

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22518Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-518

**Dulera Inhalation Aerosol
(mometasone furoate and formoterol fumarate)**

Schering-Plough

Addendum #2 to Chemistry Review #1

Date: June 11, 2010

Recommendation: Approval

**Alan C. Schroeder, Ph.D.
ONDQA/Division III/Branch VIII**

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 22-518
2. REVIEW #: 1 (addendum #2)
3. REVIEW DATE: June 11, 2010
4. REVIEWER: Alan C. Schroeder, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Original NDA
Amendment
Amendment
Amendment
Amendment
Amendment
Amendment
Amendment (PI labeling)
Amendment (response to IR)
Amendment (response to IR)
Amendment (methods validation package)
Amendment – seq. #22 (response to IR)

Document Date

May 21, 2009
June 16, 2009
July 16, 2009
July 24, 2009
September 4, 2009
October 29, 2009
November 25, 2009
August 12, 2009
January 14, 2010
January 29, 2010
February 3, 2010
March 5, 2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment – seq. #23 (labeling update)
Amendment
Amendment (response to IR)

Document Date

March 5, 2010
March 16, 2010
May 26, 2010

7. NAME & ADDRESS OF APPLICANT:

Name:

Schering-Plough Corporation

Chemistry Review Data Sheet

Address: 2000 Galloping Hill Rd.
Kenilworth, NJ 07033
Greg Howe
Representative: Senior Manager and Liaison
Global Regulatory Affairs-CMC
908-740-2954
Telephone:

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: , Dulera 100/5 Inhalation Aerosol, Dulera 200/5 Inhalation Aerosol

b) Non-Proprietary Name:

mometasone furoate 100 mcg and formoterol fumarate dihydrate 5 mcg inhalation aerosol
mometasone furoate 200 mcg and formoterol fumarate dihydrate 5 mcg inhalation aerosol

c) Code Name/# (ONDC only): SCH 418131, MF/F, or MFF258

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4 (new combination)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: glucocorticosteroid and selective long-acting beta2-agonist.

11. DOSAGE FORM: aerosol, metered (inhalation aerosol)

12. STRENGTH/POTENCY:

mometasone furoate 100 mcg and formoterol fumarate dihydrate 5 mcg inhalation aerosol
mometasone furoate 200 mcg and formoterol fumarate dihydrate 5 mcg inhalation aerosol

13. ROUTE OF ADMINISTRATION:

respiratory (inhalation)

14. Rx/OTC DISPENSED: Rx OTC

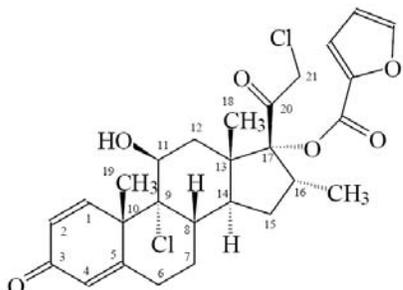
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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



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

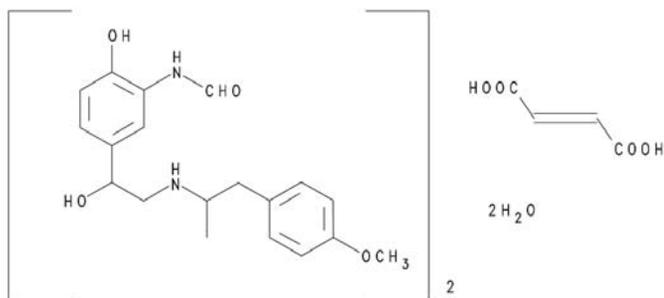
Molecular Formula: $C_{27}H_{30}Cl_2O_6$ Molecular Weight: 521.443

Mometasone Furoate

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

\pm 2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dihydrate

Molecular Weight: 840.9
Molecular Formula:
($C_{19}H_{24}N_2O_4$) $_2$ • $C_4H_4O_4$ • $2H_2O$



Formoterol fumarate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
12380	II	Astellas Pharma Inc	formoterol fumarate	1	Adequate	July 15, 2009	IR letter
(b) (4)	IV	(b) (4)	(b) (4)	1	Adequate	December 22, 2009	
	V			1	Adequate	Nov. 19, 2009	

Chemistry Review Data Sheet

			(b) (4)			(Dr. Tim Robison, pharm/tox reviewer)	
(b) (4)	III		(b) (4)	1	Adequate.	November 30, 2009	
11732	III	3M Pharm.	Aluminum can	1	Adequate.	11/02/2009 (Dr. Craig Bertha)	
15999	III	3M Pharm.	(b) (4) aluminum canisters	1	Adequate	11/02/2009 (Dr. Craig Bertha)	Supporting DMFs for DMF 15999 are adequate. There is a separate pharm/tox review (1/06/10) for DMF 15999 for canister extractables – levels were found to be reasonably safe.
19023	III	3M Pharm	pMDI actuator	1	Adequate	1/05/2010	Supporting DMFs for DMF 19023 are adequate.
20406	III	3M Drug Delivery Systems Div.	3M integrated dose counter	1	Adequate	10/22/2009 (Dr. Craig Bertha)	

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:

Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70,283	mometasone furoate/formoterol fumarate inhalation aerosol
IND	52,214	mometasone furoate inhalation aerosol
NDA	21,067	Asmanex Twisthaler
NDA	20,831	Foradil Aerolizer

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	not requested		
EES	Sites are acceptable	3/22/2010	E. Johnson (per EES)
Pharm/Tox	The presence of drug related impurities and degradation products, leachables, foreign particulates, and other impurities in the drug product appear to be reasonably safe.	12/4/2009 and 1/15/2010 (2 reviews)	Timothy Robison, Ph.D.
Biopharm	N.A.		
LNC	N.A.		
Methods Validation	Pending. It was submitted to the (b) (4) on 4/14/2010. Completion of this assignment is not required prior to a regulatory action on the NDA.		
EA	claim of categorical exclusion is adequate.	1/22/10 (chemistry review #1)	Alan Schroeder, Ph.D
Microbiology	Recommend approval	11/30/2009	John W. Metcalfe, Ph.D.
Radiopharmaceutical	N.A.		

The Chemistry Review for NDA 22-518

The Executive Summary

The recommendation (“approval”) remains unchanged from the previous addendum (March 12, 2010).

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for APPROVAL from a CMC perspective.

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

Post marketing agreements are listed below:

(b) (4) will be utilized as the different laboratory (other than that of the manufacturer) to periodically verify the information on the supplier’s certificate of analysis for HFA 227. (11/25/09 amendment)

The applicant has agreed to re-evaluate the oleic acid individual fatty acid specifications within a period of two years after approval of the NDA, based on additional data. (11/25/09 amendment)

The applicant agreed to “introduce methodology identical or equivalent/better than that contained within USP-NF General Chapter <401> for control of fatty acid composition in oleic acid. (1/14/2010 amendment)

The applicant has agreed (after approval of this NDA) to re-evaluate the drug product specifications for APSD and the drug product specifications for degradation products “using the data from all available commercial stability batches once there are a minimum of 3 stability batches for each drug product strength where at least one batch has data through 24 months, the second batch has at least 12 months of stability data, and a third batch has at least 6 months of stability data.” (11/25/09 amendment)

The applicant has agreed to maintain specifications (i.e., a list of tests, the acceptance criteria and the test methods) in NDA 22-518 for each of the two drug substances. (1/14/10 amendment)

The applicant has agreed “to further investigate the changes in particle size distribution of the emitted plume over the use life of the drug product and to report the progress and results to the Agency within 6 months of the date of the information request” (February 19, 2010). (3/05/10 amendment)

Executive Summary Section

II. Summary of Chemistry Assessments

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

The drug product is named Dulera Inhalation Aerosol (mometasone furoate and formoterol fumarate). It is intended for oral inhalation. Mometasone Furoate is an anti-inflammatory corticosteroid. Formoterol Fumarate is a long-acting beta2-agonist.

The drug products are manufactured with a (b) (4) valve (b) (4) a 16 mL aluminum canister which is (b) (4) press and breathe actuator with an integrated, displacement driven dose counter. (b) (4)

(b) (4). The (b) (4) canister, pMDI actuator and integrated dose counter are from 3M Pharmaceuticals. Each of the container closure components has CMC information that is cross-referenced to an individual DMF. All of the supporting DMFs have been found to be adequate during the review cycle. The applicant has not described any changes linked to the DMFs subsequent to the review of the DMFs. These MDIs are not overwrapped and are packaged in cartons. The target total mass per metered actuation (for all product strengths) is given by the applicant (based on a theoretical valve delivery for a (b) (4) (b) (4) as 69.5903 mg. “After priming, each actuation of the inhaler delivers (b) (4) 115, or 225 mcg of mometasone furoate and 5.5 mcg of formoterol fumarate dihydrate in 69.6 mg of suspension from the valve and delivers (b) (4) 100, or 200 mcg of mometasone furoate and 5 mcg of formoterol fumarate dihydrate from the actuator.” The target canister fill is (b) (4) (for all product strengths). Based on this figure, a total batch of (b) (4) would yield (b) (4) filled canisters (b) (4) (b) (4).

(b) (4). The route of administration is oral inhalation. Aerodynamic particle size distribution is controlled in the drug product specifications, and particle size distribution of each drug substance is controlled in the drug substance specifications. The drug product formulation consists of the two micronized active ingredients, ethanol (b) (4) (b) (4), oleic acid (b) (4) and HFA-227 propellant (b) (4). These excipients are not new for MDI formulations and the HFA-227 propellant has been used in at least one approved MDI drug product. All CMC information pertaining to the drug substances is cross-referenced to the previously approved NDAs (i.e., Novartis’s NDA 20-831 for Foradil Aerolizer (formoterol fumarate dihydrate) and Schering’s NDA 21-067 for Asmanax Twisthaler (mometasone furoate). The drug substances (and their specifications) are the same as approved in these other referenced NDAs (specified above) for different inhalation drug products. In addition, formoterol fumarate is cross-referenced to a DMF which has been found to be adequate.

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

Executive Summary Section

The drug product is a standard press and breathe metered dose inhaler which is labeled to contain 120 actuations (60 doses). The maximum labeled dosage of the drug product is 2 actuations (1 dose) twice per day. The proposed maximum dose is 2 actuations (1 dose) of the high strength product (200/5) twice a day. The proposed expiration dating period is 24 months when the drug product is stored at controlled room temperature (see USP). The following information is from the applicant's draft labeling:

DULERA is available in ^{(b) (4)} strengths, ^{(b) (4)} DULERA 100/5, and DULERA 200/5, delivering ^{(b) (4)} 100 mcg, and 200 mcg of mometasone furoate, respectively, and 5 mcg of formoterol fumarate dihydrate per actuation. DULERA should be administered only by the orally inhaled route (see Instructions for Using DULERA in the Medication Guide). After each dose, the patient should be advised to rinse his/her mouth with water without swallowing. DULERA should be primed before using for the first time by releasing 4 test sprays into the air, away from the face, shaking well before each spray. In cases where the inhaler has not been used for more than 5 days, prime the inhaler again by releasing 4 test sprays into the air, away from the face, shaking well before each spray.

Shake well prior to each inhalation. For best results, the canister should be at room temperature before use. The mouthpiece should be cleaned using a dry wipe after every 7 days of use.

C. Basis for Approvability or Not-Approval Recommendation

This suspension MDI drug product is somewhat unusual in that ^{(b) (4)}

^{(b) (4)} Nevertheless, the stability data for the drug product are adequate. The stability data support a 24 month expiration dating period.

^{(b) (4)}

Executive Summary Section

The approach used for investigating container closure system extractables and drug product leachables is said to have followed that of the recommendations of the Product Quality Research Institute (PQRI) extractables and leachables working group. Extractables/leachables without a quantitative extractables/leachables correlation are controlled as leachables in the drug product. Extractables which are present above the safety concern threshold (SCT) of the PQRI proposal, and for which there is a quantitative extractables/leachables correlation, are controlled as extractables in the respective container closure components. There will not be leachables controls for (b) (4) (not detected in stability study) in the drug product since they were not reported above their limits of quantitation (LOQs) through the 18 month time point of the placebo stability study. Potential leachables were evaluated in separate reviews by the pharm/tox reviewer and found to be reasonably safe.

The integrated dose counter is set during manufacture to a count of 124 which takes into account the initial 4 priming actuations. The dose counter, therefore, will read 120 actuations (i.e., the label claim) after the priming actuations. Data to show equivalence in performance (Dose Content Uniformity [DCU], Aerodynamic Particle Size Distribution [APSD], spray pattern, plume geometry) between the blue to be marketed actuator with integrated dose counter and the clinical actuators (light blue) without the dose counter are referenced to DMF 19,023, which has been found to be adequate.

Samples of normally functioning drug product returned from clinical studies for laboratory analysis demonstrated that the DCU data are within the range of NDA stability data (except for two outliers). These returned samples, however, did show some tendency towards an (b) (4) of the delivered dose in their APSD. This tendency was justified by the applicant in part by the fact that these clinical returns were near the end of their shelf lives and were near the end of their use life when tested, and because they were tested with patient-used uncleaned actuators.

The (b) (4) strengths of drug products are dose proportional for DCU. (b) (4) This was discussed in the Wrap Up team meeting for this NDA (which included the clinical reviewers and the clinical Division Director); it was concluded that these results are not of clinical concern because the (b) (4) strengths of drug product are dose proportional for DCU, and because the stage grouping (b) (4) which alone did show fairly good APSD dose proportionality (in contrast to the other stage groupings), makes up a significant part of the drug (b) (4).

Single entity comparator MDI products (monoproducts) were used for comparison with the proposed drug product in clinical studies. These comparators are not proposed for marketing.

The container closure system for the mometasone furoate monoproduct is the same as for the proposed drug products. There are (b) (4) of these mometasone furoate monoproducts, differing in strength ((b) (4) 100 mcg and 200 mcg per actuation) and corresponding to the proposed drug product. Each delivers 120 actuations. There is one formoterol fumarate comparator (monoproduct) which delivers 5 mcg/actuation and delivers 120 actuations. It has a number of differences from the proposed drug product.

Executive Summary Section

The composition of the formoterol fumarate comparator MDI monoprodut (5 mcg per actuation) is different from that of the proposed drug product in the following aspects. The differences include the use of HFA 134a as the propellant instead of HFA 227, the addition of lactose (b) (4) and other small differences in the amounts of excipients and formoterol fumarate, plus a different valve (b) (4). The comparator target is (b) (4) per metered actuation (vs. the drug product, (b) (4) of formoterol fumarate per metered actuation). This comparator has a different ethanol concentration (b) (4) compared to the proposed drug product (b) (4). These differences may account for some of the differences in APSD for the formoterol fumarate comparator, compared to the proposed drug product.

The comparison of the monotherapy products with the combination drug product shows that DCU for both actives appears to be reasonably comparable for the monotherapy products and the drug product. The same is true for the APSD data for mometasone furoate (although the monotherapy comparator is not completely identical in the APSD results compared to the drug product, some variability may normally be expected). The APSD data for formoterol fumarate show differences in the individual stage data when comparing the monotherapy product with the combination product. These differences appear to be smaller when comparing stage groupings instead of individual stages, and smaller yet when comparing only fine particle mass (b) (4). This issue has been discussed with the clinical reviewers and at the mid-cycle and wrap up team meetings (including the clinical Division Director). Specific clinical concerns were not raised. Stability data have been provided for comparator performance only.

Some other single drug (mometasone furoate) MDI comparator products used earlier in development, and not described in the original NDA, are discussed in this current addendum in response to our request for information.

The Office of Compliance previously had been asked to evaluate certain aspects of data integrity in this application, due to the large number of corrections made in the October 29, 2009 amendment. These corrections do all appear to be minor. This request was made in a Considerations for Inspection memo dated January 26, 2010. The following information is from EES. The drug product manufacturing site (3M Health Care, Loughborough, UK) was inspected from 15-18 March 2010. No 483 was issued. Both the District Office and the Office of Compliance found the facility to be acceptable (22 March 2010). All NDA facilities were found to be acceptable by our Office of Compliance on 22 March 2010. We have interpreted this as implying that Compliance has no data integrity concerns pertaining to this NDA.

III. Administrative

A. Reviewer's Signature

Executive Summary Section

B. Endorsement Block

Alan C. Schroeder, Ph.D./
Prasad Peri, Ph.D./
Eunice Chung, DPAP Project Manager/

C. CC Block

5 pages has been withheld in full as B(4)
CCI/TS immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22518	ORIG-1	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE

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

/s/

ALAN C SCHROEDER
06/11/2010

PRASAD PERI
06/14/2010
I concur

Dulera® (Mometasone furoate/formoterol; fumarate) Inhalation Aerosol NDA 22-518

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033
USA

Indication: Treatment of asthma, (b) (4), in adults and children 12 years of age and older. Treatment of asthma in patients ≥12 years: 2 inhalations twice daily of DULERA 100 mcg/5 mcg, or 200 mcg/5 mcg. Starting dosage is based on prior asthma therapy. The route of administration is oral inhalation.

Presentation: Dulera Inhalation Aerosol is a standard press and breath combination product metered dose inhaler that is proposed in (b) (4) two strengths (100/5 and 200/5) of the drug products are being approved by the clinical division based on efficacy results. The (b) (4) strengths proposed in the NDA are **per actuation:** (b) (4) mometasone furoate 100 mcg/formoterol fumarate dihydrate 5 mcg, mometasone furoate 200 mcg/formoterol fumarate dihydrate 5 mcg inhalation aerosols. The MDI has a dose counter that is integrated in the actuator. The drug product for all strengths provide 120 actuations (60 doses)

EER Status: Acceptable as of 22-Mar-2010

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(c)
Methods Validation – Revalidation by Agency was requested for the APSD and DDU methods to get similar results as provided in the applicant.
Pharm/toxicology – Acceptable

Original Submission: 21-May-2009

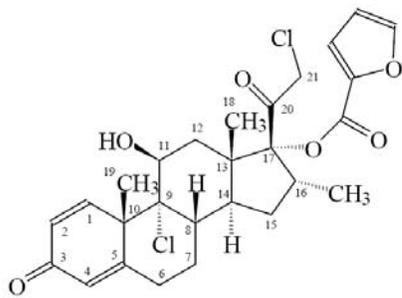
Post-Approval CMC Commitments:

- (b) (4) will be utilized as the different laboratory (other than that of the manufacturer) to periodically verify the information on the supplier's certificate of analysis for HFA 227. (11/25/09 amendment)
- The applicant has agreed to re-evaluate the oleic acid individual fatty acid specifications within a period of two years after approval of the NDA, based on additional data. (11/25/09 amendment)

- The applicant has agreed (after approval of this NDA) to re-evaluate the drug product specifications for APSD and the drug product specifications for degradation products “using the data from all available commercial stability batches once there are a minimum of 3 stability batches for each drug product strength where at least one batch has data through 24 months, the second batch has at least 12 months of stability data, and a third batch has at least 6 months of stability data.” (11/25/09 amendment)
- The applicant has agreed “to further investigate the changes in particle size distribution of the emitted plume over the use life of the drug product and to report the progress and results to the Agency within 6 months of the date of the information request” (February 19, 2010). (3/05/10 amendment)

Drug Substance:

Mometasone furoate is a corticosteroid demonstrating potent anti-inflammatory activity. It is a white powder, practically insoluble in water; slightly soluble in methanol, ethanol, and isopropanol; soluble in acetone and (b) (4) and freely soluble in (b) (4). Its partition coefficient between (b) (4) and (b) (4) is greater than (b) (4).



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

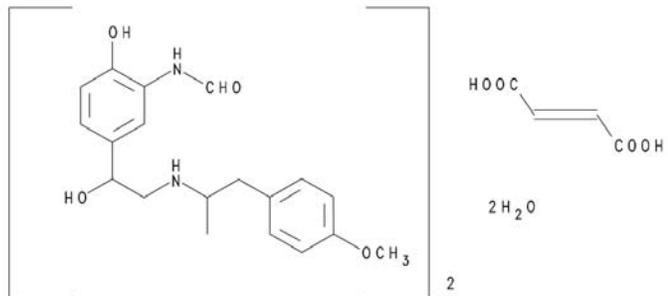
Molecular Formula: C₂₇H₃₀Cl₂O₆ Molecular Weight: 521.443

Mometasone Furoate

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT.:

±2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dihydrate

Molecular Weight: 840.9
Molecular Formula: (C₁₉H₂₄N₂O₄)₂•C₄H₄O₄•2H₂O



The active component formoterol fumarate (dihydrate), a racemate, is a long acting selective beta 2-adrenergic bronchodilator. Formoterol fumarate is a white to yellowish (b) (4) powder, which is freely soluble in glacial acetic acid, soluble in methanol, sparingly soluble in ethanol and isopropanol, slightly soluble in water, and practically insoluble in acetone, ethyl acetate, and diethyl ether. Its melting point is 138°C and its solubility in ethanol is 4.88 mg/mL. Its mean solubility in the drug product at (b) (4)

All CMC information pertaining to the drug substances is cross-referenced to the previously approved NDAs (i.e., Novartis's NDA 20-831 for Foradil Aerolizer (formoterol fumarate dihydrate) and Schering's NDA 21-067 for Asmanax Twisthaler (mometasone furoate). The drug substances (and their specifications) are the same as approved in these other NDAs (specified above) for different inhalation drug products. In addition, formoterol fumarate is cross-referenced to a DMF which has been found to be adequate.

Mometasone fumarate is manufactured, micronized, and tested by Schering Plough LTD, Singapore.

Formoterol fumarate is manufactured at Astellas Pharma Chemicals, Japan, is micronized by Novartis Pharma Stein AG, Switzerland, and tested for release and stability at Novartis Pharma Schweizerhalle AG, in Switzerland. Additional testing for formoterol fumarate is performed at Novartis International Pharmaceuticals, Ireland (release and stability), (b) (4)
(b) (4)

Conclusion: The drug substance is satisfactory

Drug Product:

The drug products are white suspensions containing (b) (4) alcohol dehydrated/ethanol anhydrous, (b) (4) oleic acid, and (b) (4) HFA 227. The drug products are formulated in (b) (4) strengths, each designed to deliver a minimum of 120 actuations. One therapeutic dose is obtained from two single actuations of the drug products. The container closure system (CCS) for the drug products consists of a 16 mL aluminum canister (b) (4)
(b) (4) A press and breathe actuator is provided with the pressurized canister to deliver a dose to the patient. A (b) (4) Mouthpiece Cover is provided with the actuator. The (b) (4) actuator incorporates an integrated displacement driven 3M dose counter.

An unusual feature of this drug product manufacturing is that (b) (4)

After priming, each actuation of the inhaler delivers (b) (4) 115, or 225 mcg of mometasone furoate and 5.5 mcg of formoterol fumarate dihydrate in 69.6 mg of suspension from the valve and delivers (b) (4) 100, or 200 mcg of mometasone furoate and 5 mcg of formoterol fumarate dihydrate from the actuator. The target canister fill is 13 g (for all product strengths). Based on this figure, a total batch of (b) (4) would yield (b) (4) filled canisters (b) (4)

Each of the container closure components has CMC information that is cross-referenced to an individual DMF. All of the supporting DMFs have been found to be adequate. These MDIs are not overwrapped and are packaged in cartons.

The regulatory specifications on the drug product include Appearance, Identification (TLC and HPLC), Assay for Mometasone Furoate and Formoterol Fumarate, Ethanol Content, Water Content, Dose Content Uniformity, Aerodynamic Particle Size Distribution, Impurities/ Degradation Products, Leachables, Microbial Limits, Foreign Particulates, Fill Weight, valve Delivery, Actuations per Container, Leak Rate, and Spray Pattern.

The drug product is manufactured, packaged and tested by 3M Corporation in Loughborough, England. Additional testing is done by Schering in NJ and 3M in Minnesota.

The applicant proposes a shelf life of 24 months which is supported.

Conclusion: The drug product is acceptable.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Because of the unusual nature of the drug product revalidation of the emitted dose and APSD was requested by Agency labs.

Overall Conclusion:

From a CMC perspective, the application is recommended for approvable.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22518

ORIG-1

SCHERING CORP

MOMETASONE
FUROATE/FORMOTEROL
FUMARATE

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

05/26/2010

NDA 22-518

**Dulera Inhalation Aerosol
(mometasone furoate and formoterol fumarate)**

Schering-Plough

Addendum to Chemistry Review #1

Date: March 12, 2010

**Recommendation: Approval
[Facilities inspection remains outstanding]**

**Alan C. Schroeder, Ph.D.
ONDQA/Division I/Branch II**

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 22-518
2. REVIEW #: 1 (addendum)
3. REVIEW DATE: March 12, 2010
4. REVIEWER: Alan C. Schroeder, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Original NDA
Amendment
Amendment
Amendment
Amendment
Amendment
Amendment

Document Date

May 21, 2009
June 16, 2009
July 16, 2009
July 24, 2009
September 4, 2009
October 29, 2009
November 25, 2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA (container and carton labels, medguide)
Amendment (PI labeling)
Amendment (response to IR)
Amendment (response to IR)
Amendment (methods validation package)
Amendment (response to IR)

Document Date

May 21, 2009
August 12, 2009
January 14, 2010
January 29, 2010
February 3, 2010
March 5, 2010

7. NAME & ADDRESS OF APPLICANT:

Name: Schering-Plough Corporation
Address: 2000 Galloping Hill Rd.
Kenilworth, NJ 07033

Chemistry Review Data Sheet

Representative: **Greg Howe**
Senior Manager and Liaison
Global Regulatory Affairs-CMC
908-740-2954

Telephone:

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Dulera 100/5 Inhalation Aerosol, Dulera 200/5 Inhalation Aerosol

b) Non-Proprietary Name:

mometasone furoate 100 mcg and formoterol fumarate dihydrate 5 mcg inhalation aerosol
mometasone furoate 200 mcg and formoterol fumarate dihydrate 5 mcg inhalation aerosol

c) Code Name/# (ONDC only): SCH 418131, MF/F, or MFF258

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4 (new combination)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: glucocorticosteroid and selective long-acting beta2-agonist.

11. DOSAGE FORM: aerosol, metered (inhalation aerosol)

12. STRENGTH/POTENCY:

mometasone furoate 100 mcg and formoterol fumarate dihydrate 5 mcg inhalation aerosol
mometasone furoate 200 mcg and formoterol fumarate dihydrate 5 mcg inhalation aerosol

13. ROUTE OF ADMINISTRATION:

respiratory (inhalation)

14. Rx/OTC DISPENSED: Rx OTC

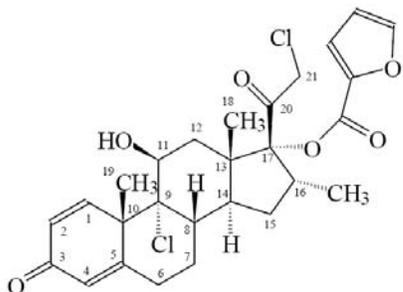
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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



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

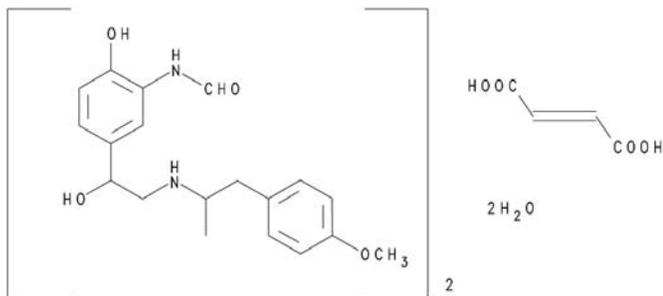
Molecular Formula: $C_{27}H_{30}Cl_2O_6$ Molecular Weight: 521.443

Mometasone Furoate

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

\pm -2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dihydrate

Molecular Weight: 840.9
Molecular Formula:
($C_{19}H_{24}N_2O_4$)₂• $C_4H_4O_4$ • $2H_2O$



Formoterol fumarate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
12380	II	Astellas Pharma Inc	formoterol fumarate	1	Adequate	July 15, 2009	IR letter
(b) (4)	IV	(b) (4)	(b) (4)	1	Adequate	December 22, 2009	
	V			1	Adequate	Nov. 19, 2009	

Chemistry Review Data Sheet

			227) safety data			(Dr. Tim Robison, pharm/tox reviewer)	
(b) (4)	III		(b) (4)	1	Adequate.	November 30, 2009	
11732	III	3M Pharm.	Aluminum can	1	Adequate.	11/02/2009 (Dr. Craig Bertha)	
15999	III	3M Pharm.	(b) (4) aluminum canisters	1	Adequate	11/02/2009 (Dr. Craig Bertha)	Supporting DMFs for DMF 15999 are adequate. There is a separate pharm/tox review (1/06/10) for DMF 15999 for canister extractables – levels were found to be reasonably safe.
19023	III	3M Pharm	pMDI actuator	1	Adequate	1/05/2010	Supporting DMFs for DMF 19023 are adequate.
20406	III	3M Drug Delivery Systems Div.	3M integrated dose counter	1	Adequate	10/22/2009 (Dr. Craig Bertha)	

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:

Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70,283	mometasone furoate/formoterol fumarate inhalation aerosol
IND	52,214	mometasone furoate inhalation aerosol
NDA	21,067	Asmanex Twisthaler
NDA	20,831	Foradil Aerolizer

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	not requested		
EES	pending (req. sent 6/16/2009)		
Pharm/Tox	The presence of drug related impurities and degradation products, leachables, foreign particulates, and other impurities in the drug product appear to be reasonably safe.	12/4/2009 and 1/15/2010 (2 reviews)	Timothy Robison, Ph.D.
Biopharm	N.A.		
LNC	N.A.		
Methods Validation	deferred at this time		
EA	claim of categorical exclusion is adequate.	1/22/10 (chemistry review #1)	Alan Schroeder, Ph.D
Microbiology	Recommend approval	11/30/2009	John W. Metcalfe, Ph.D.
Radiopharmaceutical	N.A.		

The Chemistry Review for NDA 22-518

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for APPROVAL from a CMC perspective. (NOTE: the facilities inspection is still outstanding, and this CMC recommendation does not incorporate any potential facility inspection issues).

The Office of Compliance has been asked to evaluate certain aspects of data integrity in this application, due to the large number of corrections made in the October 29, 2009 amendment. These corrections do all appear to be minor.

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

Post marketing agreements are listed below:

[REDACTED] ^{(b) (4)} will be utilized as the different laboratory (other than that of the manufacturer) to periodically verify the information on the supplier's certificate of analysis for HFA 227. (11/25/09 amendment)

The applicant has agreed to re-evaluate the oleic acid individual fatty acid specifications within a period of two years after approval of the NDA, based on additional data. (11/25/09 amendment)

The applicant agreed to “introduce methodology identical or equivalent/better than that contained within USP-NF General Chapter <401> for control of fatty acid composition in oleic acid. (1/14/2010 amendment)

The applicant has agreed (after approval of this NDA) to re-evaluate the drug product specifications for APSD and the drug product specifications for degradation products “using the data from all available commercial stability batches once there are a minimum of 3 stability batches for each drug product strength where at least one batch has data through 24 months, the second batch has at least 12 months of stability data, and a third batch has at least 6 months of stability data.” (11/25/09 amendment)

The applicant has agreed to maintain specifications (i.e., a list of tests, the acceptance criteria and the test methods) in NDA 22-518 for each of the two drug substances. (1/14/10 amendment)

The applicant has agreed “to further investigate the changes in particle size distribution of the emitted plume over the use life of the drug product and to report the progress and results to the

Executive Summary Section

Agency within 6 months of the date of the information request” (February 19, 2010). (3/05/10 amendment)

II. Summary of Chemistry Assessments

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

The drug product is named Dulera Inhalation Aerosol (mometasone furoate and formoterol fumarate). It is intended for oral inhalation. Mometasone Furoate is an anti-inflammatory corticosteroid. Formoterol Fumarate is a long-acting beta2-agonist.

The drug products are manufactured with a (b) (4) valve (b) (4) a 16 mL aluminum canister which is (b) (4) press and breathe actuator with an integrated, displacement driven dose counter. (b) (4)

The (b) (4) canister, pMDI actuator and integrated dose counter are from 3M Pharmaceuticals. Each of the container closure components has CMC information that is cross-referenced to an individual DMF. All of the supporting DMFs have been found to be adequate. These MDIs are not overwrapped and are packaged in cartons. The target total mass per metered actuation (for all product strengths) is given by the applicant (based on a theoretical valve delivery for a (b) (4)) as 69.5903 mg. “After priming, each actuation of the inhaler delivers (b) (4) 115, or 225 mcg of mometasone furoate and 5.5 mcg of formoterol fumarate dihydrate in 69.6 mg of suspension from the valve and delivers (b) (4) 100, or 200 mcg of mometasone furoate and 5 mcg of formoterol fumarate dihydrate from the actuator.” The target canister fill is (b) (4) (for all product strengths). Based on this figure, a total batch of (b) (4) would yield (b) (4) filled canisters (b) (4)

The route of administration is oral inhalation. Aerodynamic particle size distribution is controlled in the drug product specifications, and particle size distribution of each drug substance is controlled in the drug substance specifications. The drug product formulation consists of the two micronized active ingredients, ethanol (b) (4) oleic acid (b) (4) and HFA-227 propellant (b) (4). These excipients are not new for MDI formulations and the HFA-227 propellant has been used in at least one approved MDI drug product. All CMC information pertaining to the drug substances is cross-referenced to the previously approved NDAs (i.e., Novartis’s NDA 20-831 for Foradil Aerolizer (formoterol fumarate dihydrate) and Schering’s NDA 21-067 for Asmanax Twisthaler (mometasone furoate). The drug substances (and their specifications) are the same as approved in these other referenced NDAs (specified above) for different inhalation drug products. In addition, formoterol fumarate is cross-referenced to a DMF which has been found to be adequate.

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

The drug product is a standard press and breathe metered dose inhaler which is labeled to contain 120 actuations (60 doses). The maximum labeled dosage of the drug product is 2 actuations (1 dose) twice per day. The proposed maximum dose is 2 actuations (1 dose) of the high strength

Executive Summary Section

product (200/5) twice a day. The proposed expiration dating period is 24 months when the drug product is stored at controlled room temperature (see USP). The following information is from the applicant's draft labeling:

DULERA is available in (b) (4) strengths, (b) (4) DULERA 100/5, and DULERA 200/5, delivering (b) (4) 100 mcg, and 200 mcg of mometasone furoate, respectively, and 5 mcg of formoterol fumarate dihydrate per actuation. DULERA should be administered only by the orally inhaled route (see Instructions for Using DULERA in the Medication Guide). After each dose, the patient should be advised to rinse his/her mouth with water without swallowing. DULERA should be primed before using for the first time by releasing 4 test sprays into the air, away from the face, shaking well before each spray. In cases where the inhaler has not been used for more than 5 days, prime the inhaler again by releasing 4 test sprays into the air, away from the face, shaking well before each spray.

Shake well prior to each inhalation. For best results, the canister should be at room temperature before use. The mouthpiece should be cleaned using a dry wipe after every 7 days of use.

C. Basis for Approvability or Not-Approval Recommendation

This suspension MDI drug product is somewhat unusual in that

(b) (4)

Nevertheless, the stability data for the drug product are adequate. The stability data support a 24 month expiration dating period.

(b) (4)

The approach used for investigating container closure system extractables and drug product leachables is said to have followed that of the recommendations of the Product Quality Research Institute (PQRI) extractables and leachables working group. Extractables/leachables without a

Executive Summary Section

quantitative extractables/leachables correlation are controlled as leachables in the drug product. Extractables which are present above the safety concern threshold (SCT) of the PQRI proposal, and for which there is a quantitative extractables/leachables correlation, are controlled as extractables in the respective container closure components. There will not be leachables controls for (b) (4) (not detected in stability study) in the drug product since they were not reported above their limits of quantitation (LOQs) through the 18 month time point of the placebo stability study. Potential leachables were evaluated in separate reviews by the pharm/tox reviewer and found to be reasonably safe.

The integrated dose counter is set during manufacture to a count of 124 which takes into account the initial 4 priming actuations. The dose counter, therefore, will read 120 actuations (i.e., the label claim) after the priming actuations. Data to show equivalence in performance (Dose Content Uniformity [DCU], Aerodynamic Particle Size Distribution [APSD], spray pattern, plume geometry) between the blue to be marketed actuator with integrated dose counter and the clinical actuators (light blue) without the dose counter are referenced to DMF 19,023, which has been found to be adequate.

Samples of normally functioning drug product returned from clinical studies for laboratory analysis demonstrated that the DCU data are within the range of NDA stability data (except for two outliers). These returned samples, however, did show some tendency towards an (b) (4) of the delivered dose in their APSD. This tendency was justified by the applicant in part by the fact that these clinical returns were near the end of their shelf lives and were near the end of their use life when tested, and because they were tested with patient-used uncleaned actuators.

The (b) (4) strengths of drug products are dose proportional for DCU. (b) (4) This was discussed in the Wrap Up team meeting for this NDA (which included the clinical reviewers and the clinical Division Director); it was concluded that these results are not of clinical concern because the (b) (4) strengths of drug product are dose proportional for DCU, and because the stage grouping (b) (4) which alone did show fairly good APSD dose proportionality (in contrast to the other (b) (4) makes up a significant part of the drug (b) (4).

Single entity comparator MDI products (monoproducts) were used for comparison with the proposed drug product in clinical studies. These comparators are not proposed for marketing.

The container closure system for the mometasone furoate monoproduct is the same as for the proposed drug products. There are (b) (4) of these mometasone furoate monoproducts, differing in strength ((b) (4), 100 mcg and 200 mcg per actuation) and corresponding to the proposed drug product. Each delivers 120 actuations. There is one formoterol fumarate comparator (monoproduct) which delivers 5 mcg/actuation and delivers 120 actuations. It has a number of differences from the proposed drug product.

The composition of the formoterol fumarate comparator MDI monoproduct (5 mcg per actuation) is different from that of the proposed drug product in the following aspects.

Executive Summary Section

The differences include the use of HFA 134a as the propellant instead of HFA 227, the addition of lactose (b) (4) and other small differences in the amounts of excipients and formoterol fumarate, plus a different valve (b) (4) instead of the (b) (4). The comparator target is (b) (4) per metered actuation (vs. the drug product, (b) (4) of formoterol fumarate per metered actuation). This comparator has a different ethanol concentration (b) (4) compared to the proposed drug product (b) (4). These differences may account for some of the differences in APSD for the formoterol fumarate comparator, compared to the proposed drug product.

The comparison of the monotherapy products with the combination drug product shows that DCU for both actives appears to be reasonably comparable for the monotherapy products and the drug product. The same is true for the APSD data for mometasone furoate (although the monotherapy comparator is not completely identical in the APSD results compared to the drug product, some variability may normally be expected). The APSD data for formoterol fumarate show differences in the individual stage data when comparing the monotherapy product with the combination product. These differences appear to be smaller when comparing stage groupings instead of individual stages, and smaller yet when comparing only fine particle mass (b) (4). This issue has been discussed with the clinical reviewers and at the mid-cycle and wrap up team meetings (including the clinical Division Director). Specific clinical concerns were not raised. Stability data have been provided for comparator performance only.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Alan C. Schroeder, Ph.D./3-12-2010
Prasad Peri, Ph.D./
Eunice Chung, DPAP Project Manager/

C. CC Block

21 pages has been withheld in full as B(4) CCI/TS immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22518	ORIG-1	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE

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

/s/

ALAN C SCHROEDER
03/12/2010

PRASAD PERI
03/15/2010
I concur

NDA 22-518

**Dulera Inhalation Aerosol
(mometasone furoate and formoterol fumarate)**

Schering-Plough

Chemistry Review #1

Date: 1/22/2010

Recommendation: Approvable

**Alan C. Schroeder, Ph.D.
ONDQA/Division I/Branch II**

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Chemistry Review Data Sheet

1. NDA 22-518
2. REVIEW #: 1
3. REVIEW DATE: January 22, 2010
4. REVIEWER: Alan C. Schroeder, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

none

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA
Amendment
Amendment
Amendment
Amendment
Amendment
Amendment

Document Date

May 21, 2009
June 16, 2009
July 16, 2009
July 24, 2009
September 4, 2009
October 29, 2009
November 25, 2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Schering Corporation
Address:	2000 Galloping Hill Rd. Kenilworth, NJ 07033
Representative:	Susan Yule Senior Manager and Liaison Global Regulatory Affairs
Telephone:	telephone: 908-740-7435 fax: 908-740-2243

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Dulera 100/5 Inhalation Aerosol, Dulera 200/5 Inhalation Aerosol

b) Non-Proprietary Name:

mometasone furoate 100 mcg and formoterol fumarate dihydrate 5 mcg inhalation aerosol
mometasone furoate 200 mcg and formoterol fumarate dihydrate 5 mcg inhalation aerosol

c) Code Name/# (ONDC only): SCH 418131, MF/F, or MFF258

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4 (new combination)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: glucocorticosteroid and selective long-acting beta2-agonist.

11. DOSAGE FORM: aerosol, metered (inhalation aerosol)

12. STRENGTH/POTENCY:

mometasone furoate 100 mcg and formoterol fumarate dihydrate 5 mcg inhalation aerosol
mometasone furoate 200 mcg and formoterol fumarate dihydrate 5 mcg inhalation aerosol

13. ROUTE OF ADMINISTRATION:

respiratory (inhalation)

14. Rx/OTC DISPENSED: Rx OTC

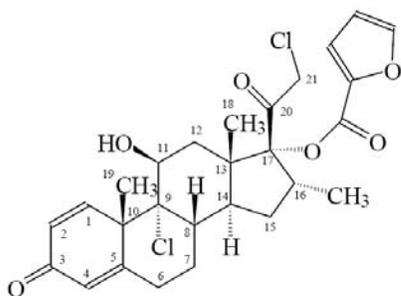
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

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

Chemistry Review Data Sheet



Mometasone Furoate

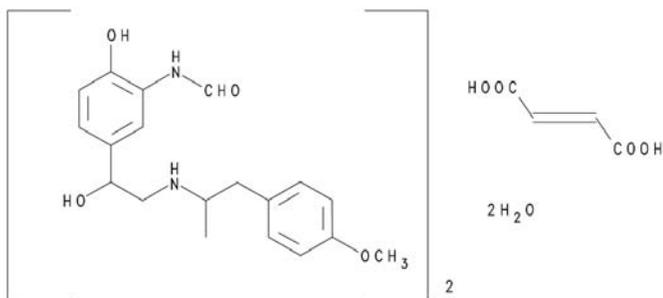
9,21-Dichloro-17-[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methylpregna-1,4-diene-3,20-dione

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

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

\pm 2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dihydrate

Molecular Weight: 840.9
Molecular Formula:
 $(C_{19}H_{24}N_2O_4)_2 \bullet C_4H_4O_4 \bullet 2H_2O$



Formoterol fumarate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
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(b) (4)	IV	(b) (4)	(b) (4)	1	Adequate	December 22, 2009	
	V			1	Adequate	Nov. 19, 2009 (Dr. Tim Robison, pharm/tox)	

Chemistry Review Data Sheet

						reviewer)	
(b) (4)	III		(b) (4)	1	Adequate.	November 30, 2009	
11732	III	3M Pharm.	Aluminum can	1	Adequate.	11/02/2009 (Dr. Craig Bertha)	
15999	III	3M Pharm.	(b) (4) aluminum canisters	1	Adequate	11/02/2009 (Dr. Craig Bertha)	Supporting DMFs for DMF 15999 are adequate. There is a separate pharm/tox review (1/06/10) for DMF 15999 for canister extractables – levels were found to be reasonably safe.
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20406	III	3M Drug Delivery Systems Div.	3M integrated dose counter	1	Adequate	10/22/2009 (Dr. Craig Bertha)	

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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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Chemistry Review Data Sheet

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NDA	21,067	Asmanex Twisthaler
NDA	20,831	Foradil Aerolizer

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	not requested		
EES	pending (req. sent 6/16/2009)		
Pharm/Tox	The presence of drug related impurities and degradation products, leachables, foreign particulates, and other impurities in the drug product appear to be reasonably safe.	12/4/2009 and 1/15/2010 (2 reviews)	Timothy Robison, Ph.D.
Biopharm	N.A.		
LNC	N.A.		
Methods Validation	not requested		
EA	claim of categorical exclusion is adequate.	same as the date of this review	Alan Schroeder, Ph.D
Microbiology	Recommend approval	11/30/2009	John W. Metcalfe, Ph.D.
Radiopharmaceutical	N.A.		

The Chemistry Review for NDA 22-518

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is approvable, pending a satisfactory recommendation from Compliance pertaining to manufacturing and testing facilities, and pending satisfactory responses to our outstanding CMC IR comments.

The Office of Compliance will be asked to evaluate certain aspects of data integrity in this application, due to the large number of corrections made in the October 29, 2009 amendment. These corrections do all appear to be minor.

It is intended that an addendum to this review will be written within the current review cycle for the review of the applicant's responses to our outstanding CMC comments (e.g., IR comments #2 and IR comments #3 sent on 12/22/09 and 1/19/10, respectively; see the end of this review, prior to the attachments section). Labeling comments are deferred to that addendum as well.

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

Post marketing agreements are listed below:

(b) (4) will be utilized as the different laboratory (other than that of the manufacturer) to periodically verify the information on the supplier's certificate of analysis for HFA 227. (11/25/09 amendment)

The applicant has agreed to re-evaluate the oleic acid individual fatty acid specifications within a period of two years after approval of the NDA, based on additional data. (11/25/09 amendment)

The applicant has agreed (after approval of this NDA) to re-evaluate the drug product specifications for APSD and the drug product specifications for degradation products "using the data from all available commercial stability batches once there are a minimum of 3 stability batches for each drug product strength where at least one batch has data through 24 months, the second batch has at least 12 months of stability data, and a third batch has at least 6 months of stability data." (11/25/09 amendment)

II. Summary of Chemistry Assessments

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

Executive Summary Section

The drug product is named Dulera Inhalation Aerosol (mometasone furoate and formoterol fumarate). It is intended for oral inhalation. Mometasone Furoate is an anti-inflammatory corticosteroid. Formoterol Fumarate is a long-acting beta2-agonist.

The drug products are manufactured with a (b) (4) valve (b) (4) a 16 mL aluminum canister (b) (4) press and breathe actuator with an integrated, displacement driven dose counter. (b) (4)

The (b) (4) canister, pMDI actuator and integrated dose counter are from 3M Pharmaceuticals. Each of the container closure components has CMC information that is cross-referenced to an individual DMF. All of the supporting DMFs have been found to be adequate. These MDIs are not overwrapped and are packaged in cartons. The target total mass per metered actuation (for all product strengths) is given by the applicant (based on a theoretical valve delivery for a (b) (4) as 69.5903 mg. “After priming, each actuation of the inhaler delivers (b) (4) 115, or 225 mcg of mometasone furoate and 5.5 mcg of formoterol fumarate dihydrate in 69.6 mg of suspension from the valve and delivers (b) (4) 100, or 200 mcg of mometasone furoate and 5 mcg of formoterol fumarate dihydrate from the actuator.” The target canister fill is (b) (4) (for all product strengths). Based on this figure, a total batch of (b) (4) would yield (b) (4) filled canisters (b) (4). The route of administration is oral inhalation. Aerodynamic particle size distribution is controlled in the drug product specifications, and particle size distribution of each drug substance is controlled in the drug substance specifications. The drug product formulation consists of the two micronized active ingredients, ethanol (b) (4) oleic acid (b) (4) and HFA-227 propellant (b) (4). These excipients are not new for MDI formulations and the HFA-227 propellant has been used in at least one approved MDI drug product. All CMC information pertaining to the drug substances is cross-referenced to the previously approved NDAs (i.e., Novartis’s NDA 20-831 for Foradil Aerolizer (formoterol fumarate dihydrate) and Schering’s NDA 21-067 for Asmanax Twisthaler (mometasone furoate). The drug substances (and their specifications) are the same as approved in these other NDAs (specified above) for different inhalation drug products. In addition, formoterol fumarate is cross-referenced to a DMF which has been found to be adequate.

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

The drug product is a standard press and breathe metered dose inhaler which is labeled to contain 120 actuations (60 doses). The maximum labeled dosage of the drug product is 2 actuations (1 dose) twice per day. The proposed maximum dose is 2 actuations of the high strength product (200/5) twice a day. The proposed expiration dating period is 24 months when the drug product is stored at controlled room temperature (see USP). The following information is from the applicant’s draft labeling:

DULERA is available in (b) (4) strengths, (b) (4) DULERA 100/5, and DULERA 200/5, delivering (b) (4) 100 mcg, and 200 mcg of mometasone furoate, respectively, and 5 mcg of formoterol fumarate dihydrate per actuation. DULERA should be administered only by the

Executive Summary Section

orally inhaled route (see Instructions for Using DULERA in the Medication Guide). After each dose, the patient should be advised to rinse his/her mouth with water without swallowing. DULERA should be primed before using for the first time by releasing 4 test sprays into the air, away from the face, shaking well before each spray. In cases where the inhaler has not been used for more than 5 days, prime the inhaler again by releasing 4 test sprays into the air, away from the face, shaking well before each spray.

Shake well prior to each inhalation. For best results, the canister should be at room temperature before use. The mouthpiece should be cleaned using a dry wipe after every 7 days of use.

C. Basis for Approvability or Not-Approval Recommendation

This suspension MDI drug product is somewhat unusual in that

(b) (4)

[REDACTED]

Nevertheless, the stability data for the drug product are adequate. The stability data support a 24 month expiration dating period.

(b) (4)

The approach used for investigating container closure system extractables and drug product leachables is said to have followed that of the recommendations of the Product Quality Research Institute (PQRI) extractables and leachables working group. Extractables/leachables without a quantitative extractables/leachables correlation are controlled as leachables in the drug product. Extractables which are present above the safety concern threshold (SCT) of the PQRI proposal, and for which there is a quantitative extractables/leachables correlation, are controlled as extractables in the respective container closure components. There will not be controls for [REDACTED] (not detected in stability study) since they were not reported above their limits of quantitation (LOQs) through the 18 month time point of

(b) (4)

Executive Summary Section

the placebo stability study. Potential leachables were evaluated in separate reviews by the pharm/tox reviewer and found to be reasonably safe.

The integrated dose counter is set during manufacture to a count of 124 which takes into account the initial 4 priming actuations. The dose counter, therefore, will read 120 actuations (i.e., the label claim) after the priming actuations. Data to show equivalence in performance (Dose Content Uniformity [DCU], Aerodynamic Particle Size Distribution [APSD], spray pattern, plume geometry) between the blue to be marketed actuator with integrated dose counter and the clinical actuators (light blue) without the dose counter are referenced to DMF 19,023, which has been found to be adequate.

Samples of normally functioning drug product returned from clinical studies for laboratory analysis demonstrated that the DCU data are within the range of NDA stability data (except for two outliers). These returned samples, however, did show some tendency towards an (b) (4) of the delivered dose in their APSD. This tendency was justified by the applicant in part by the fact that these clinical returns were near the end of their shelf lives and were near the end of their use life when tested, and because they were tested with patient-used uncleaned actuators.

The (b) (4) strengths of drug products are dose proportional for DCU. (b) (4) This was discussed in the Wrap Up team meeting for this NDA (which included the clinical reviewers and the clinical Division Director); it was concluded that these results are not of clinical concern because the (b) (4) strengths of drug product are dose proportional for DCU, and because the stage grouping (b) (4) which alone did show fairly good APSD dose proportionality (in contrast to the other stage groupings), makes up a significant part of the drug (b) (4)

Single entity comparator MDI products (monoproducts) were used for comparison with the proposed drug product in clinical studies. These comparators are not proposed for marketing.

The container closure system for the mometasone furoate monoproduct is the same as for the proposed drug products. There are (b) (4) of these mometasone furoate monoproducts, differing in strength ((b) (4), 100 mcg and 200 mcg per actuation) and corresponding to the proposed drug product. Each delivers 120 actuations. There is one formoterol fumarate comparator (monoproduct) which delivers 5 mcg/actuation and delivers 120 actuations. It has a number of differences from the proposed drug product.

The composition of the formoterol fumarate comparator MDI monoproduct (5 mcg per actuation) is different from that of the proposed drug product in the following aspects. The differences include the use of HFA 134a as the propellant instead of HFA 227, the addition of lactose (b) (4) and other small differences in the amounts of excipients and formoterol fumarate, plus a different valve (b) (4) instead of the (b) (4). The comparator target is (b) (4) per metered actuation (vs. the drug product, (b) (4) of formoterol fumarate per metered actuation). This comparator has a different ethanol concentration (b) (4) compared to the

Executive Summary Section

proposed drug product [REDACTED] (b) (4) These differences may account for some of the differences in APSD for the formoterol fumarate comparator, compared to the proposed drug product.

The comparison of the monotherapy products with the combination drug product shows that DCU for both actives appears to be reasonably comparable for the monotherapy products and the drug product. The same is true for the APSD data for mometasone furoate (although the monotherapy comparator is not completely identical in the APSD results compared to the drug product, some variability may normally be expected). The APSD data for formoterol fumarate show differences in the individual stage data when comparing the monotherapy product with the combination product. These differences appear to be smaller when comparing stage groupings instead of individual stages, and smaller yet when comparing only fine particle mass [REDACTED] (b) (4). This issue has been discussed with the clinical reviewers and at the mid-cycle and wrap up team meetings (including the clinical Division Director). Specific clinical concerns were not raised. Stability data have been provided for comparator performance only.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Alan C. Schroeder, Ph.D./1-22-2010
Prasad Peri, Ph.D./
Eunice Chung, DPAP Project Manager/

C. CC Block

203 pages has been withheld in full as B(4)
CCI/TS immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22518	ORIG-1	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE

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/s/

ALAN C SCHROEDER
01/22/2010

PRASAD PERI
01/22/2010
I Concur

ONDQA PAL's Initial Quality Assessment
OND Division of Pulmonary and Allergy Products

NDA: 22-518

Applicant: Schering Corporation.

Stamp Date: 22-May-2009

PDUFA Date: 22-Mar-2010

ONDQA 5 month date: 22-Oct. 2009

Proposed Proprietary Name: Dulera® (mometasone furoate and formoterol fumarate dihydrate) Inhalation Aerosol

Established Name: mometasone furoate and formoterol fumarate dihydrate

Dosage form and strength: Inhalation Aerosol, (b) (4)
(b) (4) DULERA® 100/5 (mometasone furoate 100 mcg and formoterol fumarate dihydrate 5 mcg), DULERA® 200/5 (mometasone furoate 200 mcg and formoterol fumarate dihydrate 5 mcg).

Route of Administration: Oral inhalation

Indications: (b) (4) treatment of asthma (b) (4) (b) (4) in patients 12 years of age and older

PAL: Prasad Peri, Ph.D. Branch II/DPA I/ONDQA

Fileability recommendation: Acceptable for filing

Review team recommendation: Single primary reviewer (Alan Schroeder, Ph.D)

Time goals:

- **Initial Quality Assessment in DFS: by 22-Jun-2009**
- **Chemistry filing memo in DFS: by 22-Jun-2009**
- Filing decision "Day 45": 6-July-2009 (tentative; to be set by Clinical Division)
- Filing review issues "Day 74": 8-Aug-2009 (tentative; to be set by Clinical Division)
- **Chemistry Review (DR/IR) letter: by 22-OCT-2009**
- Mid-cycle meeting "Month 5": 22-Oct-2009
- Wrap Up: ~15-Jan-2010
- **Final Chemistry Review "Month 8" in DFS: by 22-Dec-2010**

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	To be determined by Primary Reviewer
CDRH	<i>Not Applicable</i>
EA	To be assessed by Primary Reviewer
EES	EER sent to Office of Compliance on 16-Jun-2009
DMETS	<i>Labeling consult request will be sent as part of DPAP's request.</i>
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	Microbiological aspects to be evaluated
Pharm/Tox	Consults for impurities with structural alerts to be sent.

Related documents

IND 70,283 (FORMOTEROL FUMARATE/MOMETASONE FUROATE)

IND 52,214 (MOMETASONE FUROATE/HFA-227 MDI)

NDA 21, 067 (Asmanex Inhalation Powder)

NDA 20, 831 (Foradil Aerolizer)

DMF 12380 (FORMOTEROL FUMARATE, MANUFACTURED IN IBARAKI-KEN, JAPAN)

(b) (4)

DMF 11732 (ALUMINIUM CAN MANUFACTURED IN LANCASHIRE, GREAT BRITAIN)

DMF 15999 (b) (4) ALUMINIUM CANISTERS AS MANUFACTURED IN LANCASHIRE, GREAT BRITAIN)

DMF 19023 (PMDI ACTUATOR AS MANUFACTURED IN DUBLIN, IRELAND)

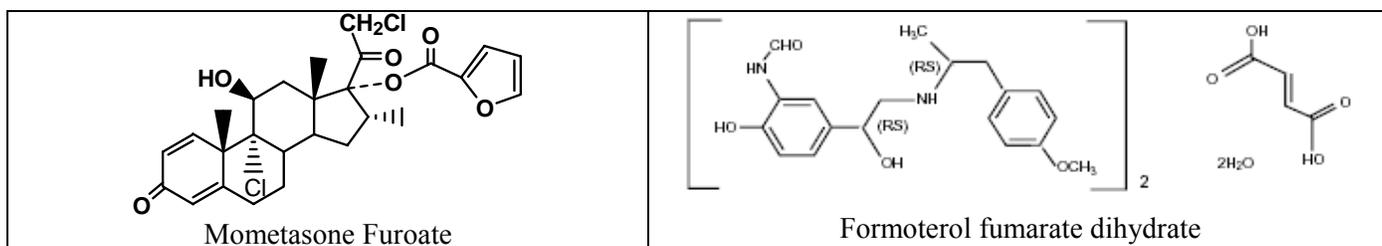
DMF 20406 (3M INTEGRATED DOSE-BY-DOSE COUNTER AS MANUFACTURED (b) (4) IN DUBLIN, IRELAND FOR 3M DRUG DELIVERY SYSTEMS DIVISION)

Summary:

- This is an electronic NDA in CTD format with electronic labeling provided in SPL format. There is a Quality Overall Summary. This NDA is filed as a 505(b)(1) application.

Drug Substance

- Drug substances mometasone furoate (anti-inflammatory corticosteroid) and formoterol fumarate (long acting beta agonist) are approved in other NDAs. They are both (b) (4) drug substances and are micronized to a size suitable for inhalation delivery.
- References to the NDA applications 21067 (Asmanex) and 20-831 (Foradil Aerolizer) are provided. In addition a DMF letter of authorization is also provided to DMF 12380 (FORMOTEROL FUMARATE, MANUFACTURED IN IBARAKI-KEN, JAPAN, by Astellas).
- The drug substance structures are shown in the table below. Although the formoterol fumarate has been referenced in DMF 12380, it appears that this DMF was last reviewed in 1998 by Dr. John Leak. There are several updates made to the DMF since then which have never been reviewed. It should be noted that this DMF was also referenced in NDA 20831 for Foradil Aeroliser. This NDA was approved in 2001.
- All information for mometasone furoate has been referenced to NDA 21067 (Asmanex Twisthaler) which was approved in the US in 2005.
- Information on the container closure system, analytical methods, and stability for mometasone and formoterol are referred to the NDA 21067 and NDA 20-831 (Foradil Aerolizer)/ DMF 12380 respectively. Specifications for the drug substances are provided and are attached later in the IQA. Note that Asmanex® Twisthaler® is owned by Schering Plough and Foradil® Aeroliser® is owned by Novartis who is a partner to Schering Corporation for this application.



Drug Product

- The drug products contain the drug substances Mometasone Furoate Anhydrous and Formoterol Fumarate Dihydrate, which are hereafter referred to as Mometasone Furoate and Formoterol Fumarate, respectively. The drug products (various strengths) are white suspensions containing (b) (4) alcohol dehydrated/ethanol anhydrous (USP-NF) (hereafter referred to as ethanol) (b) (4) oleic acid (b) (4) (USP-NF), (hereafter referred to as oleic acid) and (b) (4) HFA 227 (b) (4) DMF (b) (4) (hereafter referred to as HFA 227). The drug products are formulated in (b) (4) strengths each designed to deliver a minimum of 120 actuations. **One therapeutic dose is obtained from two single actuations of the drug products.** The function and grade of the excipients are listed in a Table shown on the next page.
- The composition of the (b) (4) per actuation drug Product is shown on the following page along with the batch formula for the commercial scale (b) (4)



Supporting NDA or IND: None.

Supporting DMF: 18948

DMF	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
12380	II	Astellas Pharmaceutica l Inc.	Formoterol Fumarate	<u>Updates To be reviewed</u>
<div style="background-color: #cccccc; width: 100%; height: 100%; position: relative;"> (b) (4) </div>				Updates to be reviewed
				To be reviewed but similar components used in other pumps likely
11732	III	3M	Aluminum canister	Adequate. Reviewed by Dr. Art Shaw on Dec. 25-2007 in support of NDA 21-658. Same material used in other cans.

ONDQA PAL's Initial Quality Assessment

DMF	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
15999	III	3M	(b) (4) Aluminum Canister	Review needed. e
20406	III	(b) (4) 3M	Dose Counter	Review Needed
19023	III	(b) (4) 3M	Press and Breath actuator	Review needed

CHEMISTRY NDA FILEABILITY CHECKLIST

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		In drug product QOS.
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?		X	

Preliminary CMC comments for the 74 day letter

1. Identify updates and changes in the CMC information for mometasone furoate and formoterol fumarate since approval of the referenced NDAs for these drug substances. Provide to NDA 22-518 full drug substance specifications (acceptance criteria and analytical procedures) for each drug substance and specify acceptance testing performed on receipt of the drug substances, as well as test data accepted on a certificate of analysis. Attach structural formulas of the drug substance and all organic impurities to the specification sheets.
2. Provide side by side comparative performance data (full profile of APSD and Emitted Dose) for the individual and mean values (including standard deviation) for the combination product versus the monotherapy products (Mometasone furoate MDI) and (Formoterol Fumarate MDI). This information may be provided graphically and in a tabular form. Clarify if the monotherapy product Formoterol Fumarate MDI was formulated in the HFA 227. If not, illustrate the challenges in developing this HFA 227 formulation and using it as a monotherapy comparator in phase three clinical trials. If there are pharmaceutical differences (APSD and Emitted Dose) in the performance aspects of the combination product and monotherapy products, interpretation of the results obtained in the clinical trials might be difficult if not impossible. The differences cannot be easily attributable to the drug product. Provide the approximate time of manufacture and time of test for the samples used in the performance testing mentioned above.
3. Clarify if the drug product characterization studies were carried out with drug product that underwent stabilization process.
4. Provide the total number of devices used in the phase 3 trials and indicate the number and percentage of devices with dose counter.
5. Update the NDA with real time stability data (e.g., 18 months and 24 months) for the additional stability batches.

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
08/04/2009
Acceptable for filing

ALI H AL HAKIM
08/04/2009

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: NDA 22518/000
Code: 570
Priority: 4S
Stamp Date: 22-MAY-2009
PDUFA Date: 22-MAR-2010
Action Goal:
District Goal: 21-JAN-2010

Sponsor: SCHERING
2000 GALLOPING HILL RD
KENILWORTH, NJ 070330530
Brand Name: MOMETASONE FUROATE/FORMOTEROL
FUMARATE
Estab. Name:
Generic Name: DULERA

Product Number; Dosage Form; Ingredient; Strengths

001; AEROSOL, METERED; MOMETASONE FUROATE;
200UGM/1INH
001; AEROSOL, METERED; FORMOTEROL FUMARATE;
5UGM/1INH
002; AEROSOL, METERED; MOMETASONE FUROATE;
100UGM/1INH
002; AEROSOL, METERED; FORMOTEROL FUMARATE;
5UGM/1INH

(b) (4)

FDA Contacts:	E. CHUNG	Project Manager	301-796-4006
	P. PERI	Review Chemist (HFD-820)	301-796-1730
	A. AL HAKIM	Team Leader	301-796-1323

Overall Recommendation: ACCEPTABLE on 22-MAR-2010 by E. JOHNSON (HFD-320) 301-796-3334

Establishment: CFN: 9610441 FEI: 3002807586

3M HEALTH CARE LTD
LE11152

LOUGHBOROUGH, LEICESTERSHIRE, UNITED KINGDOM

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-MAR-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 2126770 FEI: 2126770
3M PHARMACEUTICALS INC
3M CENTER BLDG 275, 260
ST PAUL, MN 55144

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-NOV-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 9611250 FEI: 3002808523
ASTELLAS PHARMA CHEMICALS CO., LTD., TAKAHAGI PLANT
160-2 AKAHAMA
TAKAHAGI-SHI IBARAKI, JAPAN

DMF No: 12380 AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-MAR-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 9612715 FEI: 3002807776
NOVARTIS PHARMA AG
CORK
RINGASKIDDY, CORK, IRELAND

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-JUN-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 9692042 FEI: 3002865753
NOVARTIS PHARMA STEIN AG
PRATTELN, BASEL-LANDSCHAFT, SWITZERLAND

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-JAN-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 9692043 FEI: 3002653483
NOVARTIS PHARMA STEIN AG
SCHAFFHAUSERSTRASSE
STEIN, SWITZERLAND

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MICRONIZER

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-JUL-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 2210048 FEI: 2210048
SCHERING CORP
2000 GALLOPING HILL RD
KENILWORTH, NJ 070330530

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Profile: AEROSOL DISPERSED MEDICATION OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 08-MAR-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 9614153 FEI: 3002808083
SCHERING-PLOUGH; SINGAPORE
50 TUAS WEST DRIVE
SINGAPORE, , SINGAPORE

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE LABELER
DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-MAR-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-JUN-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE
