	adequate	1/22/99	See p. 4 of CR#1
–	–	–	inadequate inadequate	1/25/99 9/8/99	See p. 86 of CR#1 See p. 66 of CR#2
–	–	–	withdrawn[1]		See p. 87 of CR#1
–	–	–	inadequate inadequate	2/4/99 9/2/99	See p. 85 of CR#1 See p. 67 of CR#2
–	–	–	inadequate	1/26/99	See p. 85 of CR#1 See p. 67 of CR#2
–	–	–	not reviewed[2]		See p. 86 of CR#1
–	–	–	inadequate	2/3/99	See p. 85 of CR#1 See p. 67 of CR#2
–	–	–	inadequate	1/26/99	See p. 85 of CR#1 See p. 67 of CR#2
–	–	–	inadequate	1/27/99	See p. 85 of CR#1 See p. 67 of CR#2
–	–	–	inadequate	1/27/99	See p. 85 of CR#1 See p. 67 of CR#2
–	–	–	inadequate	10/18/99	See p. 90 of CR#1 See p. 75 of CR#2
–	–	–	inadequate adequate	1/28/99 8/31/99	See p. 85 of CR#1 See p. 67 of CR#2
–	–	–	adequate	8/31/99	See p. 75 of CR#2 (to support DMF [redacted])
–	–	–	inadequate inadequate	8/31/99	See p. 89 of CR#1 See p. 75 of CR#2
]	]	]	inadequate inadequate	9/8/99	See p. 90 of CR#1 See p. 74 of CR#2

[1]DMF [ ] was withdrawn and applicant not seeking approval [ ] (see response to comment 15.c on p. 67 of CR#2).

[2]Schering did not use [ ] in clinical or stability batches and has deleted this material and the supplier from the vendor list (see response to comment 15.e).

RELATED DOCUMENTS:

IND [

IND]

IND 46,216 Mometasone Furoate Inhalation Powder (Schering)

NDA 19-543 Elocon (Mometasone Furoate) Ointment (Schering, approved 30-Apr-87)[1]

NDA 19-625 Elocon (Mometasone Furoate) Emulsion, Cream (Schering, approved 06-May-87)[1]

NDA 19-796 Elocon (Mometasone Furoate) Lotion (Schering, approved 30-Mar-89)[1]

NDA 20-762 Nasonex (Mometasone Furoate)[2] Nasal Spray (Schering, approved 01-Oct-97)

[1]These products are for topical dermatological application; [2]Monohydrate form of drug substance.

CONSULTS:

Consult	Date Forwarded	Status	Comments
EER	2/2/99	Pending	
Microbiology	Not forwarded.	Not needed.	See comments on pp. 28, 61of CR#1.
Biometrics (Stability)	Not forwarded.		See p. 109 of CR#1. See response to comments 13.m and 17.a below.
Pharmacology	2/2/99	Final, 3/23/99	Impurities Consult (DS/DP), see response to comment 3 and note on p. 33 of CR#2
Methods Validation	Not forwarded.		Specifications and methods should be revised prior to analysis by Agency labs.
Environmental Assessment	Firm requests categorical exclusion under 21 CFR 25.31(b).	Not needed.	See p. 111 of CR#1.
Clinical	3/22/99 10/19/99	Pending Pending	Consult requesting consideration of *in vitro* dose proportionality differences between strengths and low rate dependency. Follow up to above consult which provides data versus flow rate at constant volume in terms of the actual amount of MF collected.
Labeling & Nomenclature	Asmanex® forwarded under IND 46,216 Requested PM to send consult on Twisthaler® 9/99	Final Pending	LNC recommends against Asmanex®

REMARKS/COMMENTS: See review notes.

CONCLUSIONS & RECOMMENDATIONS: In terms of Chemistry, Manufacturing and Controls information, the application is considered **not approvable**. The deficiency comments in the attached letter should be forwarded to the applicant.

cc:
Orig. NDA 21-067
HFD-570/Division File
HFD-570/CBertha/12/1/99
HFD-570/KDunn
HFD-570/GPoochikian
HFD-570/DO'Hearn
R/D Init. by GPoochikian: 12/6/99
filename: 99-10-01.rev.doc

Craig M. Bertha, Ph.D.
Review Chemist

174 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Dunn

AUG 13 1999

DIVISION OF PULMONARY DRUG PRODUCTS
Addendum-Review of Chemistry, Manufacturing, and Controls

NDA #: 21-067 **ADENDUM CHEM. REVIEW #1** **REVIEW DATE:** 8/12/99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	11/30/98	12/1/98	12/5/98
BZ (replacement volumes)	1/28/99	1/29/99	1/29/99
BC	2/5/99	2/8/99	2/9/99
BC (devices and parts)	2/9/99	2/10/99	2/12/99
BC (marked devices)	2/26/99	3/1/99	3/4/99
BZ (DS impurities spec)	3/9/99	3/10/99	3/10/99
BC*	3/30/99	3/31/99	3/31/99

*Subject of this addendum review.

NAME & ADDRESS OF APPLICANT: Schering Corporation
Galloping Hill Road
Kenilworth, N.J.
07033

DRUG PRODUCT NAME:

Proprietary:	None proposed at this time.
Nonproprietary:	mometasone furoate inhalation powder
USAN:	mometasone furoate
Code Name/#:	SCH 32088
Chem.Type/Ther.Class:	3S

PHARMACOL. CATEGORY/INDICATION: Anti-inflammatory glucocorticoid for the prophylactic maintenance treatment of asthma

DOSAGE FORM: inhalation powder

DOSE: 200 mcg once or twice daily or 400 mcg once daily

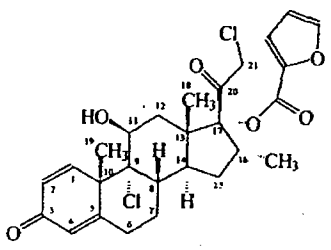
STRENGTHS: 220 mcg metered mometasone furoate/actuation (200 mcg emitted/act), 60 and 30 act (trade), 30 act (sample); metered/act (400 mcg emitted/act), 60 and 30 act (trade), 14 act (sample)

ROUTE OF ADMINISTRATION: inhalation

DISPENSED: _X_ Rx ___ OTC

SPECIAL PRODUCTS: ___ Yes _X_ No

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



Mometasone Furoate

9,21-Dichloro-17-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methylpregna-1,4-diene-3,20-dione

Molecular Formula: $C_{27}H_{30}Cl_2O_6$ Molecular Weight: 521.443

SUPPORTING DOCUMENTS:

Drug Master Files:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1 review
[			adequate	1/22/99	See p. 4 of CR#1
			inadequate	1/25/99	See p. 86 of CR#1
			not reviewed[1]		See p. 87 of CR#1
			inadequate	2/4/99	See p. 85 of CR#1
			inadequate	1/26/99	See p. 85 of CR#1
			not reviewed[2]		See p. 86 of CR#1
			inadequate	2/3/99	See p. 85 of CR#1
			inadequate	1/26/99	See p. 85 of CR#1
			inadequate	1/27/99	See p. 85 of CR#1
			inadequate	1/27/99	See p. 85 of CR#1
			inadequate		See p. 90 of CR#1
			inadequate	1/28/99	See p. 85 of CR#1
			Inadequate		See p. 89 of CR#1
			inadequate		See p. 90 of CR#1

[1]It does not appear that the [ ] has been used for the clinical or primary stability batches of drug product. DMF [ ] review will not take place until clarification and comparative data are provided.

[2]It is not clear why the DMF LOA was provided from [ ] DMF [ ] for, what Schering terms, the [ ] which is listed in the letter from [ ] as [ ] DMF [ ] did not indicate the use of this for any of the parts. Clarification will be sought and no review of this DMF will be done at this time.

RELATED DOCUMENTS:

IND [
IND]
IND 46,216 Mometasone Furoate Inhalation Powder (Schering)
NDA 19-543 Elocon (Mometasone Furoate) Ointment (Schering, approved 30-Apr-87)[1]
NDA 19-625 Elocon (Mometasone Furoate) Emulsion, Cream (Schering, approved 06-May-87)[1]
NDA 19-796 Elocon (Mometasone Furoate) Lotion (Schering, approved 30-Mar-89)[1]
NDA 20-762 Nasonex (Mometasone Furoate)[2] Nasal Spray (Schering, approved 01-Oct-97)

[1]These products are for topical application; [2]Monohydrate form of drug substance.

CONSULTS:

Consult	Date Forwarded	Status	Comments
EER	2/2/99	Pending	
Microbiology	Not forwarded.		See comments on pp. 28, 61of CR#1.
Biometrics (Stability)	Not forwarded.		Specifications should be modified pending analysis see p. 109 of CR#1.
Pharmacology	2/2/99	Pending	Impurities Consult (DS/DP)
Methods Validation	Not forwarded.		Specifications and methods should be revised prior to analysis by Agency labs.
Environmental Assessment	Firm requests categorical exclusion under 21 CFR 25.31(b).	Not needed.	See p. 111 of CR#1.
Clinical	3/22/99	Pending	Consult requesting consideration of *in vitro* dose proportionality differences between strengths and flow rate dependency.
Labeling & Nomenclature	Not requested.		No trademark proposed to date.

REMARKS/COMMENTS: See review notes.

CONCLUSIONS & RECOMMENDATIONS: In terms of Chemistry, Manufacturing and Controls information, the application remains **not approvable**, as concluded in chemistry review (CR) #1 dated 4/9/99. In addition to the deficiency comments resulting from CR#1 forwarded to the applicant in the 5/4/99 Agency letter, the deficiency comments in the attached draft letter to this addendum review should be forwarded to the applicant. A facsimile of these latter comments may be forwarded prior to the Agency correspondence.

cc:
Orig. NDA 21-067
HFD-570/Division File
HFD-570/CBertha/8/12/99
HFD-570/KDunn
HFD-570/GPoochikian
HFD-570/DO'Hearn
R/D Init. by GPoochikian: 8/13/99
filename: 99-03-30.rev.doc

Craig M. Bertha, Ph.D.
Review Chemist

5 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Toyer

APR - 9 1999

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-067 **CHEM. REVIEW #** 1 **REVIEW DATE:** 3/23/99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	11/30/98	12/1/98	12/5/98
BZ (replacement volumes)	1/28/99	1/29/99	1/29/99
BC	2/5/99	2/8/99	2/9/99
BC (devices and parts)	2/9/99	2/10/99	2/12/99
BC (marked devices)	2/26/99	3/1/99	3/4/99
BZ (DS impurities spec)	3/9/99	3/10/99	3/10/99

NAME & ADDRESS OF APPLICANT: Schering Corporation
Galloping Hill Road
Kenilworth, N.J.
07033

DRUG PRODUCT NAME:

Proprietary:	None proposed at this time.
Nonproprietary:	mometasone furoate inhalation powder
USAN:	mometasone furoate
Code Name/#:	SCH 32088
Chem.Type/Ther.Class:	3S

PHARMACOL. CATEGORY/INDICATION: Anti-inflammatory glucocorticoid for the prophylactic maintenance treatment of asthma

DOSAGE FORM: inhalation powder

DOSE: 200 mcg once or twice daily or 400 mcg once daily

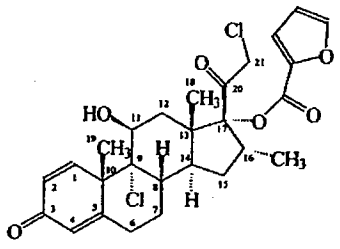
STRENGTHS: 220 mcg metered mometasone furoate/actuation (200 mcg emitted/act), 60 and 30 act (trade), 30 act (sample); metered/act (400 mcg emitted/act), 60 and 30 act (trade), 14 act (sample)

ROUTE OF ADMINISTRATION: inhalation

DISPENSED: _X_ Rx ___ OTC

SPECIAL PRODUCTS: ___ Yes _X_ No

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



Mometasone Furoate

9,21-Dichloro-17-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methylpregna-1,4-diene-3,20-dione

Molecular Formula: $C_{27}H_{30}Cl_2O_6$ Molecular Weight: 521.443

SUPPORTING DOCUMENTS:

Drug Master Files:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1 review
[		[	adequate	1/22/99	See p. 4 of CR#1
			inadequate	1/25/99	See p. 86 of CR#1
			not reviewed[1]		See p. 87 of CR#1
			inadequate	2/4/99	See p. 85 of CR#1
			inadequate	1/26/99	See p. 85 of CR#1
			not reviewed[2]		See p. 86 of CR#1
			inadequate	2/3/99	See p. 85 of CR#1
			inadequate	1/26/99	See p. 85 of CR#1
			inadequate	1/27/99	See p. 85 of CR#1
			inadequate	1/27/99	See p. 85 of CR#1
			inadequate		See p. 90 of CR#1
			inadequate	1/28/99	See p. 85 of CR#1
			Inadequate		See p. 89 of CR#1
	]	]	inadequate		See p. 90 of CR#1

[1]It does not appear that the [ ] has been used for the clinical or primary stability batches of drug product. DMF [ ] review will not take place until clarification and comparative data are provided.

[2]It is not clear why the DMF LOA was provided from [ ] DMF [ ] for. what Schering terms, [ ] which is listed in the letter from [ ] DMF [ ] did not indicate the use of this for any of the parts. Clarification will be sought and no review of this DMF will be done at this time.

RELATED DOCUMENTS:

IND [
IND]
IND 46,216 Mometasone Furoate Inhalation Powder (Schering)
NDA 19-543 Elocon (Mometasone Furoate) Ointment (Schering, approved 30-Apr-87)[1]

NDA 19-625 Elocon (Mometasone Furoate) Emulsion, Cream (Schering, approved 06-May-87)[1]
NDA 19-796 Elocon (Mometasone Furoate) Lotion (Schering, approved 30-Mar-89)[1]
NDA 20-762 Nasonex (Mometasone Furoate)[2] Nasal Spray (Schering, approved 01-Oct-97)

[1]These products are for topical application; [2]Monohydrate form of drug substance.

CONSULTS:

Consult	Date Forwarded	Status	Comments
EER	2/2/99	Pending	
Microbiology	Not forwarded.		See comments on pp. 28, 61 of CR#1.
Biometrics (Stability)	Not forwarded.		Specifications should be modified pending analysis see p. 109 of CR#1.
Pharmacology	2/2/99	Pending	Impurities Consult (DS/DP)
Methods Validation	Not forwarded.		Specifications and methods should be revised prior to analysis by Agency labs.
Environmental Assessment	Firm requests categorical exclusion under 21 CFR 25.31(b).	Not needed.	See p. 111 of CR#1.
Clinical	3/22/99	Pending	Consult requesting consideration of *in vitro* dose proportionality differences between strengths and — flow rate dependency.
Labeling & Nomenclature	Not requested.		No trademark proposed to date.

REMARKS/COMMENTS: See review notes,

CONCLUSIONS & RECOMMENDATIONS: In terms of Chemistry, Manufacturing and Controls information, the application is considered **not approvable**. The deficiency comments in the attached letter should be forwarded to the applicant.

cc:
Orig. NDA 21-067
HFD-570/Division File
HFD-570/CBertha/3/23/99
HFD-570/DToyer
HFD-570/GPoochikian
HFD-570/DO'Hearn
R/D Init. by GPoochikian: 4/9/99
filename: 99-03-09.rev.doc

Craig M. Bertha, Ph.D.
Review Chemist

315 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling