

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205641Orig1s000

CHEMISTRY REVIEW(S)

**NDA 205-641 CR01 Addendum 01**

Date	23-Apr-2014
NDA	205-641
Applicant	Merck Sharp & Dohmn Corp.
Drug	Asmanex HFA
Reviewer	Xiaobin Shen, Ph.D.

NDA 205-641 was recommended for approval in chemistry review 01 signed off on 18-Mar-2014. At the end of the review the Agency listed two comments to be communicated to the applicant; the applicant provided their responses to these comments on 22-Apr-2014 in Amendment 0010. This review evaluates the applicant responses.

The 1st Agency comment was –

Update your post-approval long term ongoing stability study protocol to specify the storage orientation (valve up, down, or horizontal).

The applicant response is –

The Sec.3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment is updated to specify the valve down orientation for the stability study.

Evaluation: Adequate.

The 2nd Agency comment was –

As required under 21 CFR 314.81(b)(1)(ii), commit to immediately discuss with the Agency any aberrations of the drug product from its approved specifications and to withdraw the affected lots from the market as warranted.

The applicant response is –

Merck Sharp & Dohme Corp. (Merck) maintains suitable procedures within the Merck Manufacturing Division that ensures compliance with the requirements of 21 CFR 314.81 (b)(1)(ii) for Asmanex[®] HFA. Consistent with these Quality procedures, Merck will discuss aberrations of drug product from approved specifications with FDA in a timely manner and withdraw affected batches from the market as warranted.

Evaluation: Adequate.

Both comments are satisfactorily addressed.

Xiaobin Shen, Ph.D.
Chemistry Reviewer

Prasad Peri, Ph.D.
Branch VIII Chief, ONDQA

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

/s/

XIAOBIN SHEN

04/23/2014

The responses are adequate. The NDA remains recommended for approval from CMC perspective.

CRAIG M BERTHA

04/23/2014

Signing for Dr. P. Peri

NDA 205-641

**Asmanex HFA
(Mometasone Furoate)**

Merck Sharp & Dohme Corp.

**Xiaobin Shen, Ph.D.
for
Division of Pulmonary, Allergy and Rheumatology Drug
Products**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Substance and Drug Product.....	7
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	9
III. Administrative.....	9
A. Reviewer’s Signature.....	9
B. Endorsement Block.....	9
C. CC Block	9
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S DRUG SUBSTANCE [Mometasone Furoate]	10
P DRUG PRODUCT [Mometasone Furoate, Metered Dose Inhaler]	12
R REGIONAL INFORMATION	48
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	48
A. Labeling & Package Insert	48
B. Environmental Assessment Or Claim Of Categorical Exclusion	53

Chemistry Review Data Sheet

1. NDA 205-641
2. REVIEW #: 1
3. REVIEW DATE: 13-Mar-2014
4. REVIEWER: Xiaobin Shen, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

NA

Document Date

NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Document Date

27-Jun-2013

Other amendments older than the last listed do not have CMC related information for review.

7. NAME & ADDRESS OF APPLICANT:

Name: Merck Sharp & Dohme Corp.

Address: One Merck Drive, P.O. Box 1000, Whitehouse, NJ 08889

Scott Hambaugh
Representative 351 N. Sunnyside Pike
(Agent): P.O. Box 1000, UG2C-26
North Wales, PA 19454-2505

Telephone: 267-305-5867

Fax: 732-594-4980

Email: Scott.hambaugh@merck.com

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

- a) Proprietary Name: Asmanex HFA
b) Non-Proprietary Name (USAN): Mometasone Furoate
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Corticosteroid

11. DOSAGE FORM: Metered Dose Inhaler

12. STRENGTH/POTENCY: 100 mcg and 200 mcg per actuation

13. ROUTE OF ADMINISTRATION: Inhalation by the oral route

14. Rx/OTC DISPENSED: X Rx ___ OTC

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

___ SPOTS product – Form Completed

X Not a SPOTS product

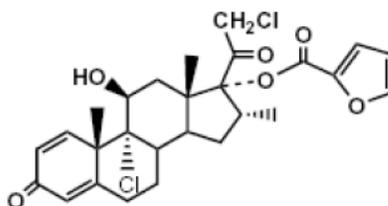
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: 9,21-dichloro-11(Beta),17-dihydroxy-16 (alpha)-methylpregna-1,4-diene-3,20-dione 17-(2-furoate)

United States Adopted Name (USAN): Mometasone furoate

Compendial name: Mometasone furoate

Chemical structure:



Molecular formula: C₂₇H₃₀Cl₂O₆

Molecular weight: 521.44 g/mol

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	4	(b) (4)	(b) (4)	4		*See note below.	
				4		*See note below.	
				4		*See note below.	
	3			4		*See note below.	
	3			4		*See note below.	
	3			1		21-Feb-2014	
	3			4		*See note below.	

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) (4). The DMFs have new amendments since their last review (b) (4). There is no safety and quality concern expected based on the reviews conducted at time of (b) (4) approval. This table will be updated in a review addendum once the DMF amendments are reviewed.

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22518	MF/formoterol fumarate inhalation aerosol (Dulera®) for asthma (b) (4)
NDA	21067	MF inhalation powder (Asmanex® Twisthaler® for prophylaxis for asthma
IND	70283	MF/formoterol fumarate inhalation aerosol
IND	52214	MF inhalation aerosol
IND	46216	MF inhalation aerosol
Pre-IND	112669	MF inhalation aerosol

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	06-AUG-2013	
Pharm/Tox	Not needed		
Biopharm	Not needed		
Methods Validation	Not needed		
EA	Not needed		
Microbiology	Not needed		

The Chemistry Review for NDA 205-641

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval.

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

NA.

II. Summary of Chemistry Assessments

This NDA has [REDACTED] (b) (4)
[REDACTED] The differences between this Asmanex[®] and the Dulera[®] products are —

1. Dulera[®] is a combination product that contains two actives, namely, mometasone fuorate and formoterol fumarate actives; while Asmanex[®] only contains a single active mometasone fuorate, which is at the same strengths as the Dulera[®].
2. The Dulera[®] metered dose inhalers have a green mouthpiece cover; while the Asmanex[®] metered dose inhalers have a pink mouthpiece cover; both products use the same blue actuator.

Essentially, when manufacturing the Asmanex[®] products, the applicant has excluded the formoterol fumarate active, which is [REDACTED] (b) (4) by weight, from the Dulera[®] products and replaced it with [REDACTED] (b) (4). The colorant of metered dose inhaler mouthpiece cover has also been changed from green to pink. [REDACTED] (b) (4)
[REDACTED]

The submitted NDA therefore referenced to the already approved NDA 22-518 for support of the common contents between both products. Correspondingly, the focuses of this review are on the information unique to this NDA, what is common and already deemed acceptable in the Dulera[®] NDA commercially available will not be further evaluated.

A. Description of the Drug Substance and Drug Product

Executive Summary Section

Mometasone Furoate drug substance is the same as used in the Asmanex[®] Twisthaler[®] and Dulera[®] drug products, all information is referenced to those two approved NDAs (21-067 and 22-518) that are currently marketed.

The drug products are manufactured as 100 mcg and 200 mcg per actuation strengths pressurized metered dose inhalers (pMDI) designed to deliver a minimum of 120 actuations. Each dose is achieved with two single actuations of the product. The drug product formulation contains (b) (4) ethanol (b) (4) (b) (4) oleic acid, both are USP grade and have additional quality controls required for inhalation use documented in the supporting NDA 22-518, and (b) (4) HFA 227 as excipients. The HFA 227 also functions as propellant. The product formulation is packaged and sealed in its container closure system that is also an integral part of the drug product. The container closure system quantifies and delivers the active when the user actuates the product. Specifically, the container closure system consists of a 16 mL aluminum canister (b) (4) closed with a (b) (4) valve. A (b) (4) press and breathe actuator with the mouthpiece cap is provided with the pressurized canister to deliver a dose to the patient. The (b) (4) actuator incorporates an integrated displacement driven dose counter. All excipients and container closure system used (b) (4) the color of the cap cover is pink. The pink actuator cover is supported by DMF (b) (4) that is deemed adequate.

The drug product specifications include appearance, identification, assay, related substances, dose content uniformity, aerodynamic particle size distribution, ethanol content, water content, degradation products of ethanol, leachables, microbial limits, foreign particulate, microscopic examination, fill weight, valve delivery, number of actuations per container, leak rate and spray pattern. All acceptance limits are the same as those of the corresponding quality attributes for the Dulera[®] products and supported by the actual release and stability results. This is expected because the excluded second active formoterol fumarate is less than (b) (4) of the Dulera[®] formulation.

Almost all release and real time stability results met the proposed and fully justified drug product specifications. Low rate occurrence of out of specification dose content uniformity results, at a maximum of (b) (4) for individual and (b) (4) for mean data per product strength, have been observed from the stability results available for up to 24 months when stored at long term (25°C/60% RH) conditions. Such occurrences appear to be random and most likely associated with the commonly seen large variations of pMDI products. The occurrences are acceptably justified and its rate is similar to that of Dulera[®]. As expected, the stability results exhibit similar trends as those of Dulera[®].

Overall, the provided stability data support the applicant proposed 36 month product expiry in consideration of the referenced support of 36 month stability data from the (b) (4)

Executive Summary Section

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 deliver a minimum of 120 actuations. It is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older.

It should be administered twice daily (morning and evening) via oral inhalation; Each dose is achieved with 2 actuations.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission provided acceptable information on the chemistry, manufacturing, and controls of the Asmanex[®] pMDI. The product is recommended for approval based on the following:

- The drug substance and product specifications provided adequate controls;
- The drug product excipients are of USP/NF grade and have additional quality controls to make them suitable for inhalation use;
- The drug product container closure systems are acceptable for pharmaceutical use.
- Both drug substance and drug product are stable in the studied stability period and support the currently claimed 36 months of drug product expiry.

III. Administrative**A. Reviewer's Signature**

Review is digitally signed off in DARRTS.

B. Endorsement Block

Chemist Name/Date: Xiaobin Shen, Ph.D. / 13-Mar-2014.

Acting CMC Lead Name/Date: Craig M. Bertha, Ph.D. / 13-Mar-2014.

Project Manager Name/Date: Youbang Liu, Ph.D. / 13-Mar-2014

C. CC Block

47 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

XIAOBIN SHEN

03/14/2014

The NDA is recommended for approval from CMC perspective. Please send the two comments at end of the review to the applicant.

CRAIG M BERTHA

03/18/2014

I concur

**Asmanex® HFA (Mometasone Furoate) Inhalation Aerosol
NDA 205641**

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

Applicant: Merck Sharp & Dohme Corp.
One Merck Drive
P.O. Box 1000
Whitehouse, NJ 08889

Indication: Asmanex® is a corticosteroid drug product indicated for the prophylactic maintenance treatment of asthma in patients 12 years and older (not for acute bronchospasm)

Presentation: There are two strengths of the inhalation aerosol drug product: 100 and 200 mcg of mometasone furoate (MF) per actuation delivered from the mouthpiece. The drug product formulation is a suspension of MF in HFA-227 (1,1,1,2,3,3,3-heptafluoropropane) and ethanol, with oleic acid as a surfactant. The inhalation aerosol also includes a numerical dose counter, and is designed to deliver 120 actuations.

EER Status: Acceptable.

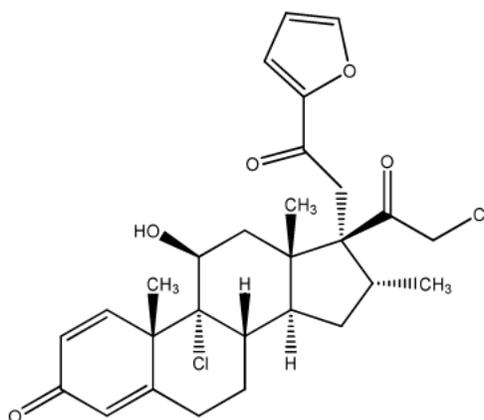
Consults: EA – categorical exclusion provided
Statistics – N/A
Methods Validation – Deemed not necessary to be forwarded to Agency laboratory.
Microbiology – N/A
Pharmacology/toxicology – N/A

Original Submission: 27-JUN-2013

Re-submissions: N/A

Post-Approval CMC Agreements: None beyond the typical stability commitment (see comments for applicant in CMC review #1).

Drug Substance: The drug substance is mometasone furoate, a glucocorticoid, and information has been provided by the applicant by cross-reference to their approved NDAs 22518 (Dulera Inhalation Aerosol) and 21067 (Asmanex Inhalation Powder), both for the oral inhalation route of administration.



Mometasone Furoate

Conclusion: Drug substance is acceptable.

Drug Product: The drug product is a suspension-based inhalation aerosol, which contains (b) (4) mometasone furoate (MF), (b) (4) (b) (4) ethanol, (b) (4) oleic acid, with the remainder HFA-227 propellant (1,1,1,2,3,3,3-heptafluoropropane). There are two strengths of the drug product included in the application, 100 and 200 mcg MF/actuation (b) (4)

that there is no formoterol fumarate suspended in the formulation, the applicant has not presented additional pharmaceutical development studies. This is not unreasonable as the MF monotherapy product was deemed to be suitably comparable in terms of dose delivery characteristics to be used in the supportive clinical studies for Dulera® (see p. 172 of CMC review #1 for N22518 dated 22-JAN-2010).

The label recommends twice daily dosage of Asmanex® at 100 and 200 mcg strengths, with a starting dosage based on prior therapy. The current proposed expiration dating period of 36 months is found to be acceptable based on evaluation of all data provided.

Conclusion: Drug product is satisfactory.

Overall Conclusion: From a CMC perspective, the application is recommended for approval.

Craig M. Bertha, Ph.D.
Acting CMC Lead, Branch IIIV
DNDQA III I/ONDQA

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

/s/

CRAIG M BERTHA
03/18/2014

Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

APPLICATION INFORMATION

1. NEW DRUG APPLICATION NUMBER: N205641

Asmanex® HFA is the trademark proposed by the applicant for mometasone furoate (MF) formulated as an inhalation aerosol for the treatment of asthma. The applicant claims that the two strengths of the Asmanex® HFA inhalation aerosol “ (b) (4)

” Therefore, it is recommended that the reviewer familiarize him or herself with the approved Dulera® Inhalation Aerosol combination and combination drug product of NDA 22518, and associated CMC reviews, as it is likely that much of the material and data supporting and control strategy for the current NDA is analogous or similar to what was approved for Dulera®. For example, (b) (4)

. Additionally, the Asmanex® HFA drug product uses the same container closure system as the Dulera® drug product except that the mouthpiece cap color differs.

2. Drug Name: Asmanex® HFA¹ (mometasone furoate) Inhalation Aerosol

¹ Typically applicants are discouraged from using “HFA” as part of the proprietary name if there had been no previously approved chlorofluorocarbon inhalation aerosol version. However, it is noted that having the HFA present in this particular case might be considered beneficial to help distinguishes this drug product from the approved Asmanex® Twisthaler® Inhalation Powder drug product.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205641

Received Date: 27-JUN-2013

The chemistry classification code is **type 3 – New Dosage Form**. There are two strengths of the drug product, with 100 and 200 mcg of MF per actuation delivered from the mouthpiece. The drug product formulation is a suspension of MF in HFA-227 (1,1,1,2,3,3,3-heptafluoropropane) and ethanol, with oleic acid as a surfactant.

3. RECEIVED DATE: 27-JUN-2013 (Applicant: Merck Sharp & Dohme Corp.)

4. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	4	(b) (4)	(b) (4)	18-APR-2013	Last reviewed 22-DEC-2009
				17-JUL-2012	Verify LOA in file; not reviewed for specified (b) (4)
				17-JUL-2012	Verify LOA in file
3				12-JUL-2012	Not reviewed for specified (b) (4)
3				29-APR-2013	Verify LOA in file; Refer to review of 02-NOV-2009 for Dulera®
3				29-APR-2013	Refer to review of 06-JAN-2010 supporting Dulera®
3		29-APR-2013	Refer to review of		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205641

Received Date: 27-JUN-2013

		(b) (4)		22-OCT-2009 supporting Dulera®
--	--	---------	--	--------------------------------------

b. Recommended Consults

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	X	<input type="checkbox"/>	Request evaluation of stability data if trends in parameters will limit expiry (e.g., water content, ethanol content, leachables, degradants).
Clin Pharm	<input type="checkbox"/>	X	
EES	X	<input type="checkbox"/>	Submitted to OC by ONDQA PM on 18 & 22-JUL-2013
Pharm/Tox	<input type="checkbox"/>	X	Compare controls (tests/acceptance criteria) for drug product impurities and leachables to that applied for the approved Dulera® application. If comparable, then there would be no need to request the pharmacology/toxicology team evaluate these controls.
Methods Validation	<input type="checkbox"/>	X	Left to reviewer discretion if any drug product methods are questionable, but MF is not an NME so it is not mandatory that any methods be assessed by the Agency laboratory.
EA	<input type="checkbox"/>	X	Applicant claims environmental introduction concentration allows exclusion as per 21 CFR 25.31(b); reviewer can evaluate if any data are needed to support claim.
New Drug Micro	<input type="checkbox"/>	X	Inhalation Aerosol drug products are not sterile. Drug product specification is consistent with recommendations of USP <1111> for oral inhalation drug products. The microbiology team has been notified of the application and will determine if any microbiology review is needed.
CDRH	<input type="checkbox"/>	X	(b) (4) N22518 (Dulera® Inhalation Aerosol) according to the applicant.
Other	<input type="checkbox"/>	X	N/A

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205641

Received Date: 27-JUN-2013

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
NDA		22518	MF/formoterol fumarate inhalation aerosol (Dulera®) for asthma (b) (4)
NDA		21067	MF inhalation powder (Asmanex® Twisthaler®) for propylaxis for asthma
IND		70283	MF/formoterol fumarate inhalation aerosol
IND		52214	MF inhalation aerosol
IND		46216	MF inhalation powder
pre-IND		112669	MF inhalation aerosol

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205641

Received Date: 27-JUN-2013

d. Previous Communications with the Applicant to note (see module 1.6.3 for complete detail):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
Written responses	09-SEP-2011	pre-IND 112669	Agency responds to CMC, clinical, and clinical pharmacology questions
Written responses	14-SEP-2011	pre-IND 112669	Clarification regarding above written response

OVERALL PRODUCT QUALITY CONCLUSIONS AND RECOMMENDATIONS

Is the Product Quality Section of the application fileable from a CMC perspective?

Yes	No	CMC Filing Issues
X	<input type="checkbox"/>	1.

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?

Yes	No	
<input type="checkbox"/>	X	

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?

Yes	No	Biopharmaceutics Filing Issues
<input type="checkbox"/>	<input type="checkbox"/>	To be separately assessed by the biopharmaceutics team

Are there potential biopharmaceutics review issues to be forward to the Applicant with the 74 day letter?

Yes	No	
<input type="checkbox"/>	<input type="checkbox"/>	See above

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205641

Received Date: 27-JUN-2013

Does the submission contain any of the following elements?

	Yes	No	Comments
Botanical Products	<input type="checkbox"/>	X	
Combination Products	X	<input type="checkbox"/>	
Nanotechnology	<input type="checkbox"/>	X	
PET	<input type="checkbox"/>	X	
QbD Elements	<input type="checkbox"/>	X	
SPOTS	<input type="checkbox"/>	X	

Is a team review recommended?

Yes	No	Suggested expertise for team
<input type="checkbox"/>	X	

CMC Summary: Critical Issues and Complexities

(This section is formatted to expand as far as needed by author.)

Background: The drug substance is MF, which is a glucocorticosteroid to be used for the treatment of asthma. The current drug product (b) (4)

This inhalation aerosol drug product includes a dose counter.

All CMC information related to the drug substance, the glucocorticoid mometasone furoate (b) (4), is referenced to the Asmanex® Twisthaler® Inhalation Powder N21067, although a copy of the drug substance specification from that application is included in S.4.1. The specification from N21067 is appropriate for the current application as the formulation is suspension-based. There is no obvious reason, based on this preliminary review, for the reviewer to evaluate any aspects related to the MF drug substance covered by N21067. Note that the Dulera® Inhalation Aerosol also uses the same drug substance.

The drug product is a suspension-based inhalation aerosol, which contains (b) (4) mometasone furoate (MF), (b) (4) (b) (4) ethanol, (b) (4) oleic acid, with the remainder HFA-227 propellant (1,1,1,2,3,3,3-heptafluoropropane). There are two strengths of the drug product included in the application, 100 and 200 mcg MF/actuation.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205641

Received Date: 27-JUN-2013

The ethanol and oleic acid are listed as compendial grade (USP/NF). The reviewer should refer to our draft guidance regarding additional considerations for controls for these two excipients when used as part of an inhalation aerosol formulation (see section C.III.2). (b) (4)

(b) (4) the applicant has not presented additional pharmaceutical development studies. This is not unreasonable as the MF monotherapy product was deemed to be suitably comparable in terms of dose delivery characteristics to be used in the supportive clinical studies for Dulera® (see p. 172 of CMC review #1 for N22518 dated 22-JAN-2010).

As addressed in the responses to the firm's questions in the Pre-IND 112669 package dated 10-AUG-2011, not only has the applicant provided comparative release and stability data for drug product batches (DOM from 2005-2012) prepared at the planned commercial site (b) (4) with the commercial process (see P.5.4 and P.8.3), but they have also provided comparative release data for the original formulation (100 and 200 mcg strengths) prepared at (b) (4) in 1997 to the to-be-marketed product (see P.5.4.3.1). Many of the clinical trials were done in 1997 using the original formulation, so the reviewer should also evaluate the comparative data in P.5.4 for the old (1997) versus the newer (2005 and on) MF MDI and confer with the clinical team on the potential importance of any significant differences. See the listing of relevant drug product batches in tables 8 and 1 below.

Start of Applicant Material

Table 8 "Original" Asmanex pMDIs and new Mometasone Furoate pMDI Batches used in Performance Comparison

Product	Drug Product Batch Number	Strength (mcg/actuation)	Date of Manufacture (b) (4)	Site of Manufacture (b) (4)	Manufacturing Process Overview (b) (4)
Original Asmanex pMDIs	38101-039	100	(b) (4)	(b) (4)	(b) (4)
	38101-042	100			
	38101-040	200			
	38101-043	200			
New MF pMDIs	GGJ044	100			
	GGJ045	200			
	GMA049	100			
	GME096	200			
	GNB217	200			

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205641

Received Date: 27-JUN-2013

The batches presented in **Table 1** are representative of the commercial drug products and were manufactured at the commercial site.

Product Strength (mcg/Actuation)	Batch	Date of Manufacture	Batch Size (units)	Use of Batch
100	GGJ044	(b) (4)	(b) (4)	Clinical/ Stability
100	GMA049			Stability
200	GGJ045			Clinical/Stability
200	GME096			Stability
200	GNB217			Stability

End of Applicant Material

Also addressed in the Pre-IND correspondence was the issue of drug product characterization studies. Due to the similarity of the drug product to Dulera®, the studies are truncated as agreed, with only the dose proportionality studies to be repeated (see P.5.4.2 for data). The Pre-IND correspondence also addressed what stability data were agreed upon to be included in the application. The applicant has provided the agreed upon stability data (see table 1 reproduced below).

Start of Applicant Material

Drug product Batch Number	100 mcg per actuation		200 mcg per actuation		
	GGJ044	GMA049	GGJ045	GME096	GNB217
Storage Conditions	25°C/60% RH 40°C/75% RH	25°C/60% RH 40°C/75% RH	25°C/60% RH 40°C/75% RH	25°C/60% RH 40°C/75% RH	25°C/60% RH 40°C/75% RH
Storage Orientation	Valve Down Valve Up	Valve Down Valve Up Horizontal	Valve Down Valve Up	Valve Down Valve Up Horizontal	Valve Down Valve Up Horizontal
Manufacturing Date	(b) (4)				
Batch Size (units)	(b) (4)				
Months of Stability Data Included in this Submission	24	12	24	12	6

End of Applicant Material

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205641

Received Date: 27-JUN-2013

Description of Facility Related Risks or Complexities (i.e. foreign sites, large number of sites involved, etc.)

See EES for complete list of facilities related to this application.

Three sites have been entered into the EES request (18 & 22-JUL-2013). The drug substance manufacturer is a Merck site located in Singapore whereas the drug product manufacturer is a 3M site in England. (b) (4)

(b) (4) Thus, there are a relatively small number of sites involved in the production of the drug product, but they are foreign sites.

Biopharmaceutics Filing Review: Summary, Critical Issues and Complexities

(This section can expand as far as needed by author.)

Note: A separate filing review will be provided by the biopharmaceutics team.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205641

Received Date: 27-JUN-2013

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL					
	Parameter	Yes	No	N/A	Comment
1.	Is the CMC section organized adequately?	X	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X	<input type="checkbox"/>	<input type="checkbox"/>	
3.	Are all the pages in the CMC section legible?	<input type="checkbox"/>	<input type="checkbox"/>		All pages examined for production of this IQA were legible.
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X	<input type="checkbox"/>	<input type="checkbox"/>	The adequacy of the provided data will be determined during review.

B. FACILITIES*					
	Parameter	Yes	No	N/A	Comment
5	Is a single, comprehensive list of all involved facilities available in one location in the application?	<input type="checkbox"/>	X	<input type="checkbox"/>	See module 1.1.2 of Sequence # 0000 (attachment to Form 356h) and P.3.1
6	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.	<input type="checkbox"/>	<input type="checkbox"/>	X	(b) (4)

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205641

Received Date: 27-JUN-2013

7	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X	<input type="checkbox"/>	<input type="checkbox"/>	
	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X	<input type="checkbox"/>	<input type="checkbox"/>	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205641

Received Date: 27-JUN-2013

9	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	<input type="checkbox"/>	X	<input type="checkbox"/>	See question 5 above.
1	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X	<input type="checkbox"/>	<input type="checkbox"/>	

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT					
	Parameter	Yes	No	N/A	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	It is left to the reviewer to decide whether or not supportive information or data is needed for the request for categorical exclusion under 21 CFR 25.31(b); Applicant also claims that they know of no extraordinary circumstances regarding the EA.

D. MASTER FILES (DMF/MAF)					
	Parameter	Yes	No	N/A	Comment

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205641

Received Date: 27-JUN-2013

12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X	<input type="checkbox"/>	<input type="checkbox"/>	<i>See table on cover page.</i>
-----	---	---	--------------------------	--------------------------	---------------------------------

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)					
	Parameter	Yes	No	N/A	Comment
13.	Does the section contain a description of the DS manufacturing process?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Yes, by reference to approved NDA 21067.
14.	Does the section contain identification and controls of critical steps and intermediates of the DS (in process parameters)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
15.	Does the section contain information on impurities?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
16.	Does the section contain information regarding the characterization of the DS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
17.	Does the section contain controls for the DS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above; the NDA contains the specification sheet for the drug substance.
18.	Has stability data and analysis been provided for the drug substance?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
21.	Does the section contain container and closure information?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205641

Received Date: 27-JUN-2013

F. DRUG PRODUCT (DP)					
	Parameter	Yes	No	N/A	Comment
22.	Does the section contain quality controls of excipients?	X	<input type="checkbox"/>	<input type="checkbox"/>	By reference to approved Dulera® application NDA 22518
23.	Does the section contain information on composition?	X	<input type="checkbox"/>	<input type="checkbox"/>	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X	<input type="checkbox"/>	<input type="checkbox"/>	Reviewer is advised to compare this section to that approved for Dulera® as the (b) (4) this description should be evaluated for completeness as no actual master production record is provided.
25.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X	<input type="checkbox"/>	<input type="checkbox"/>	Refer to P.3.4 for control of critical steps; there are no intermediate products associated with the drug product manufacture
26.	Is there a batch production record and a proposed master batch record?	<input type="checkbox"/>	X	<input type="checkbox"/>	Although an executed batch record is provided for one of the 200 mcg strength (representative commercial) batches, no master production record is provided: see comment for 24 above. Note the application is submitted under 505(b)(1), not (b)(2) so the inclusion of the actual master production record is not necessarily required.
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	<input type="checkbox"/>	X	<input type="checkbox"/>	No. (b) (4)
28.	Have any biowaivers been requested?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The biopharmaceutics team will address any biowaiver requests.
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	X	<input type="checkbox"/>	<input type="checkbox"/>	By reference to the approved Dulera® NDA 22518 and associated DMFs (b) (4) and (b) (4)

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205641

Received Date: 27-JUN-2013

30.	Does the section contain controls of the final drug product?	X	<input type="checkbox"/>	<input type="checkbox"/>	
31.	Has stability data and analysis been provided to support the requested expiration date?	<input type="checkbox"/>	X	<input type="checkbox"/>	Data are provided, and plotted data are discussed relative to the proposed expiration dating period, however, no statistical analysis has been included in the application. If any important stability trends are noted that would appear to be limiting in terms of the proposed expiry, it is recommended that the reviewer ask the biometrics team to analyze the stability data for those parameters.
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	<input type="checkbox"/>	X	<input type="checkbox"/>	Unless QbD related information are contained in the current N21067 or DMFs associated with the application. Review of DMFs should only be done if new information has been submitted that has not previously been evaluated.
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	<input type="checkbox"/>	X	<input type="checkbox"/>	See comment for question 32 above.

G. METHODS VALIDATION (MV)

	Parameter	Yes	No	N/A	Comment
34.	Is there a methods validation package?	X	<input type="checkbox"/>	<input type="checkbox"/>	Some information is found in the P section of the application or by reference to NDA 21067 for the MF drug substance

H. MICROBIOLOGY

	Parameter	Yes	No	N/A	Comment
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	<input type="checkbox"/>	<input type="checkbox"/>		The microbiology team has been informed of the submission of this application and will make a determination of any review necessary, as per the pilot.

I. LABELING

	Parameter	Yes	No	N/A	Comment
36.	Has the draft package insert been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	
37.	Have the immediate container and carton labels been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205641

Received Date: 27-JUN-2013

38.	Does section contain tradename and established name?	X	<input type="checkbox"/>	<input type="checkbox"/>	
-----	--	---	--------------------------	--------------------------	--

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205641

Received Date: 27-JUN-2013

J. FILING CONCLUSION					
	Parameter	Yes	No	N/A	Comment
39.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Describe filing issues here or on additional sheets
41.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Describe potential review issues here or on additional sheets

REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

Craig M. Bertha, Ph.D., Acting CMC Lead

Prasad S. Peri, Ph.D., Branch Chief

{See appended electronic signature page}

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

/s/

CRAIG M BERTHA
07/23/2013

PRASAD PERI
07/24/2013
I concur