CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 203753

Name: Scopolamine Transdermal System, 1 mg /3 days

Sponsor: Mylan Technologies Inc.

Approval Date: June 16, 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA203753Orig1s000

CONTENTS

Reviews / Information Included in this Review

Approval Letter	
Tentative Approval Letter	
Labeling	
Labeling Review(s)	
Medical Review(s)	
Chemistry Review(s)	**X**
Pharm/Tox Review	
Bioequivalence Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Other Review(s)	
Administrative & Correspondence Documents	

Recommendation:
ANDA:
☒ **Approval**
☐ **Information Request – Minor**
(_____days for applicant to response)
☐ **Complete Response - Minor**
☐ **Complete Response – Major**

ANDA 203753

Amendment Review

Drug Name/Dosage Form	Scopolamine Transdermal System
Strength	1.0 mg/3 days
Reviewer(s)	Pinaki Desai
Applicant	Mylan Technologies Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Multiple categories/Subcategories – Sequence 0027	10/02/2018
Quality/Response to Information Request – Sequence 0028	03/05/2019

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	11/30/2018	Reviewed by Jizhou Wang
	III				N/A		
	III				N/A		
	III				N/A		(b) (4)
	III				N/A		
	III				N/A		
	IV			1	Adequate	10/31/2017	Reviewed by Pinaki Desai Seq # 0001 to 0008 do not contain any quality information. 0009: Update to include LOA for Mylan

Note: Please refer to last quality review # 1 (Panorama, Guohua Li, ANDA-203753-ORIG-1, 11/28/2014) for Type III DMFs.

STATUS: (updated 07/03/2018)

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER

Microbiology	N/A		
Facilities	Adequate		
Methods Validation	N/A		
Labeling	Adequate	01/05/2015	Chan Park
Statistics	Adequate	10/24/2017	Vivianna Cowl
BioPharmaceutics/ Dissolution	Adequate	03/28/2015	Qing Liu
Bioequivalence	Adequate	02/26/2019	Eunjung Park
Clinical Irritation/Sensitization Adhesion	 Adequate Adequate	 06/23/2016 10/27/2017	 Sarah Seung Lewis Fermaglich
Consult			
EA	N/A		

FACILITIES: **Adequate**

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
(b) (4)			Approve Facility
Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
Manufacturing, Packaging, Labeling, Quality Control Testing of Components, Testing of Finished Dosage Form	Mylan Technologies Inc. 110 Lake Street Saint Albans, VT 05478	FEI # : 1220747	Approve Facility
(b) (4)			Approve Facility

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Pinaki Desai

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Date: 3/06/2019 10:27:24AM
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Robert Berendt

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Date: 3/06/2019 10:33:49AM
GUID: 508da7380002b309c612f7e27bdf5995

Recommendation:

ANDA:

☐ **Approval**

☐ **Information Request – Minor**

(_____days for applicant to response)

☐ **Complete Response - Minor**

☒ **Complete Response – Major**

ANDA 203753

Amendment Review

Drug Name/Dosage Form	Scopolamine Transdermal System
Strength	1.0 mg/3 days
Reviewer(s)	Pinaki Desai
Applicant	Mylan Technologies Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Multiple categories/Subcategories – Sequence 0019	04/25/2018
Sample Request – Sequence 0026	06/18/2018

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II			(b) (4)	Adequate with additional comment	06/14/2018	Quality amend-12 submitted on 04/23/2018 reviewed by Jizhou Wang
	III				N/A		
	III				N/A		
	III				N/A		
	III				N/A		(b) (4)
	III				N/A		
	IV				Adequate	10/31/2017	
	IV						
	IV						
	IV						

Note: Please refer to last quality review # 1 (Panorama, Guohua Li, ANDA-203753-ORIG-1, 11/28/2014) for Type III DMFs.

STATUS: (updated 07/03/2018)

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
Facilities	Adequate		
Methods Validation	N/A		
Labeling	Adequate	01/05/2015	Chan Park
Statistics	Adequate	10/24/2017	Vivianna Cowl
BioPharmaceutics/ Dissolution	Adequate	03/28/2015	Qing Liu
Bioequivalence	Adequate	10/15/2013	Ping Ren
Clinical Irritation/Sensitization Adhesion	 Adequate Adequate	 06/23/2016 10/27/2017	 Sarah Seung Lewis Fermaglich
Pharm/Tox Consult for (b) (4)	Adequate	08/27/2014	Elena Braithwaite
EA	N/A		

FACILITIES: **Adequate**

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
(b) (4)			Approve Facility
Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
Manufacturing, Packaging, Labeling, Quality Control Testing of Components, Testing of Finished Dosage Form	Mylan Technologies Inc. 110 Lake Street Saint Albans, VT 05478	FEI # : 1220747	Approve Facility
(b) (4)			Approve Facility

Robert Berendt

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Date: 7/05/2018 08:05:29AM
GUID: 508da7380002b309c612f7e27bdf5995

Pinaki Desai

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Date: 7/05/2018 08:21:57AM
GUID: 52260ff900012d0b26101dd96ed2276f

Recommendation:
ANDA:
☐ **Approval**
☐ **Information Request – Minor**
(_____days for applicant to response)
☒ **Complete Response - Minor**
☐ **Complete Response – Major**

ANDA 203753

Amendment Review

Drug Name/Dosage Form	Scopolamine Transdermal System
Strength	1.0 mg/3 days
Reviewer(s)	Pinaki Desai
Applicant	Mylan Technologies Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Multiple categories/Subcategories – Sequence 0019	12/18/2015
Multiple categories/Subcategories – Sequence 0021	04/26/2017

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	11/22/2016	Reviewed by Jizhou Wang
	IV			1	Adequate	10/31/2017	Reviewed by Pinaki Desai **NOT FOR FOI:** Referenced for approved ANDA 076258, ANDA 201675, NDA 022254, etc.

Note: Please refer to last quality review # 1 (Panorama, Guohua Li, ANDA-203753-ORIG-1, 11/28/2014) for Type III DMFs.

STATUS: (updated 10/30/2017)

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
Facilities	Adequate		
Methods Validation	N/A		
Labeling	Adequate	01/05/2015	Chan Park
Statistics	Adequate	10/24/2017	Vivianna Cowl
BioPharmaceutics/ Dissolution	Adequate	03/28/2015	Qing Liu
Bioequivalence	Adequate	10/15/2013	Ping Ren
Clinical Irritation/Sensitization Adhesion	 Adequate Adequate	 06/23/2016 10/27/2017	 Sarah Seung Lewis Fermaglich
Pharm/Tox Consult for (b) (4)	Adequate	08/27/2014	Elena Braithwaite
EA	N/A		

FACILITIES: **Adequate**

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
(b) (4)			Approve Facility

Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
Manufacturing, Packaging, Labeling, Quality Control Testing of Components, Testing of Finished Dosage Form	Mylan Technologies Inc. 110 Lake Street Saint Albans, VT 05478	FEI # : 1220747	Approve Facility
		(b) (4)	Approve Facility

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Robert Berendt

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Date: 11/05/2017 07:16:53AM
GUID: 508da7380002b309c612f7e27bdf5995

Pinaki Desai

Digitally signed by Pinaki Desai
Date: 11/06/2017 08:04:07AM
GUID: 52260ff900012d0b26101dd96ed2276f

A. Check List

Solid IR/Oral Sol. RPN < 60 or Injection/Ophthalmic Q1/Q2 = RLD – 2 Tier	☐
First Generic – 3 Tier	☒
Other Criteria under "Exceptions List" for Table 1 of SOP – 3 Tier	☒

B. Approvability: – ***CMC is adequate***

ANDA 203753

Scopolamine Transdermal System, 1.0 mg/3 days

Mylan Technologies Inc.

Chemistry Review #2

Guohua Li

Chemistry Division V

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 203753

2. REVIEW #: 2

3. REVIEW DATE: 03/04/2014, 07/08/2014, 09/22/2014

4. REVIEWER: Guohua Li, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
Original submission SD 1, eCTD 0000	12/01/2011
Guohua Li, Primary review	10/09/2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	**Document Date**
Quality/Response to information request, SD #8	02/27/2014
Response to ECD/Quality (SD #10)	06/26/2014
Response to ECD/Quality (SD #12)	09/11/2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Technologies, Inc.
Address:	110 Lake St. St. Albans VT 05478 USA
Representative:	N/A
Telephone: Fax:	802-5277792 802-5278155

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: None
Non-Proprietary Name (USAN): Scopolamine Transdermal System, 1.0 mg/3 days

9. LEGAL BASIS FOR SUBMISSION:

RLD Product: Transderm Scōp® (NDA #017874)
RLD Company: Novartis
RLD strength: 1.0 mg/3 days
Dosage form of RLD: Extended Release Film

10. PHARMACOL. CATEGORY:

Indicated in adults for prevention of nausea and vomiting associated with motion sickness and recovery from anesthesia and surgery.

11. DOSAGE FORM:

Film, Extended Release

12. STRENGTH/POTENCY:

1.0 mg/ 3 days

13. ROUTE OF ADMINISTRATION:

Transdermal

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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

_____SPOTS product – Form Completed

___X_Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

___X___Not a NANO product

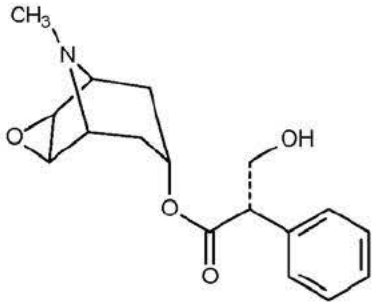
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s)

(1R,2R,4S,5S,7s)-9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]-non-7-yl (2S)-3-hydroxy-2-phenylpropanoate[1]

(αS)-α-(hydroxymethyl)benzeneacetic acid (1α,2β,4β,5α,7β)-9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl ester[1]

Structural Formula



Molecular Formula

$C_{17}H_{21}NO_4$

Molecular Weight

303.35 g/mole

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		3	Adequate/IR		Reviewed by J. Wang
	IV			4	NA		
	III				Inadequate	11/04/2010	Reviewed by Caroline Strasinger
	III			3	Adequate/IR	05/13/2014	Reviewed by Robert Berendt
	III			3	Adequate	04/15/2011	Reviewed by Shahnaz Read
	III			1	Adequate	01/17/2014	Reviewed by Robert Berendt

Chemistry Review Data Sheet

[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)

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending	03-Sep-2014	
Methods Validation	N/A		
Labeling	Inadequate	08/22/2014	Chan Park
Bioequivalence -dissolution	Inadequate	09/15/2014	Agrawal, Arun
Toxicology/Clinical	BE study with clinical endpoints: Inadequate	01/08/2014	Sarah Seung
EA	Per FDA Guidance (1998): Claim of Categorical Exclusion is granted as the drug substance is derived from cultivated plant.	09/22/2014	Guohua Li
Radiopharmaceutical	N/A		
Samples requested	None		

19. ORDER OF REVIEW

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

20. EES INFORMATION

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
[redacted] (b) (4)			
Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
Manufacturing, Packaging, Labeling, Quality Control Testing of Components, Testing of Finished	Mylan Technologies Inc. 110 Lake Street Saint Albans, VT 05478	FEI # : 1220747	AC (01-Dec-2013)

Chemistry Review Data Sheet

Dosage Form			
(b) (4)			

Chemistry Review for ANDA 203753

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC is adequate.

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

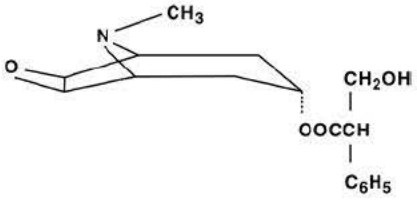
N/A

II. Summary of Chemistry Assessments

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

Drug Substance

Scopolamine is α-(hydroxymethyl) benzeneacetic acid 9-methyl-3-oxa-9-azatricyclo [3.3.1.$0_{2,4}$] non-7-yl ester. The molecular formula is $C_{17}H_{21}NO_4$ and its structural formula is



Scopolamine is a crystalline powder that has a molecular weight of 303.35 and a pKa of 7.55 to 7.81.

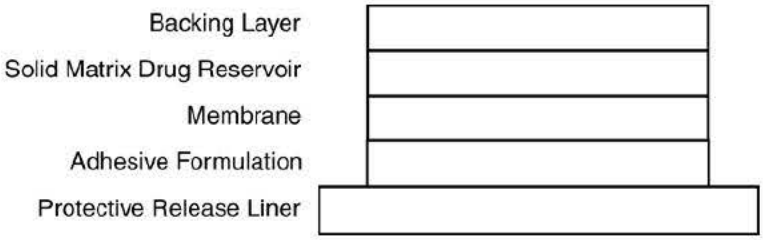
Drug Product

Scopolamine transdermal system is a circular flat patch designed for continuous release of scopolamine following application to an area of intact skin on the head, behind the ear. Each system contains (b) (4) mg of scopolamine base. Scopolamine transdermal system is a 1.8 cm^2 film, with four layers. Proceeding from the visible surface towards the surface attached to the skin, these layers are: (1) a backing layer of peach-colored polyethylene/polyester film; (2) a solid matrix drug reservoir layer of silicone adhesive, scopolamine and povidone; (3) a microporous polypropylene membrane; and (4) an adhesive formulation of silicone adhesive, povidone and scopolamine. A protective, oversized release liner of fluoropolymer-coated polyester, which covers the adhesive formulation layer, is removed before the system is used. The inactive components, silicone adhesive and povidone, (b) (4).

Executive Summary Section

Scopolamine transdermal systems are packaged with an additional piece of protective film above the system within each pouch. This piece of protective film is removed and discarded at the time of use.

Cross section of the system:



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

MDD= (b) (4) mg;

ICH Q3B (R2): RT=0.1%, IT=0.5%, QT=1.0%

DOSAGE AND ADMINISTRATION

Initiation of Therapy: To prevent the nausea and vomiting associated with motion sickness, one scopolamine transdermal system (programmed to deliver approximately 1.0 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. To prevent postoperative nausea and vomiting, the patch should be applied the evening before scheduled surgery. To minimize exposure of the newborn baby to the drug, apply the patch (b) (4) to cesarean section. Only one patch should be worn at any time. Do not cut the patch.

Handling: After the patch is applied on dry skin behind the ear, the hands should be washed thoroughly with soap and water and dried. Upon removal, the patch should be discarded. To prevent any traces of scopolamine from coming into direct contact with the eyes, the hands and the application site should be washed thoroughly with soap and water and dried. (A patient brochure is available).

HOW SUPPLIED: The scopolamine transdermal system is a peach-colored circular patch, 1.8 cm^2, on a clear, oversized, rectangular release liner, which is removed prior to use. Each scopolamine transdermal system contains (b) (4) mg of scopolamine and is programmed to deliver *in vivo* approximately 1.0 mg of scopolamine over 3 days. Scopolamine transdermal system is available in packages of 4 patches, 10 patches and 24 patches. Each patch is packaged in a protective pouch. Patient instructions are included.

4 patches NDC 0378-6470-99

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

RLD has labeled storage at controlled room temperature between 20ºC-25ºC (68ºF-77ºF)

Executive Summary Section

Basis for Approvability or Not-Approval Recommendation

CMC is recommended for approval.

Proprietary Name of Drug Product	None
Non-Proprietary Name of Drug Product	Scopolamine Transdermal System, 1.0 mg/3 days
Non-Proprietary Name of Drug Substance	Scopolaminum
Company Name	Mylan Technologies Inc.
Dosage Form	Film, extended release
Strength(s)	1.0 mg/3 days
Route of Administration	Transdermal
Proposed Indication(s)	Indicated in adults for prevention of nausea and vomiting associated with motion sickness and recovery from anesthesia and surgery.

2.3.S DRUG SUBSTANCE [Scopolamine, (b) (4)

*2.3.S.1 General Information [Scopolamine, (b) (4)

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

Firm's Response:

Established Name
Scopolamine (Hyoscine)

Compendial Name
Scopolamine is not listed in the USP. It is listed in the Ph. Eur as Hyoscine

Chemical Name(s)
(1R,2R,4S,5S,7s)-9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]-non-7-yl (2S)-3-hydroxy-2-phenylpropanoate[1]

(αS)-α-(hydroxymethyl)benzeneacetic acid (1α,2β,4β,5α,7β)-9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl ester[1]

Company or Laboratory Code
(b) (4)

Other Non-Proprietary Name(s)
Scopolaminum[1]

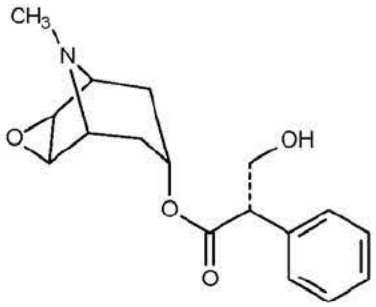
Chemical Abstracts Service (CAS) Registry Number

[51-34-3] [1]

References:

1. [redacted] (b) (4)

Structural Formula (including relative and absolute stereochemistry)



Molecular Formula

$C_{17}H_{21}NO_4$

Molecular Weight

303.35 g/mole

Reviewer's Comment (Review 2): Adequate

The information provided is consistent with literature and EP Monograph.

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

Firm's Response:

Physical Description[1]

Scopolamine appears as white or almost white, crystalline powder or colorless crystals, according to Ph Eur 7.0.

Physical form[1]

Scopolamine [redacted] (b) (4) is isomorphous and of a consistent physical form as confirmed by [redacted] (b) (4)

Solubility

Solubility in common solvents (at 20°C) [1]

Solvent	Solubility (mg/mL)	Descriptive Term (as defined in the USP)
Water	> 100 mg /mL at 15°C	Freely soluble
Methanol	>1 g /mL	Very soluble
Acetone	>1 g /mL	Very soluble

Quantitative aqueous pH solubility profile (at 37°C)

pH of the buffer	Solubility (mg/mL)	Descriptive Term (as defined in the USP)
pH # 1.1	> 50 mg/mL	Soluble
pH # 4.5	> 50 mg/mL	Soluble
pH # 6.8	> 20 mg/mL	Sparing soluble

pKa Value(s) [1]

7.55 at 23°C and 7.81 at 25°C.

pH Value(s)

pH values of drug substance (50 mg/mL solution in water)

Lot	pH (b) (4)
Lot1 # SFFK1	
Lot2 # SFFJ3	

Melting Range[1]

The melting point for Scopolamine quoted in Ph Eur 7.0 is 66°c to 70°C

UV Maxima

A saturated solution of Scopolamine in methanol has UV maxima approximately at 210 and (b) (4)

Specific Optical Rotation[1]

Scopolamine is a natural product extracted from the *Datura sanguinea* plant and thus the chirality is determined by the biosystems of the plant. (b) (4)

Chirality of this API is confirmed and controlled by testing according to Ph Eur 7.0 official specific optical rotation test method.

Hygroscopicity[1]

Scopolamine is hygroscopic when exposed to ambient conditions at 100% humidity.

(b) (4)

References:

1 (b) (4)

2 SciFinder CAS Registry Number search, 10/10/2011.

Reviewer's Comment (Review 2): Adequate

Information provided is in line with all references.

Please refer to Part I for more information about the polymorphism of API.

2.3.S.2 Manufacture (b) (4)

Who manufactures the drug substance?

How do the manufacturing processes and controls ensure consistent production of drug substance?

Firm's Response:

(b) (4)

Name, Address and Establishment Registration Number	Responsibility	Contact Person
Mylan Technologies Inc. 110 Lake Street Saint Albans, VT 05478 Establishment Registration Number: 1220747	Manufacturing, Packaging, Labeling, Quality Control Testing of Components, Testing of Finished Dosage Form	Jeffrey Lloyd Senior Director, Quality Assurance Telephone: (802) 527-7792, (b) (6) Facsimile: (802) 527-8155 Email: jeffrey.lloyd@mylan.com
(b) (4)		

Reviewer's Comment (Review 2): pending
DMF (b) (4) supporting documents are under review.

2.3.S.3 Characterization [Scopolamine, (b) (4) Limited]

How was the drug substance structure elucidated and characterized?

Firm's Response:
For the elucidation of structure and other characteristics of the drug substance, please refer to the Drug Master File [also referred to as the Active Substance Master File (ASMF)].

Reviewer's Comment (Review 2): Adequate
Please refer to review #1.

How were potential impurities identified and characterized?

Firm's Response:
(b) (4)

(b) (4)

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A APPENDICES

A.1 Facilities and Equipment (biotech only)

N/A

A.2 Adventitious Agents Safety Evaluation

Not Applicable: There are no adventitious agents.

A.3 Novel Excipients

Not Applicable: There are no novel excipients.

A.4 Nanotechnology Product Information

Office of Pharmaceutical Science MAPP 5015.9, Attachement A:

1) This review contains new information added to the table below:
Yes **No** **X** Review date:

2) Are any nanoscale materials included in this application?
(If yes, please proceed to the next questions.) Yes_____; No_____ ;
Maybe (please specify):_____

3 a) What nanomaterial is included in the product?
(Examples of this are listed as search terms in Attachment B.)

_____

3 b) What is the source of the nanomaterial?_____

4) Is the nanomaterial a reformulation of a previously approved product?

Yes_____ No_____

5) What is the nanomaterial functionality?
Carrier_____; Excipient_____; Packaging_____
API_____; Other_____

6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment?
Soluble _____; Insoluble_____

7) Was particle size or size range of the nanomaterial included in the application?
Yes_____(Complete 8); No_____ (go to 9).

8) What is the reported particle size? Mean particle size_____ ; Size range distribution_____; Other_____
9) Please indicate the reason(s) why the particle size or size range was not provided: _____
10) What other properties of the nanoparticle were reported in the application (See Attachment E)? _____
11) List all methods used to characterize the nanomaterial? _____

R REGIONAL INFORMATION

R.1 Executed Batch Records

Refer to review #1.

R.2 Comparability Protocols

Refer to review #1.

R.3 Methods Validation Package

Refer to review #1.

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Documents

Patent Certification:
Refer to review #1.

Exclusivity:
Refer to review #1.

GDEA Certification:
Refer to review #1.

Debarment Certification:
Refer to review #1.

cGMP Statement:
Refer to review #1.

Reprocessing Statement:
Refer to review #1.

Letters of Authorization:
Refer to review #1.

Request for Bio-waiver:
Citizen Petition and/or Control Request Linked to the Application:
Refer to review #1.

Environnemental Impact Considerations/Categorical Exclusions:
Please refer to Part III for this issue.

III. List of Deficiencies To Be Communicated

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 203753 APPLICANT: Mylan Technologies Inc.

DRUG PRODUCT: Scopolamine Transdermal System, 1.0 mg/3 days

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Guohua Li/05/28/2014, 06/12/2014, 07/11/2014, 07/15/2014, 09//22/2014
Chemistry Secondary Reviewer Name/Date: Dhaval K. Gaglani/05/20/2014, 06/03/2014, 07/13/2014, 07/16/14, 08/27/14, 09/23/14
Chemistry Supervisor: Bhagwant Rege/ 11/28/2014
Project Manager Name/Date:

TYPE OF LETTER: Approvable for CMC

Final Version for DARRTS 10/07/2013
CMC and Labeling are deficient. Bio and Clinical are pending. EES is acceptable
Chemist Name/Date: Guohua Li/ 9/30/2013
Chemistry Team Leader Name/Date: Bhagwant Rege, 08/07/2013, 10/3/2013
Chemistry Deputy Division Director: Bing Cai/ 10/04/2013
Project Manager Name/Date: Tania Mazza/ 10/07/2013

ANDA 203753

Scopolamine Transdermal System
1.0 mg/3 days

Mylan Technologies Inc.

CR #1
Guohua Li

OGD/Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 203753

2. REVIEW #: 1

3. REVIEW DATE: 01/03/2013

4. REVIEWER: Guohua Li, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	**Document Date**
Original submission SD 1, eCTD 0000	12/01/2011
Zhao, Zhuojun, REV-BIOEQ-02 (dissolution review)	08/29/2012 02/07/201308/08/2013
Park, Chan, Rev-Label-21 (primary review)	01/30/2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Technologies, Inc.
Address:	110 Lake St. St. Albans VT 05478 USA
Representative:	N/A
Telephone: Fax:	802-5277792 802-5278155

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: None
Non-Proprietary Name (USAN): Scopolamine Transdermal System, 1.0 mg/3 days

9. LEGAL BASIS FOR SUBMISSION:

RLD Product: Transderm Scōp® (NDA #017874)
RLD Company: Novartis
RLD strength: 1.0 mg/3 days
Dosage form of RLD: Extended Release Film

10. PHARMACOL. CATEGORY:

Indicated in adults for prevention of nausea and vomiting associated with motion sickness and recovery from anesthesia and surgery.

11. DOSAGE FORM:

Film, Extended Release

12. STRENGTH/POTENCY:

1.0 mg/ 3 days

13. ROUTE OF ADMINISTRATION:

Transdermal

14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

_____SPOTS product – Form Completed

___X_Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

___X___Not a NANO product

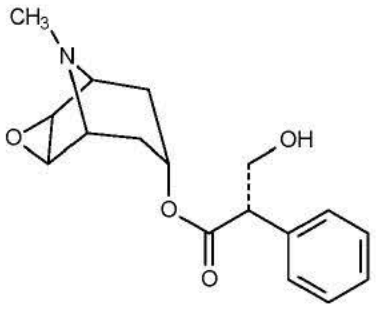
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s)

(1R,2R,4S,5S,7s)-9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]-non-7-yl (2S)-3-hydroxy-2-phenylpropanoate[1]

(αS)-α-(hydroxymethyl)benzeneacetic acid (1α,2β,4β,5α,7β)-9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl ester[1]

Structural Formula



Molecular Formula

$C_{17}H_{21}NO_4$

Molecular Weight

303.35 g/mole

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Inadequate	05/14/2013	Reviewed by Joseph Wetzel
	IV			4	NA		
	III			1	Inadequate	11/04/2010	Reviewed by Caroline Strasinger
	III			1	Adequate	04/26/2011	Reviewed by Shahnaz Read
	III			1	Adequate	04/15/2011	Reviewed by Shahnaz Read
	III			1	Adequate	11/21/2011	Reviewed by Xihao Li

[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)

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	03/25/2013	
Methods Validation	N/A		
Labeling	Inadequate	01/30/2013	Chan Park
Bioequivalence	Dissolution: Inadequate BE PK study: pending	08/19/2012 02/07/2013 08/08/2013	Zhuojun Zhao
Toxicology/Clinical	Irritation study: Pending		
EA	Pending		
Radiopharmaceutical	N/A		
Samples requested	None		

19. ORDER OF REVIEW

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

20. EES INFORMATION

(b) (4)

Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
Manufacturing, Packaging, Labeling, Quality Control Testing of Components, Testing of Finished Dosage Form	Mylan Technologies Inc. 110 Lake Street Saint Albans, VT 05478	FEI # : 1220747	AC
			(b) (4)

(b) (4)

Chemistry Review for ANDA 203753

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC portion is not approvable due to major deficiencies. The firm has provided only (b) (4) stability batch. Labeling is deficient. EES is acceptable. All other are pending.

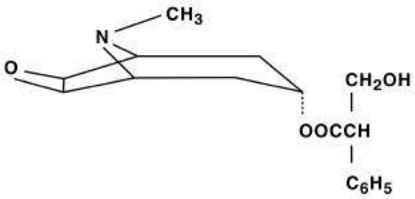
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

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

Drug Substance

Scopolamine is α-(hydroxymethyl) benzeneacetic acid 9-methyl-3-oxa-9-azatricyclo [3.3.1.0$_{2,4}$] non-7-yl ester. The molecular formula is $C_{17}H_{21}NO_4$ and its structural formula is



Scopolamine is a crystalline powder that has a molecular weight of 303.35 and a pKa of 7.55 to 7.81.

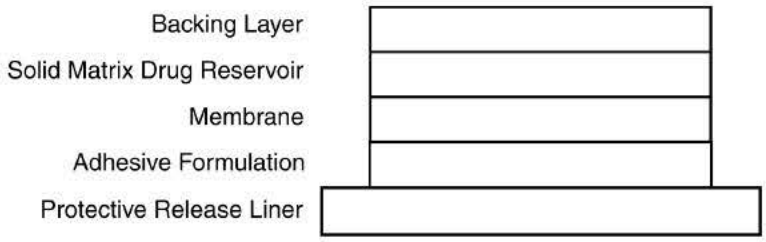
Drug Product

Scopolamine transdermal system is a circular flat patch designed for continuous release of scopolamine following application to an area of intact skin on the head, behind the ear. Each system contains (b) (4) mg of scopolamine base. Scopolamine transdermal system is a 1.8 cm^2 film, with four layers. Proceeding from the visible surface towards the surface attached to the skin, these layers are: (1) a backing layer of peach-colored polyethylene/polyester film; (2) a solid matrix drug reservoir layer of silicone adhesive, scopolamine and povidone; (3) a microporous polypropylene membrane; and (4) an adhesive formulation of silicone adhesive, povidone and scopolamine. A protective, oversized release liner of fluoropolymer-coated polyester, which covers the adhesive

formulation layer, is removed before the system is used. The inactive components, silicone adhesive and povidone, (b) (4)

Scopolamine transdermal systems are packaged with an additional piece of protective film above the system within each pouch. This piece of protective film is removed and discarded at the time of use.

Cross section of the system:



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

MDD (b) (4) mg;
ICH Q3B (R2): RT=0.1%, IT=0.5%, QT=1.0%

DOSAGE AND ADMINISTRATION

Initiation of Therapy: To prevent the nausea and vomiting associated with motion sickness, one scopolamine transdermal system (programmed to deliver approximately 1.0 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. To prevent postoperative nausea and vomiting, the patch should be applied the evening before scheduled surgery. To minimize exposure of the newborn baby to the drug, apply the patch (b) (4) to cesarean section. Only one patch should be worn at any time. Do not cut the patch.

Handling: After the patch is applied on dry skin behind the ear, the hands should be washed thoroughly with soap and water and dried. Upon removal, the patch should be discarded. To prevent any traces of scopolamine from coming into direct contact with the eyes, the hands and the application site should be washed thoroughly with soap and water and dried. (A patient brochure is available).

HOW SUPPLIED: The scopolamine transdermal system is a peach-colored circular patch, 1.8 cm^2, on a clear, oversized, rectangular release liner, which is removed prior to use. Each scopolamine transdermal system contains (b) (4) mg of scopolamine and is programmed to deliver *in vivo* approximately 1.0 mg of scopolamine over 3 days. Scopolamine transdermal system is available in packages of 4 patches, 10 patches and 24 patches. Each patch is packaged in a protective pouch. Patient instructions are included.

4 patches NDC 0378-6470-99
10 patches multipack NDC 0378-6470-97
24 patches multipack NDC 0378-6470-44
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

RLD has labeled storage at controlled room temperature between 20°C-25°C (68°F-77°F)

Basis for Approvability or Not-Approval Recommendation

CMC is not approvable.
Labeling review is deficient.
Bioequivalence and Clinical Bio are pending.
EES is acceptable

Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	None
Non-Proprietary Name of Drug Product	Scopolamine Transdermal System, 1.0 mg/3 days
Non-Proprietary Name of Drug Substance	Scopolaminum
Company Name	Mylan Technologies Inc.
Dosage Form	Film, extended release
Strength(s)	1.0 mg/3 days
Route of Administration	Transdermal
Proposed Indication(s)	Indicated in adults for prevention of nausea and vomiting associated with motion sickness and recovery from anesthesia and surgery.

2.3.S DRUG SUBSTANCE [Scopolamine, (b) (4)

2.3.S.1 General Information [Scopolamine, (b) (4)

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

Firm's Response:

Established Name
Scopolamine (Hyoscine)

Compendial Name
Scopolamine is not listed in the USP. It is listed in the Ph. Eur as Hyoscine

Chemical Name(s)

(1R,2R,4S,5S,7s)-9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]-non-7-yl (2S)-3-hydroxy-2-phenylpropanoate[1]

(αS)-α-(hydroxymethyl)benzeneacetic acid (1α,2β,4β,5α,7β)-9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl ester[1]

Company or Laboratory Code

(b) (4)

Other Non-Proprietary Name(s)

Scopolaminum[1]

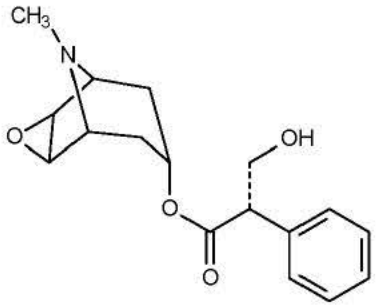
Chemical Abstracts Service (CAS) Registry Number

[51-34-3] [1]

References:

1. (b) (4)

Structural Formula (including relative and absolute stereochemistry)



Molecular Formula

$C_{17}H_{21}NO_4$

Molecular Weight

303.35 g/mole

Reviewer's Comment (Review 1): Adequate

The information provided is consistent with literature and EP Monograph.

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

Firm's Response:

Physical Description[1]
Scopolamine appears as white or almost white, crystalline powder or colorless crystals, according to Ph Eur 7.0.

Physical form[1]
Scopolamine (b) (4) is isomorphous and of a consistent physical form as confirmed (b) (4)

Solubility

Solubility in common solvents (at 20°C) [1]

Solvent	Solubility (mg/mL)	Descriptive Term (as defined in the USP)
Water	> 100 mg /mL at 15°C	Freely soluble
Methanol	>1 g /mL	Very soluble
Acetone	>1 g /mL	Very soluble

Quantitative aqueous pH solubility profile (at 37°C)

pH of the buffer	Solubility (mg/mL)	Descriptive Term (as defined in the USP)
pH # 1.1	> 50 mg/mL	Soluble
pH # 4.5	> 50 mg/mL	Soluble
pH # 6.8	> 20 mg/mL	Sparing soluble

pKa Value(s) [1]
7.55 at 23°C and 7.81 at 25°C.

pH Value(s)

pH values of drug substance (50 mg/mL solution in water)

Lot	pH
Lot1 # SFFK1	(b) (4)
Lot2 # SFFJ3	

Melting Range[1]
The melting point for Scopolamine quoted in Ph Eur 7.0 is 66°c to 70°C

UV Maxima
A saturated solution of Scopolamine in methanol has UV maxima approximately at 210 and (b) (4).

Specific Optical Rotation[1]

Scopolamine is a natural product extracted from the *Datura sanguinea* plant and thus the chirality is determined by the biosystems of the plant. (b) (4) .

Chirality of this API is confirmed and controlled by testing according to Ph Eur 7.0 official specific optical rotation test method.

Hygroscopicity[1]

Scopolamine is hygroscopic when exposed to ambient conditions at 100% humidity.

(b) (4)

References:

1 (b) (4)

2 SciFinder CAS Registry Number search, 10/10/2011.

Reviewer's Comment (Review 1): Inadequate

Information provided is in line with all references. DMF (b) (4) is inadequate.

Deficiencies:

In 2.3.S.1, all the physicochemical properties cited in the question need to be mentioned. Therefore, please provide the information on **polymorphism** of Scopolamine. Also, please include characterization data (b) (4) to support the same.

(b) (4)

DMF (b) (4) is inadequate. The DMF holder has been notified. Please ensure there is a response.

2.3.S.2 Manufacture [Scopolamine, (b) (4)

Who manufactures the drug substance?

How do the manufacturing processes and controls ensure consistent production of drug substance?

Firm's Response:

Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications

PREPARING AN EA FOR SUBMISSION TO CDER or CBER

A. Content and Format

This section describes the basic information that should be submitted in an EA if an EA is required. Attachment D contains an outline of the format for an EA. Alternative formats may be used, but the applicant should recognize that use of a standard format, such as described in this guidance, promotes efficiency in the review process.

1. Date

The EA should include the date the EA was originally prepared and the date(s) of any subsequent amendments.

2. Name of Applicant or Petitioner

The EA should identify the applicant who is submitting the application.

3. Address

The EA should contain the address where all correspondence is to be directed.

4. Description of Proposed Action

a. Requested Approval

The description of the requested approval should include the drug or biologic application number (if available), the drug or biologic product name, the dosage form and strength, and a brief description of the product packaging. For example, "XYZ Pharmaceuticals has filed an NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADE NAME (established name), 250 mg and 500 mg, packaged in OHDPE bottles. An EA has been submitted pursuant to 21 CFR part 25."

b. Need for Action

The EA should briefly describe the drug's or biologic's intended uses in the diagnosis, cure, mitigation, treatment, or prevention of disease.

c. Locations of Use

The EA should identify the location(s) where the product will be used. Depending on the type of product and its use, the locations of use are typically identified as hospitals, clinics and/or patients in their homes. If use is expected to be concentrated in a particular geographic region, this fact should be included.

d. Disposal Sites

Unless other disposal methods by the end user are anticipated, it is sufficient to state that at U.S. hospitals, pharmacies, or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy, or clinic procedures and/or that in the home,

empty or partially empty containers will typically be disposed of by a community's solid waste management system, which may include landfills, incineration, and recycling, although minimal quantities of the unused drug could be disposed of in the sewer system.

5. Identification of Substances that are the Subject the Proposed Action
The EA should contain information that allows for the accurate location of data about the substance in the scientific literature and for identification of closely related compounds. At a minimum, the information listed below should be provided, if available. For many biological products, format items 5.a.iii, b, c, and d will not apply. Other information, such as the international nonproprietary name (INN) or nonsystematic or semisystematic chemical names should be included if deemed useful in the identification of the compounds.
Usually this information need only be provided for the drug or biologic substance, but the same information also should be provided for the form of the active ingredient in the drug or biologic product if it is different from the drug or biologic substance (e.g., a salt formed in situ from a free base) or for a pharmacologically active related substance formed by conversion from a pharmacologically inactive parent compound (e.g., a prodrug product is converted to the pharmacologically active form).

a. Nomenclature
i. Established Name (U.S. Adopted Name-USAN)
ii. Brand/Proprietary Name/Tradename
iii. Chemical Names or Genus/Species of Biologic Product (e.g., virus)
- Chemical Abstracts (CA) Index Name (inverted form)
- Systematic Chemical Name (uninverted form)

b. Chemical Abstracts Service (CAS) registration number

c. Molecular Formula

d. Molecular Weight

e. Structural (graphic) Formula/Amino Acid Sequence

6. Environmental Issues
The type of information provided will vary depending on the environmental issues associated with the particular action. In general, the EA should include a succinct description of the environmental issues. The affected environment and the environmental effects and their significance should be discussed. Data and analyses to support the discussions should be provided as appropriate. Specific guidance is provided in section IV.B for the environmental issues that are most likely to be associated with human drugs and biologics. For environmental issues not specifically addressed in section IV.B (e.g., those included in sections III.C.4 and 5), applicants are encouraged to consult the appropriate Center prior to preparing the EA.

7. Mitigation Measures

Describe measures taken to avoid or mitigate any potential adverse environmental effects associated with the proposed action. If no adverse environmental effects have been identified, it should be so stated and indicated that, therefore, no mitigation measures are needed. See section IV.B.2.b for additional information regarding the discussion of mitigation measures for actions involving fauna and flora.

8. Alternatives to the Proposed Action
If no potential adverse environmental effects have been identified for the proposed action, the EA should state this. If potential adverse environmental effects have been identified for the proposed action, the EA "shall discuss any reasonable alternative course of action that offers less environmental risk or that is environmentally preferable to the proposed actions" (21 CFR 25.40(a)). The discussion should include the no-action alternative and measures that FDA or another government agency could undertake as well as those the applicant or petitioner would undertake. The EA should include a description of those alternatives that will enhance the quality of the environment and avoid some or all of the adverse environmental effects of the proposed action. The environmental benefits and risks of the proposed action and the environmental benefits and risks of each alternative should be discussed. See section IV.B.2.c for additional information regarding the discussion of alternatives for actions involving fauna and flora.

9. List of Preparers
The EA should include the name, job title, and qualifications (e.g., educational degrees) of those persons preparing the assessment and should identify any persons or agencies consulted. Contract testing laboratories should be included in the list of consultants, although this may be included in a confidential appendix. Curriculum vitae can be included in lieu of a description of an individual's qualifications.

10. References
The EA should include a list of citations for all referenced material and standard test methods used in generating data in support of the EA. Copies of referenced articles that are not generally available and that are used to support specific claims in the EA document should be attached in a nonconfidential appendix.

11. Appendices
Both confidential and nonconfidential appendices can be included. See section IV.E for additional information about the treatment of confidential information. A list of the appendices should be included in the EA summary document with a designation of confidential or nonconfidential following each of the listings. Typically, the nonconfidential appendices include data summary tables and copies of referenced articles that are generally unavailable or that were used to support specific claims in the EA. Proprietary or confidential information, such as use estimates and test reports, should be included in the confidential appendices.

Environmental Assessment Format Outline:

1. Date
2. Name of Applicant/Petitioner
3. Address
4. Description of Proposed Action
    a. Requested Approval
    b. Need for Action
    c. Locations of Use
    d. Disposal Sites
5. Identification of Substances that are the Subject of the Proposed Action
    a. Nomenclature
        i. Established Name (U.S. Adopted Name - USAN)
        ii. Brand/Proprietary Name/Trade name
        iii. Chemical Names or Genus/Species of Biologic Product (e.g., virus)
            - Chemical Abstracts (CA) Index Name
            - Systematic Chemical Name
    b. Chemical Abstracts Service (CAS) Registration Number
    c. Molecular Formula
    d. Molecular Weight
    e. Structural (graphic) Formula/Amino Acid Sequence
6. Environmental Issues
7. Mitigation Measures
8. Alternatives to the Proposed Action
9. Certification
10. List of Preparers
11. References
12. Appendices

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Guohua Li/ 9/30/2013
Chemistry Team Leader Name/Date: Bhagwant Rege, 08/07/2013, 10/3/2013
Chemistry Deputy Division Director: Bing Cai/ 10/04/2013
Project Manager Name/Date:Tania Mazza/ 10/07/2013

TYPE OF LETTER: Major Deficiencies. Labeling is deficient. Bio and clinical are pending. EES is acceptable.

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

/s/

GUOHUA LI
10/08/2013

TANIA B MAZZA
10/09/2013

BHAGWANT D REGE
10/09/2013

BING CAI
10/09/2013