

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204655Orig1s000

CHEMISTRY REVIEW(S)

NDA 204655

Nexium 24HR (esomeprazole magnesium) Delayed-Release Capsules

AstraZeneca LP

Sheldon Markofsky, Ph.D.

Division of Nonprescription Clinical Evaluation

and

Office of New Drug Quality Assessment III Branch VII

File: 204655b

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A APPENDICES (Attachments)	50
R REGIONAL INFORMATION	N/A
II. List Of Deficiencies To Be Communicated	none

Chemistry Review Data Sheet

1. NDA 204655
2. REVIEW #: 1
3. REVIEW DATE: 28-February- 2014
4. REVIEWER: Sheldon Markofsky, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA (Original)	30-May-2013
Filing Review Document	03-Jul-2013
Amendment ^a	27-Sept-2013
Amendment ^b	19-Dec-2013
Amendment ^c	31-Oct-2013
IR Letter	25-Nov-2013
Amendment ^d	25-Feb-2014

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
NDA Original	30-May-2013
Amendment ^b	19-Dec-2013
Amendment ^c	31-Oct-2013
Amendment ^d	25-Feb-2014

- a) The 9-27-13 amendment provides a microbial limits test for the post approval monitoring of the drug product and responses to questions from the Agency's 74 Day Letter to AstraZeneca.
- b) The 12-19-13 amendment provides responses to our 11-25-13 Information Requests
- c) The 10-31-13 amendment provides a revised stability commitment.
- d) The 2-25-14 amendment provides a revised dissolution specification.

7. NAME & ADDRESS OF APPLICANT:

Name: AstraZeneca LP
Address: 1800 Concord Pike
Wilmington DE
U.S. Agent: Gary P. Horowitz
Telephone: (302) 885-1008

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Nexium 24HR
 b) Non-Proprietary Name: Esomeprazole Magnesium Delayed-Release Capsules
 c) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 8
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of frequent heartburn
(occurring 2 or more days per week)

11. DOSAGE FORM: CAPSULE, DELAYED RELEASE

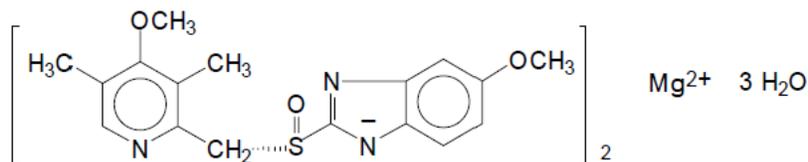
12. STRENGTH/POTENCY: 20 mg esomeprazole
(as 22.3 mg of esomeprazole magnesium trihydrate)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

Molecular formula: $C_{34}H_{36}N_6O_6S_2Mg \cdot 3H_2O$

Relative molecular mass: 767.2 g/mol (trihydrate)
713.1 g/mol (anhydrous basis)

Stereochemistry:

The molecule contains one asymmetrically substituted sulfoxide moiety, which makes the molecule chiral. In esomeprazole, the sulfur atom has the (S)-configuration.

Chemical names:

INN: Esomeprazole (parent compound)

USAN: Esomeprazole magnesium

(Chemical Abstracts)

1H-Benzimidazole, 5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-, magnesium salt, trihydrate

(IUPAC)

Bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1Hbenzimidazol-1-yl)magnesium

CAS Registry Number: 217087-09-7

Company Code Numbers: H 199/18 magnesium trihydrate

H 199/18 magnesium

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: None

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21153	Nexium Delayed-Release Capsules (Rx)
IND	53733	Nexium Capsules

18. STATUS:**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	10-17-13	
Methods Validation	Acceptable	2-28-14	S. B. Markofsky
EA	Acceptable	2-27-14	James Laurenson
Microbiology	Acceptable	11-8-13	Stephen Langille
ONDQA/Biopharmaceutics	Acceptable	2-25-14	Tien-Mien Chen

19. ORDER OF REVIEW: N/A (OGD Only)

The Chemistry Review for NDA 204655

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved.

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 and Drug Substances

1) Drug Product

The drug product, with the proposed proprietary name Nexium 24HR and the established name Esomeprazole magnesium Delayed-Release Capsules, is a proton pump inhibitor and is used for the treatment of frequent heartburn occurring 2 or more days a week. The manufacture and composition/formulation of the proposed OTC Nexium 24HR Delayed Release 20 mg capsules (b) (4)

that the OTC Nexium 24HR capsule is required to be sealed by a tamper band. The strength is based on esomeprazole anhydrous free base ($C_{17}H_{19}N_3O_3S$) (as 22.3 mg of esomeprazole magnesium trihydrate). The drug product, with an opaque amethyst body and cap, is marked with two yellow stripes printed in radial format and a yellow gelatin band. NEXIUM 20 mg is also printed in yellow in radial format on the capsule.

The drug product is packed in 45 mL square shaped bottles made of white high density polyethylene (HDPE) with (b) (4). Inside the screw closure are a liner and a seal. (b) (4)

A desiccant (b) (4) is placed inside the bottle. The 45 mL bottles contain either 14 capsules for marketing or 2 capsules for use as physician samples. The drug product will be distributed in differently sized cartons containing 1, 2, or 3 bottles.

Besides esomeprazole magnesium trihydrate, the drug product contains the following inactive ingredients: Ferric oxide, corn starch, glyceryl monostearate, hydroxyl propyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer (b) (4), polysorbate 80, sucrose, talc, triethyl citrate, gelatin, FD&C Blue #1, FD&C Red #40, D&C Red #28, titanium dioxide, (b) (4)

2) Drug Substance

The drug substance, esomeprazole magnesium trihydrate, is manufactured by AstraZeneca at their facility in Dunkerque France; and AstraZeneca references their approved NDA 21153 (Nexium Capsules) and its amendments for the CMC information related to the manufacture of this material. Esomeprazole magnesium trihydrate is a white to slightly colored (b) (4). The solubility of esomeprazole magnesium trihydrate in water is approximately 1.5 mg/mL, with a corresponding pH of 10.0.

(b) (4)

Esomeprazole magnesium trihydrate has a (u) (4) month re-test period when stored at USP defined controlled room temperature in its container closure system.

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

The recommended dose of Nexium 24HR for adults 18 years of age and older is one capsule daily (every 24 hours) for 14 days. The stability studies support an expiration-dating period of 36 months for the drug product when stored at 20-25°C (68-77°F).

C. Basis for Approvability or Not-Approval Recommendation

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved on the following basis:

- Adequate information was provided for the synthesis, purification and controls of the drug substance by reference to NDA 21153, which has been approved for the Nexium Rx capsules.
- Adequate manufacturing information to support the proposed to-be-marketed drug product

- Adequate specifications and controls for the drug product
- Satisfactory methods to support lot release and stability monitoring of the drug product
- Adequate stability data to support the recommended expiry period of the drug product
- An acceptable Environmental Assessment
- An acceptable Establishment Report for the relevant manufacturing and testing facilities

[Labeling will be finalized at a later date as part of the review team's labeling negotiation.]

Risk/Benefit Assessment

Since the specifications as well as release and stability data show no significant differences between the approved Rx capsules and the proposed OTC capsules, there are no additional quality or safety risks for this OTC switch from a CMC point of view,

III. Administrative

A. Reviewer's Signatures

Sheldon Markofsky, Ph.D. (Chemistry Reviewer)

B. Endorsement Block (OGD only)

N/A

C. CC Block (OGD only)

N/A

45 Page(s) has 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/

SHELDON B MARKOFSKY
03/05/2014

DANAE D CHRISTODOULOU
03/05/2014

I concur with the reviewer's conclusion and recommendation

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 204-655 (ONDQA)**

Division of Nonprescription Clinical Evaluation

NDA: 204,655
Applicant: AstraZeneca LP
1800 Concord Pike
Wilmington, DE 19803-8355
Stamp Date: 05/30/2013
PDUFA Date: 03/30/2014
Proposed Proprietary Name: Nexium Delayed-Release Capsules OTC
Established Name: Esomeprazole magnesium
Dosage form and strength: Capsules; 20 mg
Route of Administration: Oral
Indications: Frequent heartburn

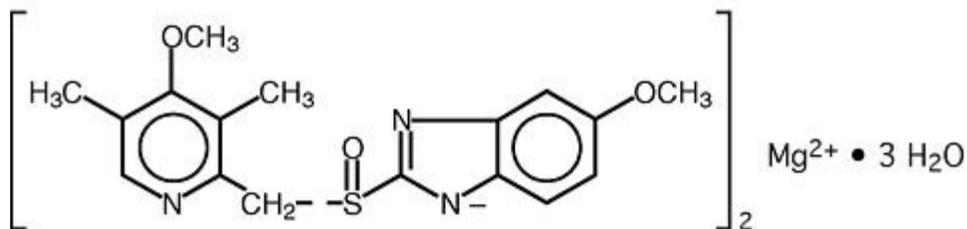
CMC Lead: Swapan K De

ONDQA Fileability: Yes

Name: bis(5-methoxy-2-[(S)-[(4-methoxy-3,5dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl) magnesium trihydrate

Molecular formula: $(C_{17}H_{18}N_3O_3S)_2 Mg \cdot 3H_2O$

Molecular Weight: $76\frac{6}{4}$.2 g/mol (trihydrate) and 713.1 g/mol (anhydrous basis)



Has all information requested during the IND phases, and at the pre-NDA meetings been included?

Yes. Relevant FDA meetings under IND 111,185 are listed in section 1.2 and section 1.6.

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FILING REVIEW FOR NDA 204-655 (ONDQA)

Summary:

This is an e-CTD 505(b)(1) NDA application for esomeprazole magnesium 20 mg capsules (Nexium® Delayed-Release Capsules OTC). Esomeprazole inhibits specifically the gastric H⁺/K⁺-ATPase enzyme, which is responsible for acid secretion in the parietal cells of the stomach. The proposed drug product is intended to treat frequent heartburn (occurs 2 or more days a week). Esomeprazole is formulated as gastro-resistant capsules containing a multitude of enteric coated pellets of esomeprazole magnesium trihydrate because esomeprazole is acid labile. The CMC information of this NDA is based on prescription Nexium® Capsules NDA 21-153 (approved February 20, 2001). This application seeks approval of esomeprazole magnesium 20 mg capsules although prescription Nexium® Capsules is approved for both 20 mg and 40 mg strengths. AstraZeneca LP is the sponsor of the NDA 21-153 and has announced that they will continue to hold the IND and NDA for the Nexium OTC product and they have entered into an agreement with Pfizer to give them the exclusive rights to market Nexium® OTC in the US. AstraZeneca has submitted a proprietary name review request for the drug product as “Nexium® 24HR” to the Division of Medication Error Prevention and Risk Management (DMEPA). The sponsor stated that they received a letter (dated April 19, 2013) from DMEPA indicating that the proprietary name “Nexium® 24HR” is conditionally acceptable.

Drug Substance:

Drug substance, esomeprazole magnesium trihydrate information is approved in the Nexium Capsules NDA 21-153 and this NDA (204-655) refers approved NDA (21-153) for all drug substance information. The manufacturer (Minakem Dunkerque, Dunkerque, FRA) of the drug substance remain same for the current NDA (204-655).

Drug Product:

[REDACTED] (b) (4)

[REDACTED]. The information on esomeprazole capsules Rx is not repeated in this submission, but is instead cross-referenced. Esomeprazole capsules OTC will be [REDACTED] (b) (4) yellow gelatin

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 204-655 (ONDQA)**

band to provide a clearly visible tamper-evident seal to fulfill the requirement as per 21CFR 221.132. In addition, the yellow band provides a clearly visible differentiation between the drug products for Rx and OTC use.

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

However, stability data for Esomeprazole capsules OTC with gelatin sealing band is provided (up to 12 months) and compared with the Esomeprazole capsules Rx batch (supportive stability batch) [REDACTED] (b) (4), to confirm equal stability between the two drug products. AstraZeneca intends to pack Esomeprazole capsules OTC in a 45 mL high-density polyethylene (HDPE) square shaped bottle and stability study is conducted using the 45-mL HDPE bottle. Stability specifications (description, assay, organic impurities and dissolution) remain as the study parameters approved for Esomeprazole capsules Rx. The sponsor has proposed 36 month shelf life for the drug product.

Components and composition of the Esomeprazole delayed-release capsules OTC 20 mg:

Components	Quantity per unit	Function	Standard
Esomeprazole delayed-release Esomeprazole capsules 20 mg (as magnesium trihydrate 22.3 mg)	1 capsule	[REDACTED] (b) (4) [REDACTED] (b) (4)	AstraZeneca
[REDACTED] (b) (4) Gelatin	[REDACTED] (b) (4)	[REDACTED] (b) (4)	NF
Ferric oxide			NF
Titanium dioxide			USP
[REDACTED] (b) (4)			USP

^a The amount of gelatin band may vary, the amount given is typical.

[REDACTED] (b) (4)

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Esomeprazole delayed-release capsules OTC Product Release Specification:

The Esomeprazole delayed-release capsules OTC 20 mg (as esomeprazole magnesium trihydrate 22.3 mg) complies with the Esomeprazole magnesium delayed-release capsules monograph in USP and meets the requirements of additional tests listed below. Other release tests include Identification of Esomeprazole, Assay of Esomeprazole, Organic impurities, Dissolution and Uniformity of Dosage units as described in NDA 21-153.

Test procedure	Acceptance criteria	Method reference
Description	A sealed, hard gelatin capsule with opaque, amethyst body and cap. The capsule is sealed with a yellow gelatin band in radial format that covers the joined portion of the body and cap. Additionally the cap is marked with two stripes in yellow printed in radial format and the body is marked NEXIUM 20 mg printed in yellow in radial format.	Visual inspection
Identification	Positive identity	Atomic absorption spectroscopy

Magnesium

Note:  (b) (4)

Esomeprazole delayed-release capsules OTC Product Stability Specification:

Drug product stability testing results for only one registration batch of Esomeprazole delayed-release capsules OTC 20 mg (Batch #11, Drug substance Lot# 30054504 & 30054506) has been provided based on an agreement with Agency dated May 13, 2011. Supporting stability data from one batch (Batch #2259, Drug substance Lot# 30054504 & 30054506) of Esomeprazole Capsules Rx manufactured from same lots of drug substance is also included. The stability study parameters description, assay, organic impurities and dissolution are the same as the study parameters approved for Esomeprazole capsules Rx. The analytical procedures for stability testing are identical to those used for release testing. Stability data for the submission

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 204-655 (ONDQA)

batch and supportive batch have been provided up to 12 months at long term conditions (25°C/60% RH) and up to 6 months at accelerated conditions (40°C/75% RH). The applicant has proposed three years shelf-life of the Esomeprazole delayed-release capsules OTC 20 mg.

Critical Issues:

Drug substance:

- Although Drug substance manufacturing facility remains unchanged, it is stated in eCTD section 2.3.S that “there are no changes to the drug substance for this submission, except for ‘2.3.S.2.1 Manufacture(s)’”. This statement needs to be clarified.
- An environmental analysis report has been provided in eCTD section 1.12.14 and needs to be consulted to Environmental Assessment Review Team at OPQ.

Drug Product:

- There is detailed formulation development section in 3.2P which should be evaluated in-depth.
- Has adequate justification been provided for not including the microbial limits test in the release specification of Esomeprazole delayed-release capsules OTC? Microbiological Attributes section 3.2.P.2.5 is included and needs a consult review by a microbiologist.
- In vitro dissolution comparison among the Esomeprazole delayed-release capsules OTC and Rx should be consulted to the Biopharmaceutics team in ONDQA.
- Is the submitted 12-month stability data for one batch of drug product is enough to support the proposed 3-year shelf-life of the Esomeprazole delayed-release capsules OTC with altered container closure system which is different from the approved prescription Esomeprazole delayed-release capsules product?

PRODUCT QUALITY (Small Molecule)
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Comments and Recommendations:

The application is fileable. The CMC information remains very similar as approved in NDA 21-153. Submitted manufacturing facilities have been entered into the EES. The reviewer should confirm the accuracy and completeness of the EES entries. This NDA does not qualify as a QbD submission based on the criteria in the ONDQA interim policy (no design space, PAT, RTRT, reduced end-product testing etc.).

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 204-655 (ONDQA)**

NDA Number: 204-655

Established/Proper Name:
esomeprazole magnesium

Applicant:
AstraZeneca LP

Letter Date: 05/30/2013

Stamp Date: 05/30/2013

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

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		In standard eCTD format.
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			N/A

**PRODUCT QUALITY (Small Molecule)
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7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		One facility (same as NDA 21-153). Listed in eCTD Section 3.2.S.2.1
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		Six facilities. Listed in eCTD Section 3.2.P.3.1

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

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

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	<p>Has an environmental assessment report or categorical exclusion been provided?</p>	X		<p>An environmental analysis of esomeprazole has been provided.</p>

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D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?		X	Refers to NDA 21-153
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		X	Refers to NDA 21-153
14.	Does the section contain information regarding the characterization of the DS?		X	Refers to NDA 21-153
15.	Does the section contain controls for the DS?		X	Refers to NDA 21-153
16.	Has stability data and analysis been provided for the drug substance?		X	Refers to NDA 21-153
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	N/A
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	N/A

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E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		Refers to NDA 21-153. Additional steps are included.
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		Refers to NDA 21-153. Additional steps are included.
21.	Is there a batch production record and a proposed master batch record?	X		Refers to NDA 21-153. Additional steps are included.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		Pharmaceutical development section has adequate information.
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	N/A
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	N/A

**PRODUCT QUALITY (Small Molecule)
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F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?		X	Needs to be requested based on reviewers judgment.

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		DMF numbers for the manufacturers of container closure is included in eCTD section 3.2.P.7

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

**PRODUCT QUALITY (Small Molecule)
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J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.		X	
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	Yes, if anything comes out on initial review by the reviewer.

{See appended electronic signature page}

Swapan K De
CMC Lead
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment

Date 06/20/2013

{See appended electronic signature page}

Danae D Christodoulou
Acting-Branch Chief
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment

Date 07/03/2013

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

/s/

SWAPAN K DE
07/03/2013

DANAE D CHRISTODOULOU
07/03/2013