

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202236Orig1s000

CHEMISTRY REVIEW(S)

Chemistry, Manufacturing and Controls (CMC) MEMORANDUM

Date: April 30, 2012

To: NDA 202-236

From: Eugenia Nashed, PhD
Chemist, Division of New Drug Quality Assessment III, Branch VIII

Through: Prasad Peri, PhD
Branch Chief, Division of New Drug Quality Assessment III, Branch VIII

Product: Dymista (azelastine hydrochloride / fluticasone propionate) Nasal Spray (suspension), 137µg/50 µg per spray (0.1%/0.037%)

Applicant: Meda Pharmaceuticals

Meda Pharmaceuticals submitted a 505(b)(2) new drug application (NDA 202-236) on April 1, 2011, for Dymista (azelastine hydrochloride / fluticasone propionate) Nasal Spray (suspension), 137µg/50 µg per spray (0.1%/0.037%). It is a fixed combination of antihistamine (antagonist of H₁ receptor) and corticosteroid (agonist of glucocorticosteroid receptor) drug substances for the relief of symptoms of seasonal allergic rhinitis in adults and children aged 12 years and older. The drug product is a multidose nasal spray suspension contained in an amber glass bottle, fitted with a metering (b) (4) spray pump from (b) (4). Each spray of the suspension delivers 137 µg of azelastine hydrochloride (equivalent to 125 µg of azelastine base) and 50 µg of fluticasone propionate. Azelastine hydrochloride is solubilized in the formulation while the micronized fluticasone propionate occurs as a suspension. It will be the first combination nasal spray product on the US market. The PDUFA due date for this application is May 1, 2012.

The CMC team recommends APPROVAL action for this NDA based on adequate supportive data submitted to this NDA and ACCEPTABLE recommendation for the manufacturing and testing sites provided by the Office of Compliance. Refer to EES report dated April 30, 2012, reproduced at the end of this document.

24 months drug product expiry period is supported for the trade (120 sprays) and sample (28 sprays) presentations of the drug product when stored at 20°-25°C (68°-77°F).

Since the last Chemistry review (CMC review dated March 26, 2012), minor changes to the drug product specifications and labeling were implemented to reflect the recommendations from the review team. All changes are acceptable and copies of the final drug product specifications and carton and container are reproduced below.

Final Drug Product Specifications dated March 27, 2012

DRUG PRODUCT SPECIFICATIONS FOR DYMISTA™ (AZELASTINE HYDROCHLORIDE/FLUTICASONE PROPIONATE) NASAL SPRAY, 137 MCG/50 MCG (0.1%/0.037%)

Document No.: SP-011-03

Revision Date: 27 Mar 2012

Supersedes: SP-011-02, 23 Mar 2012

Effective Date:

Approval Signature: F. Baez Date _____
Associate Director, Corporate Quality Assurance

Approval Signature: C. Yayac Date _____
Senior Manager, Regulatory Affairs

All testing is conducted by Cipla Ltd., Goa, India.

Table 1: Bulk Suspension Release Specifications

Test	Limit	Analytical Method
Description	(b) (4)	Visual
Azelastine Hydrochloride Identification (HPLC)	(b) (4)	AM 001-FGNA012V5
Fluticasone Propionate Identification (HPLC)	(b) (4)	AM 001-FGNA012V5
pH	(b) (4)	USP <791>
Osmolality	(b) (4)	USP <785>
Viscosity	(b) (4)	USP <911>
Benzalkonium Chloride Assay	(b) (4)	AM 010-FGNA012V5
Phenylethyl Alcohol Assay	(b) (4)	AM 011-FGNA012V5
Azelastine Hydrochloride Assay	(b) (4)	AM 001-FGNA012V5
Fluticasone Propionate Assay	(b) (4)	AM 001-FGNA012V5

Table 2: Packaged Product Specifications

Test	Limit	Analytical Method
Description	White, homogeneous, redispersible suspension free from visible foreign matter in an amber glass bottle (b) (4) and white actuator with a (b) (4) dust cap.	Visual
Azelastine Hydrochloride Identification (HPLC) ³	(b) (4)	AM 001-FGNA012V5
Azelastine Hydrochloride Identification (TLC) ³	(b) (4)	AM 002-FGNA012V5
Fluticasone Propionate Identification (HPLC) ³	(b) (4)	AM 001-FGNA012V5
Fluticasone Propionate Identification (TLC) ³	(b) (4)	AM 002-FGNA012V5
pH	(b) (4)	USP <791>
Pump Delivery Beginning Individual Beginning Mean Beginning	(b) (4)	AM 007-FGNA012V5
Pump Delivery End Individual End Mean End	(b) (4)	AM 007-FGNA012V5

Test	Limit	Analytical Method
Net Content ^a Trade: Individual Mean Sample: Individual Mean	(b) (4)	USP <755>
Viscosity		USP <911>
Weight Loss ^b		AM 013-FSGNA012V5
Number of Sprays	Sample: Not less than 28 sprays Trade: Not less than 120 sprays	AM 007-FGNA012V5
Droplet Size Distribution Mean D10 Mean D50 Mean D90 Mean Span Mean % < 10 µm	(b) (4)	AM 004-FGNA012V5
Spray Pattern ^a Shape Mean D _{max} Mean Ovality Ratio		AM 005-FGNA012V5
Particle Size Distribution Presence or absence of agglomeration, crystal growth, or change in morphology Mean % of Particles ≤ 2.5 µm Mean % of Particles ≥ 2.5 and ≤ 5 µm Mean % of Particles ≥ 5 µm and ≤ 10 µm		AM 006-FGNA012V5

Test	Limit	Analytical Method
Particulate Matter Under Magnifying Glass Under Microscope Particles > 250 µm Particles 100-250 µm	(b) (4)	AM 006-FGNA012V5
Azelastine Hydrochloride Spray Content Uniformity (Label Claim: 137 µg/spray) Mean % Delivered Dose from Beginning of Container (µg/spray)		AM 007-FGNA012V5

Test	Limit	Analytical Method
Azelastine Hydrochloride Spray Content Uniformity (Label Claim: 137 µg/spray) Mean % Delivered Dose from End of Container (µg/spray)	(b) (4)	AM 007-FGNA012V5
Fluticasone Propionate Spray Content Uniformity (Label Claim: 50 µg/spray) Mean % Delivered Dose from Beginning of Container (µg/spray)	(b) (4)	AM 007-FGNA012V5

Test	Limit	Analytical Method
Fluticasone Propionate Spray Content Uniformity (Label Claim: 50 µg/spray) Mean % Delivered Dose from End of Container (µg/spray)	(b) (4)	AM 007-FGNA012V5
Azelastine Hydrochloride Impurities/Degradation Products		AM 008-FGNA012V5
Single Maximum Unspecified Total Impurities/Degradation Products		
Fluticasone Propionate Impurities/Degradation Products		AM 009-FGNA012V5
Single Maximum Unspecified Single Specified Unknown		
Total Impurities/Degradation Products		
Benzalkonium Chloride Assay		AM 010-FGNA012V5

Test	Limit	Analytical Method
Phenylethyl Alcohol Assay	(b) (4)	AM 011-FGNA012V5
Edetate Disodium Assay		AM 012-FGNA012V5
Azelastine Hydrochloride Assay		AM 001-FGNA012V5
Fluticasone Propionate Assay		AM 001-FGNA012V5
Microbial Limits Total Aerobic Microbial Count Total Combined Yeasts and Molds Count Specified Microorganisms		USP <61>, USP <62>
Residual Solvents ^{a, e}	Meets the requirement of USP <467> Class 1, 2, and 3 residual solvents	USP <467>

(b) (4)

(b) (4)

AM 011-FGNA012V5.

Table 3: Specified (b)(4) Impurities and Degradation Products

Common Name(s)	Chemical Name	Structure
(b) (4)		

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

Application:	NDA 202236/000	Action Goal:	
Stamp Date:	01-APR-2011	District Goal:	
Regulatory:	01-MAY-2012		
Applicant:	MEDPOINTE 265 DAVIDSON AVE STE 300 SOMERSET, NJ 088734120	Brand Name:	DYMISTA
		Estab. Name:	
		Generic Name:	
Priority:	4	Product Number; Dosage Form; Ingredient; Strengths	
Org. Code:	570		001; SPRAY; AZELASTINE HYDROCHLORIDE; .1% 001; SPRAY; FLUTICASONE PROPIONATE; .0365%
Application Comment:			
FDA Contacts:	S. PATWARDHAN	Project Manager	(HF-01) 3017964085
	E. NASHED	Review Chemist	(HFD-820) 3017961723
	A. SCHROEDER	Team Leader	3017961749
Overall Recommendation:	ACCEPTABLE	on 30-APR-2012	by A. INYARD (HFD-323) 3017965363
	PENDING	on 02-MAY-2011	by EES_PROD
	PENDING	on 02-MAY-2011	by EES_PROD

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

Establishment: CFN: FEI: 3004081307
 CIPLA LIMITED
 L138-147 L150 S103-105 S107-112 M61-63
 VERNA, SALCETTE, GOA, , INDIA

DMF No: AADA:

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

Establishment Comment: THE CIPLA LTD. LOCATED IN GOA, INDIA IS RESPONSIBLE FOR MANUFACTURING, PACKAGING, LABELING, RELEASE TESTING OF THE DRUG PRODUCT. (on 18-APR-2011 by S. PATWARDHAN (HF-01) 3017964085)
Profile: AEROSOL DISPERSED MEDICATION OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	02-MAY-2011				PATWARDHAN
SUBMITTED TO DO ADM PROFILE LAST INSPECTED 2008	03-MAY-2011	GMP Inspection			SMITHDE
UNDER REVIEW	09-MAY-2011				PHILPYE
DO RECOMMENDATION	19-JUL-2011			ACCEPTABLE INSPECTION	STOCKM
OC RECOMMENDATION	19-JUL-2011			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

DMF No: (b) (4) AADA: (b) (4)

Responsibilities: (b) (4)

Establishment Comment:

Profile:

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	02-MAY-2011				PATWARDHAN
OC RECOMMENDATION	03-MAY-2011			ACCEPTABLE BASED ON PROFILE	SMITHDE

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

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

DMF No: (b) (4) **AADA:** (b) (4)

Responsibilities: (b) (4)

Establishment Comment: (b) (4)

Profile: (b) (4)

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO DD	02-MAY-2011				PATWARDHAN
SUBMITTED TO DD 4+ YEARS SINCE LAST INSPECTION	03-MAY-2011	GMP Inspection			SMITHDE
ASSIGNED INSPECTION TO (b) (4)	15-MAY-2011	GMP Inspection			PHILPYE
INSPECTION PERFORMED			(b) (4)		MARVIN.JONES

(b) (4)

DD RECOMMENDATION	30-APR-2012			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
DD RECOMMENDATION	30-APR-2012			ACCEPTABLE	INYARDA

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

DISTRICT RECOMMENDATION

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/s/

EUGENIA M NASHED
04/30/2012

PRASAD PERI
04/30/2012
I concur

NDA 202236

Dymista™ (azelastine hydrochloride / fluticasone propionate) Nasal Spray
(suspension), 137µg/50 µg per spray (0.1%/0.037%)

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

Applicant: Meda Pharmaceuticals
265 Davidson Avenue,
Somerset, NJ 08873-4120

Indication: For relief of symptoms of seasonal allergic rhinitis in adults and adolescents 12 years and older.

Presentation: Nasal Spray Suspension, (b)(4) per spray supplied in an amber glass bottle with (b)(4) Nasal Spray Pump. Two presentations are proposed for the drug product, the commercial product (120 sprays, 23.0 g fill) and a sample product (28 sprays, 6.4 g fill). The recommended dose is one spray per nostril twice daily, for a total daily dose up to 548 µg of azelastine hydrochloride and 200 µg of fluticasone propionate.

EER Status: Final status is PENDING

Consults:	EA –	Categorical exclusion provided
	Statistics –	N/A
	Methods Validation –	Not recommended
	Biopharm–	N/A
	Microbiology –	Acceptable
	Pharm/toxicology –	Acceptable

Original Submission: 1-April-20011

Post-Approval CMC Agreements: None

Background:

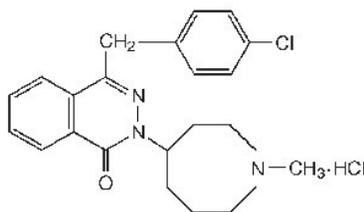
This is the first fixed dose combination for a nasal spray. The drug product was discussed at several meetings with the sponsor under IND 77363. This drug product represents a new paradigm in allergy treatment. So far no company has sought approval for a Nasal Spray combination and the OND division anticipates that this approval will lead to several other combination products being developed. Note that the applicant also has two single ingredient azelastine nasal sprays (NDAs 20114 and NDA 22203) in the market as well.

Drug Substance:

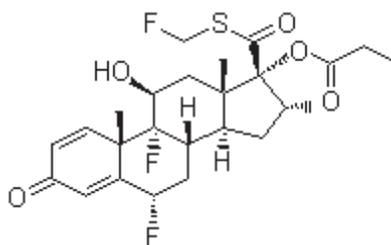
There are two active pharmaceutical ingredients (APIs) in this drug product: Azelastine hydrochloride is manufactured by (b)(4) (referenced in DMF (b)(4)), and fluticasone propionate (referenced in DMF (b)(4)) is manufactured by (b)(4)

(b) (4) Both DMFs have acceptable review status but (b) (4) (manufacturer of azelastine) site does not have an acceptable recommendation from CDER's Office of Compliance as yet. **Hence the NDA is still recommended for approval pending an acceptable OC recommendation**

Azelastine hydrochloride (antagonist of H₁ receptor) is a white, odorless, crystalline powder with a bitter taste. It has a molecular weight of 418.37. It is sparingly soluble in water, methanol, and propylene glycol and slightly soluble in ethanol, octanol, and glycerin. It has a melting point of 225°C and a pH of 5.2. Its chemical name is (±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride. Its molecular formula is C₂₂H₂₄ClN₃O•HCl with the following chemical structure:



Fluticasone propionate (glucocorticosteroid receptor agonist) is a white powder with a melting point of 273°C, a molecular weight of 500.6, and the empirical formula is C₂₅H₃₁F₃O₅S. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol. Fluticasone propionate is a synthetic corticosteroid having the chemical name S-(fluoromethyl)-6α,9-difluoro-11β,-17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate, and the following chemical structure:



CMC information related to each of the above APIs is supported by the corresponding Drug Master File. All Drug Master Files (DMFs) associated with the drug substances were reviewed and found acceptable.

Conclusion: The Fluticasone manufacturing site has been found to be acceptable but the Azelastine manufacturing site is not yet acceptable from a GMP perspective.

Drug Product:

The drug product is manufactured by Cipla in Goa, India. The drug product site has an acceptable GMP status.

The drug product, Dymista (azelastine hydrochloride/fluticasone propionate) Nasal Spray, is a fixed combination of antihistamine (antagonist of H₁ receptor) and corticosteroid (agonist of glucocorticosteroid receptor) drug substances for the relief of symptoms of seasonal allergic rhinitis

in adults and children aged 12 years and older. When approved, this will be the first combination nasal spray product on the US market. Both APIs are present in several US-approved drug products, e.g., Astelin (azelastine hydrochloride) Nasal Spray (NDA 20-114, Meda 1996), and Flonase (fluticasone propionate) Nasal Spray (NDA 20-121, GSK 1994).

The drug product is a multidose nasal spray suspension contained in an amber glass bottle, fitted with a metering (b) (4) spray pump from (b) (4). Each spray of the suspension delivers 137 µg of azelastine hydrochloride (equivalent to 125 µg of azelastine base) and 50 µg of fluticasone propionate. Azelastine hydrochloride is solubilized in the formulation while the micronized fluticasone propionate occurs as a suspension.

The drug contains an isotonic, (b) (4) aqueous formulation of 0.1% azelastine hydrochloride and suspended 0.037% fluticasone propionate USP with a pH 6.0 (b) (4). The excipients consist of glycerin, microcrystalline cellulose and carboxymethylcellulose sodium (b) (4), polysorbate 80, edetate disodium (EDTA), benzalkonium chloride (0.1 mg/g); phenylethyl alcohol (2.5 mg/g) and purified water. The fill weight of 23 g delivers at a minimum 120 sprays after priming (commercial pack), and the fill weight of 6.4 g delivers at a minimum 28 sprays after priming (sample pack).

The control strategy used for assuring the drug product quality uses the typical attributes as specified in the Nasal Spray Guidance document: they include Description, ID (HPLC and TLC) for Azelastine and Fluticasone, pH, Pump Delivery, Net Content, Viscosity, Weight Loss, Number of Sprays, Droplet Size Distribution, Spray Pattern, Particle Size Distribution of Fluticasone (b) (4), Spray Content Uniformity, Azelastine and Fluticasone Impurities, Assay for Benzalkonium Chloride, Phenylethyl alcohol, Azelastine, Fluticasone propionate, Microbial limits and Residual Solvents. Leachables are indirectly controlled in the container closure extractables.

The submitted stability data support the requested expiry period of 24 months for the currently manufactured drug product, when stored at 20-25°C, and when protected from light.

Updated specifications were provided to the application on March 29, 2012 which reflect the Agency proposed recommendations.

Conclusion: Drug product is satisfactory.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval, pending acceptable recommendation from Office of Compliance with regards to all manufacturing and testing facilities.

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
DPA III/ONDQA

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/s/

PRASAD PERI
04/05/2012

NDA 202-236

**Dymista (azelastine hydrochloride / fluticasone propionate)
Nasal Spray (suspension), 137µg/50 µg per spray (0.1%/0.037%)**

Meda Pharmaceuticals

**Eugenia M. Nashed, Ph.D.
Office of New Drug Quality Assessment, Division III**

Division of Pulmonary, Allergy, and Rheumatology Products

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Chemistry Review Data Sheet

1. NDA 202-236
2. REVIEW #: 1
3. REVIEW DATE: 26-March-2012
4. REVIEWER: Eugenia M. Nashed, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	<u>Stamp Date</u>	<u>Assigned Date</u>
Original NDA	01-Apr-2011	01-Apr-2011	16-May-2011
Amendment BZ	29-Apr-2011	29-Apr-2011	16-May-2011
Amendment BL (Label)	19-May-2011	19-May-2011	23-May-2011
Amendment BZ (Resp. 74 day let.)	01-Jul-2011	01-Jul-2011	08-Jul-2011
Amendment BC (Resp. 74 day let.)	01-Aug-2011	01-Aug-2011	04-Aug-2011
Amendment BZ (Resp. 74 day let.)	16-Sep-2011	17-Sep-2011	18-Sep-2011
Amendment BC (Resp. 74 day let.)	23-Sep-2011	24-Sep-2011	26-Sep-2011
Amendment BZ (Resp. Nov IR.)	07-Dec-2011	07-Dec-2011	09-Dec-2011
Amendment BL (Label)	27-Feb-2012	27-Feb-2012	27-Feb-2012
Amendment BC (Resp. March IR)	23-March-2012	26-March-2012	26-March-2012
Amendment BL (PI, Carton, Vial)	23-March-2012	26-March-2012	26-March-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Meda Pharmaceuticals, Inc.

Address: 265 Davidson Avenue, Suite 300, Somerset, NJ 08873-4120

Representative: Brenda Jadney, Associate Director, Regulatory Affairs

Telephone: 732-564-2362

Fax: 732-564-2443

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Dymista™

b) Non-Proprietary Name (USAN): Azelastine hydrochloride and fluticasone propionate Nasal Spray

c) Code Name/# (ONDC only):

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

- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2) (new combination)

PHARMACOL. CATEGORY: Fixed combination of anti-histamine (antagonist of H¹ receptor) and corticosteroid (agonist of glucocorticosteroid receptor) for relief of symptoms of seasonal allergic rhinitis in adults and adolescents 12 years and older.

11. DOSAGE FORM: Nasal Spray Suspension, (b) (4)

12. STRENGTH/POTENCY: Azelastine hydrochloride/fluticasone propionate, 137 µg /50 µg per spray (0.1%/0.037%).

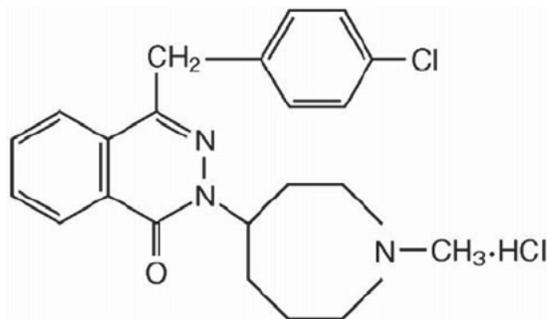
13. ROUTE OF ADMINISTRATION: Intranasal,
One spray per nostril twice a day14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

_____ SPOTS product – Form Completed

X Not a SPOTS product

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

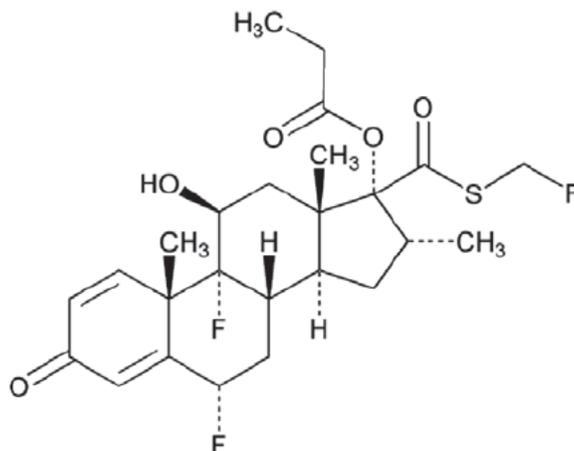
Azelastine Hydrochloride



Molecular Formula: $C_{22}H_{24}ClN_3O \cdot HCl$ Molecular Weight: 418.37 g/mol CAS: 80474-14-2

(±)-1-(2H)-Phthalazinone,4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride (CAS, USAN)

Fluticasone Propionate



Molecular Formula: $C_{25}H_{31}F_3O_5S$ Molecular Weight: 500.6 g/mol CAS: 80474-14-2

S-Fluoromethyl 6 α , 9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrost-1,4-diene-17 β -carbothioate (USP)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS (b) (4)
	2			1	Adequate	21-June-2007 S. Zimmerman	
	2			1	Adequate	21-Oct-2009 K. Furnkranz	
	3			1	Adequate	12-Sep-2011 C. Bertha	
	3			1	Adequate	30-Jul-2010 C. Bertha	
	3			1	Adequate	01-Oct-2009 M. Shaikh	
	3			1	Adequate	02-Sep-2010 Chong Ho Kim	
	3			1	Adequate	12-May-2011 Edwin Jao	
	3			1	Adequate	28-Jan-2011 Yong De Lu	

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 Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
INDs					
(b) (4)	Meda	Azelastine Nasal Spray			
69,785	Meda	Azelastine Nasal Spray	Pending		Referenced for this NDA.
77,363	Meda	Azelastine/Fluticasone Combo Nasal Spray			
NDAAs					
20-114	Meda	Astelin Nasal spray	Approved		Marketed. Referenced for this NDA.
22-203	Meda	Astepro Nasal Spray, 0.1%	Approved		Marketed. Referenced for this NDA.
22-371	Meda	Astepro Nasal Spray, 0.15%	Approved		Marketed. Referenced for this NDA.
21-127	Meda	Optivar Ophthalmic Solution	Approved		Marketed. Referenced for this NDA.

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORW'D	STATUS/ REVIEWER	COMMENTS
Biometrics	None			
EES	GMP Inspections	May 2, 2011	Pending	AC for drug product and fluticasone propionate manufacturing and testing. VAI for azelastine hydrochloride (Inspection Jul 2011, with F483). Overall recommendation is PENDING.
Pharm/Tox			Adequate Sep 23, 2011 Marcie Wood	Evaluation of Impurities and Leachables
Biopharm	None			
DMETS			Pending	
Methods Validation	None			The analytical methods are standard. MV request is not planned for this NDA.
DDMAC	Labeling		Pending	
EA	None			Categorical Exclusion was requested per 21 CFR 25.15(a) and 25.31 (b) and it was found acceptable.
Microbiology	(b) (4) Microbial controls	June, 2011	Acceptable Jan 12, 2012 Denise Miller	Additional analytical method for <i>B. cepacia</i> was requested and added to the microbial controls.

The Chemistry Review for NDA 202-236

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for APPROVAL from the CMC perspective, providing that an acceptable recommendation will be issued for all manufacturing and testing sites from the Office of Compliance.

The Establishment Evaluation Request (EER) for this NDA is pending as of the completion date of this review. Acceptable (AC) status is indicated in the EES for Cipla establishments in India responsible for the manufacturing and testing of (b) (4) drug product (Goa). Voluntary Action Indicated (VAI) status is listed in the EES for the azelastine hydrochloride drug substance manufacturing site (b) (4). The cGMP inspection was completed at this establishment in July 2011, with FDA Form 483 issued.

24 months expiry period is supported for the trade (120 sprays) and sample (28 sprays) presentations of the drug product when stored at 20°-25°C (68°-77°F).

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

None.

II. Summary of Chemistry Assessments

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

The drug product, Dymista (azelastine hydrochloride/fluticasone propionate) Nasal Spray, is a fixed combination of anti-inflammatory (antagonist of H₁ receptor) and corticosteroid (agonist of glucocorticosteroid receptor) drug substances for the relief of symptoms of seasonal allergic rhinitis in adults and children aged 12 years and older. When approved, this will be the first combination nasal spray product on the US market.

The drug product is a multidose nasal spray suspension contained in an amber glass bottle, fitted with a metering (b) (4) spray pump (b) (4). Each spray of the suspension delivers 137 µg of azelastine hydrochloride (equivalent to 125 µg of azelastine base) and 50 µg of fluticasone propionate. Azelastine hydrochloride is solubilized in the formulation while the micronized fluticasone propionate occurs as a suspension. Both APIs are present in several US-approved drug products, e.g., Astelin

(azelastine hydrochloride) Nasal Spray (NDA 20-114, Meda 1996), and Flonase (fluticasone propionate) Nasal Spray (NDA 20-121, GSK 1994).

The drug contains an isotonic, (b) (4) aqueous formulation of 0.1% azelastine hydrochloride and suspended 0.037% fluticasone propionate USP with a pH 6.0 (b) (4). The excipients consist of glycerin, microcrystalline cellulose and carboxymethylcellulose sodium (b) (4) polysorbate 80, edetate disodium (EDTA), benzalkonium chloride (0.1 mg/g); phenylethyl alcohol (2.5 mg/g) and purified water. The fill weight of 23 g delivers at a minimum 120 sprays after priming (commercial pack), and the fill weight of 6.4 g delivers at a minimum 28 sprays after priming (sample pack).

Azelastine hydrochloride is manufactured by (b) (4) and fluticasone propionate is manufactured by (b) (4). The drug product is manufactured by Cipla in Goa, India.

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

The drug product, Dymista (azelastine hydrochloride/fluticasone propionate) Nasal Spray suspension is indicated for the relief of the symptoms of seasonal allergic rhinitis in adults and children aged 12 years and older. The recommended dose is one spray per nostril twice daily, for a total daily dose up to 548 µg of azelastine hydrochloride and 200 µg of fluticasone propionate.

The drug product needs to be shaken gently and primed with six sprays before the initial use. It should be stored in the upright position with the cap in place at controlled room temperature 20° - 25°C (68° - 77°F). It should be protected from light. It should not be stored in the refrigerator or freezer.

C. Basis for Approvability or Not-Approval Recommendation

This application is recommended for approval from the CMC perspective based on data and information submitted in the original NDA and several NDA amendments provided in response to Agency information request (IR) letters and teleconferences. The CMC approval recommendation is conditional on the acceptable cGMP endorsement from the Office of Compliance, which is currently pending.

Upon brief review of the originally submitted data, potential approvability issues were identified and forwarded to the Applicant (June 13, 2011, 74-day letter) with 8 CMC comments concerning comparability of the clinical combination products and monocomponent drug products, and inadequacy of the proposed specifications, analytical methods and stability data for the drug product. Partial responses dated Jul 1, Aug 1, Sep 16, and Sep 23, 2011, were reviewed and IR letter dated Nov 17, 2011, was forwarded to the Applicant with 6 CMC comments concerning ruggedness of the container closure, controls for the (b) (4) excipient, inadequate drug product specifications and methods,

and drug product expiry period. The Applicant's response dated Dec 7, 2011, led to an IR letter dated March 19, 2012, with 4 CMC comments addressing the inadequacy of the response regarding deficient specifications and methods for drug product, an unjustified expiry period and deficient controls for (b) (4) excipient. Following our teleconference on March 22, 2012, a complete response was submitted by e-mail on March 23, and hard copy on March 27, 2012. Additional data concerning the (b) (4) content of phenylethyl alcohol and data comparing the dose performance of the drug product before and after manufacturing changes, implemented to improve ruggedness of the container closure, will be submitted in the first annual report. Final specifications with three non-overlapping cut off points for particle size distribution of fluticasone propionate in the drug product formulation will be submitted by March 29, 2012, and will be addressed in the addendum to this review and in the secondary CMC review. The incoming response is not expected to impact the overall approval recommendation for this drug product from the CMC perspective.

See below, a summary of the most important CMC issues addressed throughout the review of this application.

- **Comparability of the Clinical Combination Products to the Reference Monocomponent Drug Products.**

The drug product is a fixed combination of two active pharmaceutical ingredients (API) for local delivery to the nose with a metered spray pump. As such, the dose performance parameters may have a significant impact on the locally delivered doses, especially since one of the APIs (azelastine hydrochloride) is soluble in the drug product formulation while the other (fluticasone propionate) is micronized and suspended in the formulation. The dose performance comparison data for the combination and monotherapy products were not submitted with the original NDA. In response to Agency IR letters (June 13, and Nov 17, 2011) the dose performance data comparison charts were submitted in amendment dated Sep 23, and Dec 7, 2011, and are evaluated on page 51 of this review.

(b) (4)
the overall dose performance results are considered to be within the acceptable range of variations of NMT (b) (4). The *in vitro* dose performance characteristics of the combination products and monotherapy products used in the pivotal clinical trials are considered comparable from the CMC perspective.

- **Product Formulation and Container Closure.**

(b) (4)
The issue was addressed in Agency IR letters (Nov 17, 2011 and March 19, 2012) and discussed during teleconference with the Applicant on March 22, 2012. The Applicant proposed to submit a detailed report with their investigation of (b) (4)

(b) (4) in the first annual report. In the interim, the acceptance criteria (b) (4) to reflect the data at 24 months (Expiry). The safety (b) (4) was discussed with the Microbiology review team and the (b) (4) levels observed in the product on storage were found acceptable since adequate, supportive-of-this-level, data for the (b) (4) effectiveness were submitted (Microbiology Review dated Jan 12, 2012).

- **Controls for Drug Product Dose Performance.**

The originally submitted controls for drug product dose performance were not adequate. The proposed tests did not assure uniformity of the delivered dose through the container life (beginning and end of container life testing) and the proposed acceptance criteria were not reflective of the data. Detailed comments requesting revisions to the methods and acceptance criteria for the spray weight, spray content uniformity, droplet size distribution, spray pattern and digital microscopic method for particle size distribution were forwarded to the Applicant in IR letters (Nov 17, 2011, and March 19, 2012) and discussed in details during teleconferences on Nov 22, 2011 and March 22, 2012. The final acceptance criteria and methods for the dose performance attributes were submitted in the amendment dated March 23, 2012, and are considered adequate to support this NDA application. Refer to drug product specifications dated March 23, 2012, on page 88 of this review. Revised acceptance criteria with three non-overlapping cut-off particle size ranges for the digital microscopic method tracking the particle size distribution of fluticasone propionate in the drug product suspension will be submitted on March 27, 2012. The incoming revisions are not expected to have an impact on the approvability of this application.

- **Ruggedness for the Container Closure System.**

During examination of the submitted samples of the container closure system it was noted that the actuator is wobbly and separates easily from the glass vial during attempts to remove the dust cap. Also, a separation of the actuator from the pump was noted during the shipment of the clinical supplies. The issue was addressed with the Applicant in the IR letters and during the teleconferences in Sep and Oct, 2011, and March 22, 2012. Based on the submitted report (Dec 7, 2011) the assembly of the final container closure at Cipla had to be changed (b) (4). The solution was reached by the joined team of the manufacturer of pump and actuator (b) (4) Cipla and the manufacturer of the filling equipment. Preliminary data on the improvement of the consistency for the travel distance setting (b) (4) were submitted and are discussed on page 122 of this review. The issue was discussed with the CMC review team and a decision was reached that it is unlikely that the implemented manufacturing changes will impact substantially the drug product dose performance. Therefore the proposed final report containing the “before change” and “after change” confirmatory data was requested as a submission in the annual report rather than as a prior-approval submission.

- **Revision of Expiry Period for the Drug Product**

The originally proposed expiry period of (b) (4) was not adequately supported by the submitted test results. Out-of-trend instability changes were noted for several tested attribute (b) (4)

The issues were addressed in the IR letters and during teleconferences with the Applicant, who proposed (b) (4) the expiry for the drug product to 24 months when stored at controlled room temperature of 20°-25°C (68°-77°F). The 24 months expiry period is supported by the currently submitted data.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Eugenia Nashed/March 26, 2012
Chemistry Lead/Date: Alan Schroeder/March 27, 2012
Chemistry Branch Chief Name/Date: Prasad Peri/Refer to DARRTS sign off date

C. CC Block

138 Pages 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/

EUGENIA M NASHED
03/27/2012

PRASAD PERI
03/27/2012
I concur

**ONDQA Review for
 OND Division of Pulmonary Allergy and Rheumatology Products
 Initial Quality Assessment and Filing Review
 Date: May 27, 2011**

NDA: 202236

Product Name: Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.37% Nasal Spray

Applicant: Meda Pharmaceuticals

Stamp Date: April 1, 2011

PDUFA Date: February 1, 2012

ONDQA 5 month date: September 1, 2011

Proposed Proprietary Name: (Not yet determined)

Established Name: Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray

Dosage form and strength: nasal spray, each spray delivers 137 mcg of azelastine hydrochloride (equivalent to 125 mcg of azelastine base) and 50 mcg of fluticasone propionate

Route of Administration: nasal

Indications: CMC Lead (acting): Alan C. Schroeder, Ph.D. /DNDQA III/ONDQA

Filability recommendation: Fileable.

Review team recommendation: Single primary reviewer (Dr. Eugenia Nashed)

Recommended briefing level: Division (This drug product is the first corticosteroid/antihistamine nasal spray)

Time goals:

- Initial Quality Assessment in DFS: prior to June 14, 2011
- Filing decision “Day 45”: May 16, 2011
- Filing review issues “Day 74”: June 14, 2011
- **Chemistry Review (DR/IR) letter: by September 1, 2011**
- Mid-cycle meeting “Month 5”: 8/23/2011
- Wrap Up: 12/12/2011
- **Final Chemistry Review “Month 8” in DFS: December 1, 2011**
- PDUFA: February 2, 2012

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm	
CDRH	recommended for Human Factors studies
EA	To be assessed by Primary Reviewer
EES	EER sent to Office of Compliance on May 2, 2011
DMETS	Labeling consult request will be sent as part of DPARP’s request.
Methods Validation	Methods validation for non-compendial methods may be requested of FDA laboratories if deemed necessary by the reviewer after test methods are finalized.
Microbiology	A consult is needed for microbiological characterization and

CONSULTS/ CMC RELATED REVIEWS	COMMENT
	evaluation.
Pharm/Tox	DS and DP impurities/degradants/leachables to be evaluated for safety.

Notes:Background

This NDA is submitted as a 505(b)(2) application. The following information is from the cover letter to the NDA.

This fixed combination new drug product has a proposed indication (b) (4)

The recommended dose is one spray per nostril twice daily.

“Each actuation of the MP29-02 nasal spray pump delivers 137 mcg of azelastine hydrochloride and 50 mcg of fluticasone propionate such that one spray per nostril twice daily delivers 548 mcg of azelastine hydrochloride and 200 mcg of fluticasone propionate. This combination product has been designed to deliver the same doses of the active ingredients as would be delivered were Astelin and Flonase to be dosed individually.

Azelastine hydrochloride exhibits H¹-receptor antagonistic activity, whereas fluticasone propionate is a potent glucocorticoid receptor agonist. It was shown that, due to different primary mechanisms of action of the single agents, combination therapy with azelastine and fluticasone provides greater efficacy than therapy with each agent alone.

The Azelastine Hydrochloride drug substance used in this combination product is also used in the currently marketed Astelin@ Nasal Spray (NDA 20-114), Astepro@ 0.1% Nasal Spray (NDA 22-203), Astepro@ 0.15% Nasal Spray (NDA 22-371), and in the currently marketed Optivar@ Ophthalmic Solution (NDA 21-121). The Fluticasone Propionate USP drug substance used in this combination product is a compendia item described in the United States Pharmacopeia (USP) and the European Pharmacopeia (Ph. Eur.). The chemistry, manufacturing and controls for Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray are included in this submission. These are the monotherapy comparator drug products which have identical ingredients to the proposed drug product except for the absence of one drug substance in each.

Reference is made to the discussions held between the FDA Division of Pulmonary, Allergy and Rheumatology Products and Meda Pharmaceuticals Inc. during the August 17, 2010 Pre-NDA meeting. As agreed, in the development section of this NDA, we have included information and data supporting the comparability of the Azelastine Hydrochloride 0.1% Nasal Spray and Fluticasone Propionate 0.037% Nasal Spray monotherapy comparator products to the proposed marketed combination product that were studied in the clinical trials. These data, presented in table and graph format, demonstrate the pharmaceutical comparability of the in vitro dose delivery of the two monotherapies and the proposed marketed combination product. The applicant does not intend to market the single drug comparator drug products.

Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray will be supplied as a 23 g trade package delivering 120 metered sprays in an amber glass bottle fitted with a metered-dose spray pump unit. Each bottle contains 23 mg (1 mg/g) of azelastine hydrochloride and 8.5 mg (0.37 mg/g) of fluticasone propionate. The product will be manufactured by Cipla Ltd. in their Goa, India facility which has undergone a general FDA Inspection in February 2011.”

Proposed proprietary names of the product have been proposed but not yet agreed to.

Drug substance

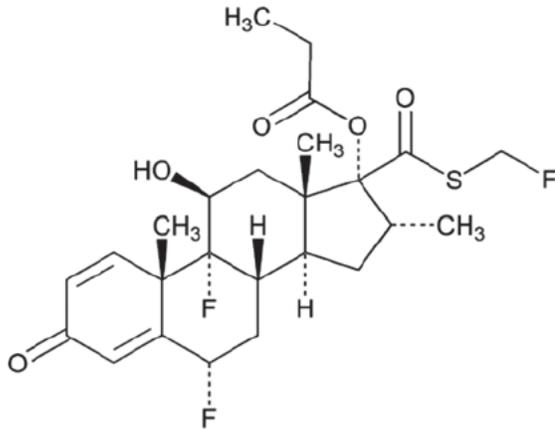
FLUTICASONE PROPIONATE:

This drug substance is manufactured by (b) (4) (Most CMC information for fluticasone propionate in this NDA is referenced to DMF (b) (4)). (b) (4) performs full release testing prior to shipment to the drug product manufacturing site (Cipla Ltd. Goa, India) and the drug product manufacturing site at Goa performs full release testing upon receipt prior to release for drug product manufacture. (Information is from 2.3.S.)

DMF (b) (4) was last reviewed for quality by Dr. Ken Furnkranz on September 24, 2009, and was found to be adequate in support of a nasal spray product. Subsequently additional amendments and an annual report have been submitted but not reviewed.

applicant's information begins

The following fluticasone propionate structural formula is provided in Section 2.3.S:



Fluticasone propionate is quite insoluble in water. (b) (4)
 The drug substance is micronized (b) (4)
 Drug substance specifications from the NDA:

Table 1: Specifications for Fluticasone Propionate Drug Substance

Test	Acceptance Criteria	Analytical Method
Description	Fine, white powder	Visual
Identification A (IR)	(b) (4)	USP <197M>
Identification B (HPLC)	(b) (4)	USP
Specific Rotation (°)	(b) (4)	USP <781S>
Water (% w/v)	(b) (4)	USP <921>, Method 1
Limit of (b) (4) (% w/w) ^a	(b) (4)	In house Method GAM 31U/54-ACF0202EV4
Assay (content of C ₂₅ H ₃₁ F ₃ O ₅ S) (% w/w)	(b) (4)	USP

Table 1: Specifications for Fluticasone Propionate Drug Substance (Continued)

Test	Acceptance Criteria	Analytical Method
Related Compounds (%) (b) (4)	(b) (4)	USP
Residual Solvents (ppm) (b) (4)	(b) (4)	In house Method GAM 31U/54-ACF0202EV4
Particle Size D10 D50 D90 D97	(b) (4)	In house Method GAM 20-ACF0202AV3
Residue on Ignition (% w/w)	(b) (4)	USP <281>
Heavy Metals (ppm)	(b) (4)	USP <231>, Method II
Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests Total Aerobic Microbial Count (cfu/g) Total Combined Yeasts and Mold Count (cfu/g)	(b) (4)	USP <61>

Table 1: Specifications for Fluticasone Propionate Drug Substance (Continued)

Test	Acceptance Criteria	Analytical Method
Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms	(b) (4)	USP <62>
(b) (4)		

applicant’s information ends

Non-compendial analytical procedures as part of the above specifications, and validation data for these analytical procedures, are referenced to DMF (b) (4)

Applicant’s information begins:

“The analytical procedures for residual solvents and particle size have been validated by (b) (4) The microbiological test method is performed according to USP <61> and the test method has been validated for Fluticasone Propionate according to USP <1227>, Validation of Microbial Recovery from Pharmacopeial Articles. The microbiological method was found suitable for its intended use. Validation reports for each noncompendial analytical method in Section 3.2.S.4.2 for which validation is required are listed in Section 3.2.S.4.3.”

Applicant’s information ends.

AZELASTINE HYDROCHLORIDE

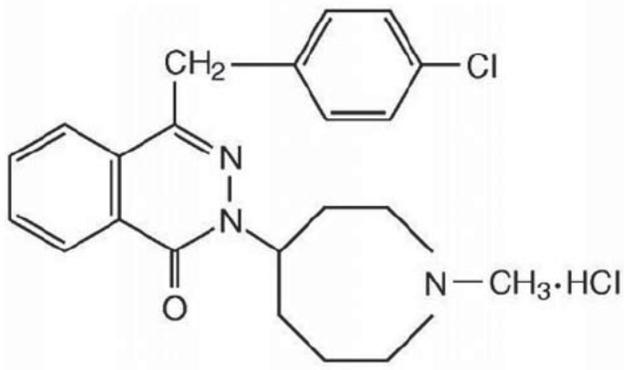
This drug substance is said to be used in a number of currently marketed nasal sprays and an ophthalmic solution. (See Section 2.3.S.1)

The drug substance is manufactured by (b) (4) and CMC information is referenced to DMF (b) (4) DMF (b) (4) was last reviewed by Dr. Stuart Zimmerman on June 21, 2007, and found to be adequate for an ophthalmic solution. This information is from DARRTS which does not include a link to the DMF review. An amendment and multiple annual reports have been submitted subsequent to the date of Dr. Zimmerman’s review.

applicant’s information begins:

“Drug substance manufactured at the (b) (4) site was used in the Registration Batches. The (b) (4) site has been sold to another company and Azelastine

Hydrochloride is not currently being manufactured at the (b) (4) facility. All future manufacture of Azelastine Hydrochloride drug substance will take place at the (b) (4) site. Related documentation for the drug substance manufactured at the (b) (4) site is now stored at the (b) (4) site.”

Structural Formula**Molecular Formula** $C_{22}H_{24}ClN_3O \cdot HCl$ **Molecular Weight**

418.37

The drug substance is sparingly soluble in water 1.0 g / 100 mL. It is a racemic mixture,
[Drug substance specifications:]

Table 1: Specifications for Azelastine Hydrochloride

Test	Specification	Method ^a
Description	White to light beige, odorless, crystalline powder	00007601.B01B4061
Identification (IR)	(b) (4)	00007601.A01B5245
Identification (Chloride)	(b) (4)	00007601.A01B5239
UV Absorption	(b) (4)	00007601.A01B5243
UV Spectrum	(b) (4)	00007601.A01B5243
Microbial Limits (purity)	(b) (4)	00007601.A02M5097
Clarity	(b) (4)	00007601.A01B5242 00007602.D03B5166
Color	(b) (4)	00007601.A01B5242
Melting Range	(b) (4)	00007601.A01B5236
Water Content	(b) (4)	00007601.A01B5244
Residue on Ignition	(b) (4)	00007601.A01B5238
Heavy Metals	(b) (4)	00007601.A01B5240
	(b) (4)	00007601.A01B5237
	(b) (4)	00007601.A01B5241
Optical Rotation	(b) (4)	00007601.A01B5246
pH	(b) (4)	Current Eur. Pharm. 00007601.B02B6094 00007601.B02B6094 00007601.B02B6094

Table 1: Specifications for Azelastine Hydrochloride (Continued)

Test	Specification	Method
Unknown Impurities, Individual	(b) (4)	00007601.B02B6094
Total Impurities	(b) (4)	00007601.B02B6094
Assay (HPLC)	(b) (4)	00007601.A01B5249
Residual Content	(b) (4)	00007601.A01B5248

^a Copies of the methods can be found in DMF (b) (4)

applicant's information ends

Non-compendial methods and their validation information are referenced to DMF (b) (4)
 Batch analyses are provided. Reference standards, the container closure system and stability information are all referenced to DMF (b) (4)

Drug product

applicant's information begins (multiple pages of this review)

AZELASTINE HYDROCHLORIDE 0.1% AND FLUTICASONE
PROPIONATE 0.037% NASAL SPRAY [3.2.P.1]

“The proposed commercial drug product Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray is a multidose, metered spray nasal drug product. The drug product is an isotonic (b) (4) aqueous formulation of 0.1% azelastine hydrochloride and suspended 0.037% fluticasone propionate USP with a pH between (b) (4). The excipients consist of glycerin, microcrystalline cellulose and carboxymethylcellulose sodium (b) (4) polysorbate 80, edetate disodium, benzalkonium chloride (0.1 mg/g); phenylethyl alcohol (2.5 mg/g) and purified water. Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray will be manufactured in both trade and promotional sample presentations packaged in a Type I amber glass bottle filled to nominally contain 23 g per bottle (trade presentation) or 6 g per bottle (promotional sample presentation), with a (b) (4) spray pump closure for intranasal delivery. After initial priming (6 actuations), each metered spray delivers a 0.137 mL mean volume containing 137 µg of azelastine hydrochloride (equivalent to 125 µg of azelastine base) and 50 µg of fluticasone propionate. Each 23 g bottle of Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray provides 120 metered sprays (trade presentation) and each 6 g bottle provides 28 metered sprays (promotional sample presentation).”

[Composition –next page]

Table 1: Formulation Components and Composition of Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray

Ingredient	Function	µg/spray ^a	mg/g	% w/w
Drug Substances:				
Azelastine Hydrochloride	Active ingredient	137	1.00	0.100
Fluticasone Propionate USP	Active ingredient	50	0.365	0.0365
Excipients:				
Glycerin USP	(b) (4)			
Microcrystalline Cellulose and Carboxymethylcellulose Sodium NF	(b) (4)			
Polysorbate 80 NF	(b) (4)			
Edetate Disodium USP	(b) (4)			
Benzalkonium Chloride NF ^b	(b) (4)		0.1	0.01
Phenylethyl Alcohol USP	(b) (4)		2.5	0.25
Purified Water USP	(b) (4)			
(b) (4)				

^a Based on a target weight of 137 mg drug product per spray.

2.3.P.1.2. “Monotherapy Comparator Drug Products

The monotherapy comparator drug products used in the clinical program (refer to Section 3.2.P.5.4, Table 1) were formulated and packaged to be identical to the proposed marketed drug product Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray except for the absence of either azelastine hydrochloride or fluticasone propionate in the drug products. The monotherapy comparator drug products Azelastine Hydrochloride 0.1% Nasal Spray and Fluticasone Propionate 0.037% Nasal Spray are also isotonic (b) (4) aqueous formulations with a pH between (b) (4). The ingredients in the monotherapy comparator drug products are identical to those used for Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray except for the absence of one of the actives. All of the ingredients in the monotherapy comparator drug products have the same quality standards or grades and function as the proposed marketed drug product.”

For clinical use, the monotherapy comparator drug products were packaged using components identical to those used for the trade presentation of the proposed marketed product Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray, i.e., a Type I amber glass bottle filled to nominally contain 23 g per bottle with a (b) (4) spray pump closure for intranasal delivery.”

[Selected pharmaceutical development information from 2.3.P.2:]

“Since the selected drug product excipients are mostly common to those for the commercial azelastine hydrochloride and/or fluticasone propionate drug products (Section 3.2.P.2.1.1.2), drug substance/excipient compatibility studies were not performed other than the studies described in Section 3.2.P.2.1.1.2. Compatibility of the drug substances with the excipients has also been demonstrated through the Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray stability studies as discussed in Section 3.2.P.8.1.1. These stability data also demonstrate the compatibility of the drug substances with each other.”

“Fluticasone propionate drug substance is practically insoluble in water (Section 3.2.S.1.3). To ensure uniform distribution in the drug product, (b) (4)

(b) (4) The proposed particle size specification for the fluticasone propionate drug substance is provided in Section 3.2.S.4.1. Fluticasone propionate drug substance can exhibit polymorphism. Fluticasone propionate manufactured by (b) (4)

(b) (4)

Various characterization studies were performed (see 3.2.P.2) for the drug product. The drug product contains no overages of active ingredients or excipients. The same batch formulation was used “throughout scale up, registration, and clinical batch manufacture, and is proposed for commercialization.”

(b) (4)

Process parameters were determined by various studies prior to manufacture of the registration batches. “The manufacturing process for the proposed commercial drug product Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray described in Section 3.2.P.3.3 and in the example executed batch record in Section 3.2.R.1 for registration batch G70453 has remained unchanged throughout development and will remain the same for proposed commercialization... There is no difference in the manufacturing process used to produce the pivotal clinical batches since the trade registration batches were used in the pivotal clinical trials (Section 3.2.P.5.4, Table 1).”

Container closure system:

Table 1: Primary Packaging Components for Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray

Container Closure	Description	Source
Pump	(b) (4)	
Actuator		
Bottle		

(b) (4) pump with a nominal 137 µL delivery designed for multidose use (b) (4) was selected for use with Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray based on the use of a (b) (4) pump with the currently marketed Astelin® (azelastine hydrochloride) Nasal Spray 0.1% as well as other approved azelastine hydrochloride nasal spray products... The nasal spray pump and actuator components comply with the relevant requirements of USP <87> and <661>.”

(b) (4) amber glass bottles were shown to comply with the relevant requirements of USP <660>. The (b) (4) bottles also comply with the relevant requirements of USP <671> with the exception of (b) (4)

The results of the light transmission testing for the (b) (4) bottles are provided in Section 3.2.P.2.4, Table 3. Subsequent ICH photostability studies documented in Section 3.2.P.2.2.1.1.8 showed no significant degradation for either azelastine hydrochloride or fluticasone propionate when samples were exposed to ICH photostability light conditions. The photostability results demonstrate that the (b) (4) amber glass bottle is acceptable for use with this product.”

(b) (4) surveyed for the presence of the following potential leachables in the Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray registration batches: (b) (4)

(b) (4)

applicant’s information ends

Comment: It is noted that the applicant did not screen for all potential leachables in the drug product, as there are some extractables which are tested for by the drug product manufacturer in the valve components that are not included as

targets in the leachables testing (examples include (b) (4) [redacted]) This will require more in depth evaluation when the primary review is conducted... The applicant claims that there are only “sporadic low levels of some leachables...at some stability test points.” The following summary is derived from the applicant’s data in Section 3.2.P.7. Limits of quantitation for the target leachables range from (b) (4) [redacted] limits of detection for target leachables range from (b) (4) [redacted] Leachables that were sporadically observed include (b) (4) [redacted]

applicant’s information begins:

Characterization studies were performed, and selected examples are described here. It was determined that **cleaning** of the actuator should not be required, however, conservatively, labeled cleaning instructions will emulate those in the Flonase Nasal Spray labeling.

“The product should be labeled to reprime the pump with one spray or until a fine mist is produced if the product has not been used for 14 or more days.”

The proposed product contains (b) (4) [redacted]

(b) (4) [redacted]

[Drug Product Manufacturer:]

Cipla Ltd.
 Plot No. L139 to L146
 Verna Industrial Estate
 Verna, Salcette 403722
 Goa
 India

[Quality of Excipients:]

All excipients are USP or NF quality.

[Drug Product Specifications from 3.2.P.5:]

Table 1: Bulk Suspension Release Specifications

Test	Limit	Analytical Method
Description	(b) (4)	Visual
Azelastine Hydrochloride Identification (HPLC)	(b) (4)	AM 001-FGNA012V5
Fluticasone Propionate Identification (HPLC)	(b) (4)	AM 001-FGNA012V5
pH	(b) (4)	USP <791>
Osmolality	(b) (4)	USP <785>
Viscosity	(b) (4)	USP <911>
Benzalkonium Chloride Assay	(b) (4)	AM 010-FGNA012V5
Phenylethyl Alcohol Assay	(b) (4)	AM 011-FGNA012V5
Azelastine Hydrochloride Assay	(b) (4)	AM 001-FGNA012V5
Fluticasone Propionate Assay	(b) (4)	AM 001-FGNA012V5

Table 2: Packaged Product Release Specifications

Test	Limit	Analytical Method
Description	White, homogeneous, redispersible suspension free from visible foreign matter in an amber glass bottle with a (b) (4) and white actuator with a (b) (4) dust cap.	Visual
Azelastine Hydrochloride Identification (HPLC)	(b) (4)	AM 001-FGNA012V5
Azelastine Hydrochloride Identification (TLC)		AM 002-FGNA012V5
Fluticasone Propionate Identification (HPLC)		AM 001-FGNA012V5
Fluticasone Propionate Identification (TLC)		AM 002-FGNA012V5
pH		USP <791>
Pump Delivery Individual Mean		AM 003-FGNA012V5
Net Content Trade: Individual Mean Sample: Individual Mean		USP <755>
Viscosity		USP <911>
Droplet Size Distribution D10 D50 D90 Span % < 10 µm		AM 004-FGNA012V5

Table 2: Packaged Product Release Specifications (Continued)

Test	Limit	Analytical Method
Spray Pattern Shape D_{max} Ovality Ratio	(b) (4)	AM 005-FGNA012V5
Particle Size Distribution		AM 006-FGNA012V5
Particulate Matter Under Magnifying Glass Under Microscope		AM 006-FGNA012V5
Azelastine Hydrochloride Spray Content Uniformity		AM 007-FGNA012V5

Table 2: Packaged Product Release Specifications (Continued)

Test	Limit	Analytical Method
Fluticasone Propionate Spray Content Uniformity	(b) (4)	AM 007-FGNA012V5
Azelastine Hydrochloride Impurities/Degradation Products	(b) (4)	AM 008-FGNA012V5
Single Maximum Unspecified Total Impurities/Degradation Products	(b) (4)	
Fluticasone Propionate Impurities/Degradation Products	(b) (4)	AM 009-FGNA012V5
Single Maximum Unspecified Single Specified Unknown Total Impurities/Degradation Products	(b) (4)	
Benzalkonium Chloride Assay		AM 010-FGNA012V5
Phenylethyl Alcohol Assay		AM 011-FGNA012V5
Edetate Disodium Assay		AM 012-FGNA012V5

Table 2: Packaged Product Release Specifications (Continued)

Test	Limit	Analytical Method
Azelastine Hydrochloride Assay	(b) (4)	AM 001-FGNA012V5
Fluticasone Propionate Assay	(b) (4)	AM 001-FGNA012V5
Microbial Limits Total Aerobic Microbial Count Total Combined Yeasts and Molds Count Specified Microorganisms	(b) (4)	USP <61>, USP <62>
Residual Solvents ^d	Meets the requirements	USP <467>
(b) (4)		

AM 011-FGNA012V5.

[Stability Specifications from 3.2.P.5]

Table 3: Stability Specifications

Test	Limit	Analytical Method
Description	White, homogeneous, redispersible suspension free from visible foreign matter in an amber glass bottle with a (b) (4) and white actuator with a (b) (4) dust cap.	Visual
pH	(b) (4)	USP <791>
Pump Delivery Individual Mean	(b) (4)	AM 003-FGNA012V5
Viscosity	(b) (4)	USP <911>
Weight Loss	(b) (4)	AM 013-FSGNA012V5
Droplet Size Distribution D10 D50 D90 Span % < 10 µm	(b) (4)	AM 004-FGNA012V5
Particle Size Distribution	(b) (4)	AM 006-FGNA012V5
Particulate Matter Under Magnifying Glass Under Microscope	(b) (4)	AM 006-FGNA012V5

Table 3: Stability Specifications (Continued)

Test	Limit	Analytical Method
Azelastine Hydrochloride Spray Content Uniformity	(b) (4)	(b) (4) AM 007-FGNA012V5
Fluticasone Propionate Spray Content Uniformity		AM 007-FGNA012V5
Azelastine Hydrochloride Impurities/Degradation Products (b) (4) Single Maximum Unspecified Total Impurities/Degradation Products		AM 008-FGNA012V5

Table 3: Stability Specifications (Continued)

Test	Limit	Analytical Method
Fluticasone Propionate Impurities/Degradation Products	(b) (4)	AM 009-FGNA012V5
(b) (4)	(b) (4)	
Single Maximum Unspecified Single Specified Unknown	(b) (4)	
Total Impurities/Degradation Products	(b) (4)	
Benzalkonium Chloride Assay	(b) (4)	AM 010-FGNA012V5
Phenylethyl Alcohol Assay	(b) (4)	AM 011-FGNA012V5
Azelastine Hydrochloride Assay	(b) (4)	AM 001-FGNA012V5
Fluticasone Propionate Assay	(b) (4)	AM 001-FGNA012V5
Microbial Limits	(b) (4)	USP <61>, USP <62>
Total Aerobic Microbial Count	(b) (4)	
Total Combined Yeasts and Molds Count	(b) (4)	
Specified Microorganisms	(b) (4)	

[Impurities, from 2.3.P.5.5]

(b) (4)

Through 36 months of storage at 25°C/60% RH and 6 months of 40°C/75% RH storage for both the trade and sample packages in both the upright and horizontal orientations, no single impurity/degradation product was observed that was at or exceeded the 1.0% identification threshold specified in ICH Q3B(R2). In one stability study for the sample package Batch G70730, after 24 months at 25°C/60%RH in the horizontal orientation, an unknown impurity/degradation product was observed at (b) (4) in the (b) (4) impurity/degradation products assay. This unknown impurity/degradation product was added to the impurity/degradation product specifications as a specified unknown impurity/degradation product with a relative retention time of (b) (4)

applicant’s information ends

Comment: The release and stability specifications should be combined into one document (regulatory specifications). The use of the excipients selected should

be verified as qualified in approved drug products (via the inactive ingredient list) at the levels chosen.

The following information pertains to drug product stability (2.3.P.8).

applicant's information begins:

“Up to thirty-six months of data at 25°C/60% RH and six months at 40°C/75% RH have been evaluated from three full-scale (b) (4) batches of Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray packaged in a (b) (4) round, amber glass bottle with a (b) (4) nasal spray pump having a (b) (4) (trade package configuration). Up to thirty-six months of data at 25°C/60% RH and six months of data at 40°C/75% RH have been evaluated from three 1/3rd scale (b) (4) batches of Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray packaged in a (b) (4) round, amber glass bottle with a (b) (4) nasal spray pump having a (b) (4) (sample package configuration). Up to twelve months of data at 25°C/60% RH have been evaluated from a full-scale (b) (4) clinical batch of Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray packaged in the trade package configuration. A discussion of the stability data obtained from these studies through 36 months of 25°C/60% RH storage and 6 months of 40°C/75% RH accelerated is provided in Section 3.2.P.8.1.1. Testing at the intermediate condition, 30°C/65% RH, was not initiated for any of the studies.” The applicant indicates that the above indicated stability studies provided results within the specifications for the registration stability program for all batches. They have also indicated that the results would meet the proposed stability specifications for commercial product. “Based on the data provided, an **expiration date of (b) (4) is proposed for the 23 g-fill trade package and (b) (4) is proposed for the 6 g-fill sample package.**” A statistical analysis of the stability data is not provided because of the real-time 36-month data (25°C/60%RH) for the trade package, and the real-time 25°C/60% RH data for the sample package.

The applicant indicated only the following drug product stability trending information: a (b) (4)

applicant's information ends

Comment: Monotherapy comparator stability data are not discussed in this IQA but also need to be evaluated. The applicant has provided summary data tables organized by

attribute for the stability data. These tables provide a side by side comparison of data for the combination drug product as well as the monotherapy comparator products.

[stability protocol and stability commitment are provided]

See Section 3.2.R.1 for executed batch records (3 batches) and the method validation package. MV samples are said to be available on request. If the reviewer decides that FDA methods validation (verification) should be performed for certain methods, the applicant should be asked for a tabular list of samples to be submitted, information supporting the integrity of the reference standards, relevant material safety data sheets and certificates of analysis for substances to be submitted.

Monotherapy Comparator Drug Products (single drug comparators):

Comparative compositions, along with the proposed combination drug product:

Applicant’s information begins:

Table 2: Formulation Comparison Table

Ingredient	Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray		Azelastine Hydrochloride 0.1% Nasal Spray		Fluticasone Propionate 0.037% Nasal Spray		Function
	Amount (b) (4)	Amount (% w/w)	Amount (b) (4)	Amount (% w/w)	Amount (b) (4)	Amount (% w/w)	
Drug Substances:							
Azelastine Hydrochloride	(b) (4)	0.100	(b) (4)	0.100	(b) (4)	N/A	Active ingredient
Fluticasone Propionate USP		0.0365		N/A		0.0365	Active ingredient
Excipients:							
Glycerin USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Microcrystalline Cellulose and Carboxymethylcellulose Sodium NF (b) (4)							
Polysorbate 80 NF							
Edetate Disodium USP							
Benzalkonium Chloride NF ⁹		0.01		0.01		0.01	
Phenylethyl Alcohol USP		0.25		0.25		0.25	
Purified Water USP							(b) (4)

(b) (4)

Applicant’s information ends.

It can be seen that the monocomparator formulations are identical to the formulation of the proposed combination drug product, except that one of the actives is missing in each case. All ingredients of the comparator products “have the same quality standards and function as the proposed marketed drug product.”

Batch release data are provided for the monotherapy single ingredient drug products used for the clinical trials (Section 3.2.P.5.4). The batches of monotherapy products “were manufactured at the same site (b) (4) and scale (b) (4) as the proposed commercial

drug product... These monotherapy comparator clinical batches were packaged using components identical to the proposed trade package configuration (Section 3.2.P.5.4).”

There are no overages in the monotherapy comparators. “Relevant physicochemical properties of the monotherapy comparators Azelastine Hydrochloride 0.1% Nasal Spray and Fluticasone Propionate 0.037% Nasal Spray, such as particle size distribution, osmolality, pH, and viscosity, are comparative to the combination drug product Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray.” [2.3.P.2.2.4]

The manufacturing process used for the monotherapy comparator Azelastine Hydrochloride 0.1% Nasal Spray was developed directly from the manufacturing process for the proposed commercial product and is identical with the exception of the removal of those steps relevant to the addition of fluticasone propionate. Two full scale batches (G71093 and G91066) were manufactured successfully and placed on stability. A representative executed batch record for Azelastine Hydrochloride 0.1% Nasal Spray clinical batch G90766 is provided in Section 3.2.R.1. The results from the stability studies are discussed in Section 3.2.P.8.1.2.” [2.3.P.2.3] Control of critical steps and intermediates for the monotherapy comparators are indicated to be the same as for the proposed drug product.

“The manufacturing process for the monotherapy comparator Fluticasone Propionate 0.037% Nasal Spray was developed directly from the manufacturing process for the proposed commercial product and is identical with the exception of the removal of those steps relevant to the addition of the azelastine hydrochloride. Two full scale batches (G71092 and G91067) were manufactured successfully and placed on stability. A representative executed batch record for Fluticasone Propionate 0.037% Nasal Spray clinical batch G90767 is provided in Section 3.2.R.1. The results from the stability studies are discussed in Section 3.2.P.8.1.3.” [2.3.P.2.3]

Analytical methods used to test the monotherapy comparators are indicated to be the same as for the proposed drug product.

(b) (4)

“Through 18 months of storage at 25°C/60% RH in both the upright and horizontal orientations, the maximum single unknown impurity/degradation product (b) (4)

(b) (4) was (b) (4) This is below the 1.0% identification threshold specified in ICH Q3B(R2).” [2.3.P.5.5]

The applicant does not plan to market the monotherapy clinical comparator drug products.

Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED
(b) (4)			

Letters of authorization for the above DMFs: yes, see Module 1.4.1.

IND for this drug product:

Filing Check List (reproduced from filing meeting slides):

	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?	yes		There are exceptions – some of the scanned data provided (e.g. in method validations reports) is not completely legible
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	Not found in cover letter or form 356h or manufacturing sections of d.s. or d.p.
6	Has an environmental assessment report or categorical exclusion been provided?	x		Module 1.12.14
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		Reviewer will determine whether stability data support the proposed expiry. No analysis is provided because full shelf life data are provided.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		Apparently. Reviewer will verify this. One exception, placebo information needs to be provided if not present.
11	Have draft container labels been provided?	x		draft container and carton labels are provided
12	Has the draft package insert been provided?	x		Includes SPL labeling.
13	Has an investigational formulations section been provided?	x		Only some preformulation information are provided, but that should be OK since d.p. formulation was unchanged through development
14	Is there a Methods Validation package?	x		some additional information will be needed with the samples if MV is to be requested (reviewer's decision)

Certain review issues which were noted are listed below for consideration by the reviewer

The use of the excipients selected should be verified as qualified in approved drug products (via the inactive ingredient list) at the levels chosen.

It is noted that drug product leachables (on stability) were only evaluated at annual intervals, and it should be determined whether this reduced amount of stability data is adequate to determine any trends. It should also be determined whether all important stability attributes have been included in the stability studies.

The adequacy of specifications for particle size distribution and droplet size distribution should be evaluated. Particle size distribution uses a microscopic method. Droplet size distribution uses a laser diffraction method. Consider if a cascade impactor method should be required. See section 1.6, meeting notes.

In the stability studies, it is summarized that no foreign particulate matter was observed using magnifying glass and microscope methods. It should be evaluated whether this method is adequate in sensitivity and specificity to detect foreign particulate matter.

It may be noted that the pNDA meeting minutes indicate the possibility (before or after approval) of stability data from an alternate site or device modifications. Neither of these possibilities has been observed so far in the NDA.

Most characterization studies mentioned in the guidance appear to have been performed, however, it is not clear whether the applicant has performed such studies to evaluate device robustness or the effect of dosing orientation. This should be checked. In addition, the characterization studies involving temperature cycling were not conducted according to the recommended approach (i.e., multiple cycles per day) but instead the drug product was kept at 2-8°C for 2 days, followed by 40°C for two days, and repeating this cycle three times. Some assessment should be made whether the applicant's approach was adequate.

IND Information relevant to CMC review:

See section 1.6.3, correspondence regarding meetings.

CMC Comments to the 74-day Filing Letter (including comments provided by Dr. Eugenia Nashed).

1. We expect that the drug product used in the pivotal clinical trials is the same as the drug product to-be-marketed and described in the label. Provide a table summarizing in details all differences in manufacturing, formulation, and components for development batches of drug product used in the biopharmacological and clinical studies. Include a discussion of observed in vitro differences and evaluate the potential impact on the drug product performance in vivo for variations in the formulation. Present graphical performance comparisons for the delivered dose, droplet size distribution, particle size distribution, plume geometry and any other available attributes for performance characteristics.
2. Change the drug product name in the labeling to include the proprietary name and define the target mass (in mcg) of API delivered per spray (ex-actuator). You may include the percentage concentration in addition, e.g., 137 µg/50 µg (0.1 %/0.037 %). Refer to the ex-actuator content data supporting your proposed spray content values. Submit revised NDA sections as applicable.
3. Submit complete CMC information/data for the comparator and placebo drug products used in pivotal clinical studies and compare data with that from the study drugs. Include manufacturing information, specifications, and release and stability data. Provide graphical comparisons of performance attributes for the monocomparators to the study drugs for each dose.
4. Submit an updated list of manufacturing and testing facilities for the study drugs (including monocomparators) and placebo products used in the pivotal clinical trials and for the to be marketed presentations of the drug product. Include a statement that all facilities are ready for inspection.

5. Combine the release and stability specifications for drug product into a single document. Indicate in this document which attributes are not tested on stability. Specify differences in analytical methods, if any, between release and stability specifications.
6. Provide concise summaries of analytical method validation data with detailed references to the actual data. Currently, some pages of raw data (e.g. MV reports) are not very legible and need to be re-submitted, for example, page 24 of the analytical method validation report for droplet size distribution.
7. Submit stability data summary as requested during our pre-NDA meeting. Provide graphical presentations and evaluation of observed stability trends for any trending attributes. Compare drug product performance in different storage conditions/orientations for each presentation of drug product.
8. Include osmolality and viscosity attributes as part of the regulatory drug product specifications, or provide adequate justification for not doing so.

Recommendation: The NDA is suitable for filing from a CMC standpoint.

Attachment A: Nanotechnology product evaluating questions:

<p>1, This review contains new information added to the table below: <input checked="" type="checkbox"/> Yes; <input type="checkbox"/> No</p> <p>Review date: _____</p>
<p>2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes _____; No <input checked="" type="checkbox"/> _____; Maybe (please specify) _____</p>
<p>3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____</p>
<p>3 b) What is the source of the nanomaterial? _____</p>
<p>4) Is the nanomaterial a reformulation of a previously approved product?</p> <p>Yes _____ No _____</p>
<p>5) What is the nanomaterial functionality?</p> <p>Carrier _____; Excipient _____; Packaging _____</p> <p>API _____; Other _____</p>
<p>6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment?</p> <p>Soluble _____; Insoluble _____</p>
<p>7) Was particle size or size range of the nanomaterial included in the application?</p> <p>Yes _____ (Complete 8); No _____ (go to 9).</p>
<p>8) What is the reported particle size?</p> <p>Mean particle size _____; Size range distribution _____; Other _____</p>
<p>9) Please indicate the reason(s) why the particle size or size range was not provided:</p> <p>_____</p> <p>_____</p>
<p>10, What other properties of the nanoparticle were reported in the application (See Attachment E)? _____</p>
<p>11) List all methods used to characterize the nanomaterial? _____</p> <p>_____</p>

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

05/27/2011

Recommendation: fileable

PRASAD PERI

05/28/2011

I concur