

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202342Orig1s000

CHEMISTRY REVIEW(S)

NDA 202342

**Esomeprazole Strontium Delayed Release Capsules
24.65 mg and 49.3 mg**

Hanmi USA Inc.

Raymond P. Frankewich, Ph.D.

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV**

**CMC REVIEW
For the Division of Gastroenterology and Inborn Errors Products
(CDER/ODEIII/DGP, HFD-180)**

Table of Contents

Table of Contents	2
CMC Review Data Sheet	3
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	7
II. Summary of CMC Assessments	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used	8
C. Basis for Approvability or Not-Approval Recommendation	8
III. Administrative	8
CMC Assessment	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data	9
P DRUG PRODUCT	9
P.3 Manufacture	9
P.7 Container Closure System	14

CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 202342
2. REVIEW #: 3
3. REVIEW DATE: July 17, 2013
4. REVIEWER: Raymond P. Frankewich, Ph.D.
5. PREVIOUS DOCUMENTS: See Review #2

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	June 6, 2013
Amendment (Labeling)	July 16, 2013

7. NAME & ADDRESS OF APPLICANT:

Name: Hanmi USA Inc.
Address: 200 Park Avenue
Florham Park, NJ 07932
Representative: Parexel International, LLC
Bethesda Crescent
4600 East-West Highway, Suite 350
Bethesda, MD 20814
Telephone: 301-634-8026
301-634-8010
Fax: 301-634-8040

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	None
b) Non-Proprietary Name (USAN):	Esomeprazol strontium
c) Code Name/# (ONDQA only):	HM70231
d) Chem. Type/Submission Priority (ONDQA only):	
• Chem. Type:	2
• Submission Priority:	S

CMC Review Data Sheet

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

10. PHARMACOL. CATEGORY: Treatment of GERD patients (b) (4)

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 20 mg, 40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

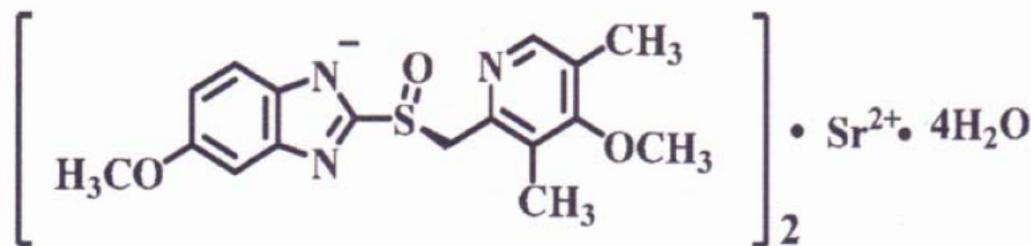
SPOTS product – Form Completed

Not a SPOTS product

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

Chemical name: (-)-5-Methoxy-2-[(S)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-1H-benzimidazole strontium tetrahydrate.

Structural formula:



Molecular formula: $(C_{17}H_{18}N_3O_3S)_2 \cdot Sr \cdot 4H_2O$

Molecular weight: 848.50 (tetrahydrate)*
776.44 (anhydrous)

CMC Review Data Sheet

*The established name by USAN, *esomeprazole strontium* is defined as the name of the chemical compound, *esomeprazol strontium tetrahydrate*.

In this review, *esomeprazol strontium* is exclusively used as an established name for describing the chemical compound, *esomeprazol strontium tetrahydrate*.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	December 7, 2006	Review by G. Holbert, Ph.D.
	III			1	Adequate	July 7, 2010	Review by C. Strasinger, Ph.D.
	III			1	Adequate	April 1, 2011	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		
NDA		

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	-	-
EES	Acceptable	7/17/2013	April Alexandrow (Coordinator),
Pharm/Tox	N/A	-	-
Biopharm	Acceptable	6/13/2011	Sandra Suarez Sharp, Ph.D
LNC	N/A	-	-
Methods Validation	N/A, according to the current ONDQA policy (see review)	-	-
DMEPA	N/A		-
EA	Claim for categorical exclusion is granted.	6/14/2011 (CMC Review #1)	Raymond P. Frankewich, Ph.D.
Microbiology	N/A	-	-

Executive Summary Section

The CMC Review for NDA 202342

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has been resubmitted, following a tentative approval action (date of action was April 29, 2012). At the time of the tentative approval, there were no CMC issues.

In this resubmission, the applicant has provided additional CMC information regarding manufacturing process, manufacturing facilities, and container closure system. The information is evaluated in this review.

Request for inspection (EER) of all manufacturing facilities was re-submitted because the current submission is considered a Class 1 Re-submission. Office of Compliance (OC) has made a final recommendation of Acceptable.

Therefore, from the ONDQA perspective, this NDA is recommended for approval.

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

NA

II. Summary of CMC Assessments

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

See Review #1 (6/14/2011) and Review #2 (4/22/2013) unless otherwise stated.

(1) Drug Substance

See Review #1 (6/14/2011) and Review #2 (4/22/2013).

(2) Drug Product

In this resubmission (6/6/2013), additional detail is provided regarding manufacturing process parameters and in-process testing. The information is summarized and discussed in this review.

Executive Summary Section

Also, it is noted that the drug product packaging facility has changed its name and ownership. In addition, section 3.2.P.7 (5 pages total) is resubmitted with the new name of the facility. The new name is (b) (4), located in (b) (4), or (b) (4) (the name in the original NDA was (b) (4), or (b) (4)). There has been no change in the packaging facility other than ownership and name.

Request for inspection (EER) of all manufacturing facilities was re-submitted because the current submission is considered a Class 1 Re-submission. Office of Compliance (OC) has made a final recommendation of Acceptable.

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

See Review #1.

C. Basis for Approvability Recommendation

See Review #2 and Addendum.

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

(See appended electronic signature page)

Raymond P. Frankewich, Ph.D., Review Chemist, Branch II, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Moo Jhong Rhee, Ph.D., Branch Chief, Branch II, ONDQA

C. CC Block: entered electronically in DFS

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/s/

RAYMOND P FRANKEWICH
07/17/2013

MOO JHONG RHEE
07/17/2013
Chief, Branch IV

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 26, 2013
FROM: Raymond P. Frankewich, Ph.D., Review Chemist, Branch IV, DNDQA II/ONDQA
THROUGH: Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV, DNDQA II/ONDQA
TO: NDA 202634
SUBJECT: Final Recommendation

The previous CMC Review #2, dated 4-18-2013, made a recommendation of not approval of this NDA because of the following unresolved issues:

- Label/labeling issues were not satisfactorily resolved from the CMC perspective.

Labels/labeling were revised according to our recommendations in CMC Review #2. In **Attachment 1**, recommended changes to the labeling that were sent to the applicant are provided.

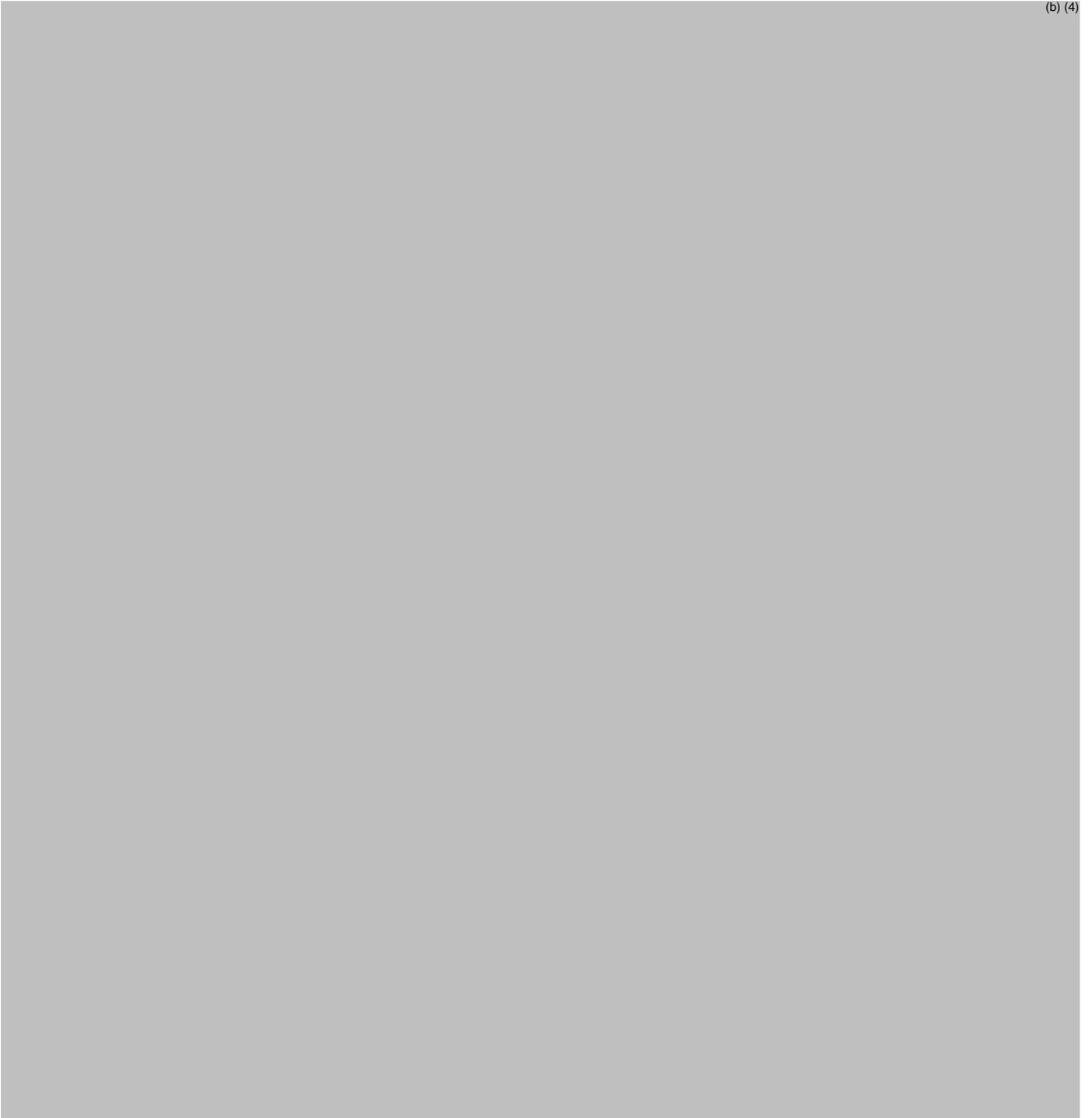
Recommendation:

Therefore, from the ONDQA's perspective, this NDA is now recommended for **APPROVAL** with an expiration dating period of 24 months.

Attachments

Attachment 1

Labeling – Package Insert – selected sections



(b) (4)

2 Pages Of Draft Labeling Have Been Withheld In Full As b4 (CCI/TS) Immediately Following
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/s/

RAYMOND P FRANKEWICH
04/26/2013

MOO JHONG RHEE
04/29/2013
Chief, Branch IV

NDA 202342

HM70231 (esomeprazole strontium) Delayed Release Capsules

Hanmi USA Inc.

Raymond P. Frankewich, Ph.D.

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV**

**CMC REVIEW
For the Division of Gastroenterology and Inborn Errors Products
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The Executive Summary	7
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A. Recommendation and Conclusion on Approvability	7
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II. Summary of CMC Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s).....	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation	8
III. Administrative.....	8
CMC Assessment.....	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	9
S DRUG SUBSTANCE.....	9
S.1 General Information.....	9
P DRUG PRODUCT	11
P.5 Control of Drug Product	11
P.8 Stability	19
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	24
A. Labeling & Package Insert.....	24
III. List Of Deficiencies to be Communicated.....	33

CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 202342
2. REVIEW #: 2
3. REVIEW DATE: April 18, 2013
4. REVIEWER: Raymond P. Frankewich, Ph.D.

5. PREVIOUS DOCUMENTS:

Original Submission	
Correspondence (C)	October 15, 2010
Amendment (BC)	March 31, 2011
Amendment (BC)	May 13, 2011
Amendment	February 1, 2011
Amendment (BC)	May 27, 2011 (electronic)
Amendment (BC)	May 31, 2011 (electronicdissolutiondata)
Amendment (BC)	June 3, 2011 (electronic)

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	June 10, 2011
Amendment	June 27, 2011
Amendment	September 19, 2011
Amendment	October 13, 2011
Resubmission	October 29, 2012
Amendment	November 20, 2012
Amendment	March 19, 2013
Amendment	April 2, 2013
Amendment (labeling)	April 9, 2013

7. NAME & ADDRESS OF APPLICANT:

Name: Hanmi USA Inc.

CMC Review Data Sheet

Address: 200 Park Avenue
Florham Park, NJ 07932

Representative: Parexel International, LLC
Bethesda Crescent
4600 East-West Highway, Suite 350
Bethesda, MD 20814

Telephone: 301-634-8026
301-634-8010

Fax: 301-634-8040

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None

b) Non-Proprietary Name (USAN): Esomeprazol strontium

c) Code Name/# (ONDQA only): HM70231

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

- Chem. Type: 2
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of GERD patients (b) (4)

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 20 mg, 40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

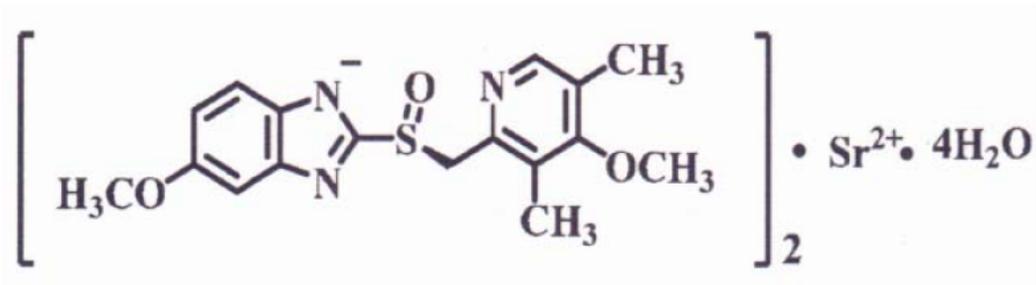
Not a SPOTS product

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

Chemical name: (-)-5-Methoxy-2-[(S)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-1H-benzimidazole strontium tetrahydrate.

CMC Review Data Sheet

Structural formula:

Molecular formula: $(C_{17}H_{18}N_3O_3S)_2 \cdot Sr \cdot 4H_2O$ Molecular weight: 848.50 (tetrahydrate)*
776.44 (anhydrous)

*The established name by USAN, *esomeprazol strontium* is defined as the name of the chemical compound, *esomeprazol strontium tetrahydrate*.

In this review, *esomeprazol strontium* is exclusively used as an established name for describing the chemical compound, *esomeprazol strontium tetrahydrate*.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	December 7, 2006	Review by G. Holbert, Ph.D.
	III			1	Adequate	July 7, 2010	Review by C. Strasinger, Ph.D.
	III			1	Adequate	April 1, 2011	

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

CMC Review Data Sheet

- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		
NDA		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	-	-
EES	Acceptable	2/1/2013	April C. Inyard (Coordinator), Elizabeth L. Johnson (Pre-approval Manager)
Pharm/Tox	N/A	-	-
Biopharm	Acceptable	6/13/2011	Sandra Suarez Sharp, Ph.D
LNC	N/A	-	-
Methods Validation	N/A, according to the current ONDQA policy (see review)	-	-
DMEPA	N/A		-
EA	Claim for categorical exclusion is granted.	6/14/2011 (CMC Review #1)	Raymond P. Frankewich, Ph.D.
Microbiology	N/A	-	-

Executive Summary Section

The CMC Review for NDA 202342

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has been resubmitted, and previous Review #1 (6/14/2011) and subsequent addendum (10/21/2011) indicate that the application has provided sufficient information to assure identity, quality, strength, and purity of the drug product, and inspection of facilities were acceptable (7/25/2011). However, label/labeling issues were not resolved during the first review cycle due to the CR action of the application (11/15/2011).

This Review #2 updates the CMC sections based on the new information in this resubmission, but this new information does not affect the previous conclusion.

The only pending issue is naming issue for the label/labeling, which is *not* satisfactorily resolved yet from the CMC perspective (see p. 33).

Therefore, from the ONDQA perspective, this NDA is *not deemed ready* for approval at this time in its present form per 21 CFR 314.125(b)(6).

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

NA

II. Summary of CMC Assessments

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

See the Review #1 (6/14/2011), unless otherwise stated.

(1) Drug Substance

GMP inspection of the proposed manufacturing site for the drug substance took place on [REDACTED] ^{(b)(4)}. DO Recommendation issued July 22, 2011 was "Acceptable", based on the inspection. Subsequently, OC has issued an "Acceptable" recommendation on July 25, 2011 based on the DO Recommendation.

Executive Summary Section

After this application was resubmitted, an inspection request was re-submitted to OC on December 20, 2012, and OC has made an “Acceptable” recommendation on December 28, 2012.

(2) Drug Product

In this resubmission (10/29/2012), additional stability data through 24 months storage was provided for HM70231 capsules, An expiration dating period of (b) (4) was requested by the applicant based on these data. However, due to increasing trends in the impurity data, expiration dating period beyond 24 months is not recommended.

In a telephone conference on March 14, 2013, the applicant agreed to change the expiration date (b) (4) to 24 months.

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

See the Review #1.

C. Basis for Not-Approval Recommendation

21 CFR 314.125.(b)(6)

- As of this review, the established name (esomeprazole strontium) and strength (20mg, 40mg) of the drug product in the labels and labeling have not been satisfactorily finalized.

III. Administrative**A. Reviewer’s Signature:**

(See appended electronic signature page)

Raymond P. Frankewich, Ph.D., Review Chemist, Branch II, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Moo Jong Rhee, Ph.D., Branch Chief, Branch II, ONDQA

C. CC Block: entered electronically in DFS

28 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/

RAYMOND P FRANKEWICH
04/22/2013

MOO JHONG RHEE
04/22/2013
Chief, Branch IV

NDA 202342

HM70231 (esomeprazole strontium) Delayed Release Capsules

Hanmi USA Inc.

Raymond P. Frankewich, Ph.D.

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV**

**CMC REVIEW
For the Division of Gastroenterology Products
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Table of Contents	2
CMC Review Data Sheet	4
The Executive Summary	8
I. Recommendations	8
A. Recommendation and Conclusion on Approvability	8
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II. Summary of CMC Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s).....	8
B. Description of How the Drug Product is Intended to be Used.....	11
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S DRUG SUBSTANCE.....	13
S.1 General Information	13
S.2 Manufacture	15
S.3 Characterization	30
S.4 Control of Drug Substance.....	36
S.5 Reference Standards or Materials	48
S.6 Container Closure System.....	48
S.7 Stability	49
P DRUG PRODUCT	53
P.1 Description and Composition of the Drug Product	53
P.2 Pharmaceutical Development.....	59
P.3 Manufacture	64
P.4 Control of Excipients	73
P.5 Control of Drug Product	75
P.6 Reference Standards or Materials	92
P.7 Container Closure System.....	93
P.8 Stability	96
A APPENDICES	101
A.1 Facilities and Equipment (biotech only)	101
A.2 Adventitious Agents Safety Evaluation	101
A.3 Novel Excipients	101
R REGIONAL INFORMATION	101

R1 Executed Batch Records101
R2 Comparability Protocols101
R3 Methods Validation Package101

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1101
 A. Labeling & Package Insert..... 101
 B. Environmental Assessment Or Claim Of Categorical Exclusion 108

III. List Of Deficiencies to be Communicated.....108

CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 202342
2. REVIEW #: 1
3. REVIEW DATE: June 14, 2011
4. REVIEWER: Raymond P. Frankewich, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	October 15, 2010
Correspondence (C)	March 31, 2011
Amendment (BC)	May 13, 2011
Amendment (BC)	February 1, 2011
Amendment	May 27, 2011 (electronic)
Amendment (BC)	May 31, 2011 (electronic-dissolution data)
Amendment (BC)	June 3, 2011 (electronic)

(NOTE: three amendments dated May 27 (containing Method Validation Package), May 31 (containing dissolution data), and June 3 (containing information about capsule shells) were provided directly to the review division in electronic submissions. The applicant will submit these amendments formally to the NDA either in paper form or directly to DARRTS).

7. NAME & ADDRESS OF APPLICANT:

Name: Hanmi USA Inc.
Address: 200 Park Avenue
Florham Park, NJ 07932

CMC Review Data Sheet

Representative: Parexel International, LLC
Bethesda Crescent
4600 East-West Highway, Suite 350
Bethesda, MD 20814

Telephone: 301-634-8026
301-634-8010

Fax: 301-634-8040

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None

b) Non-Proprietary Name (USAN): Esomeprazol strontium

c) Code Name/# (ONDQA only): HM70231

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

- Chem. Type: 2
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of GERD patients (b) (4)

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 20 mg, 40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

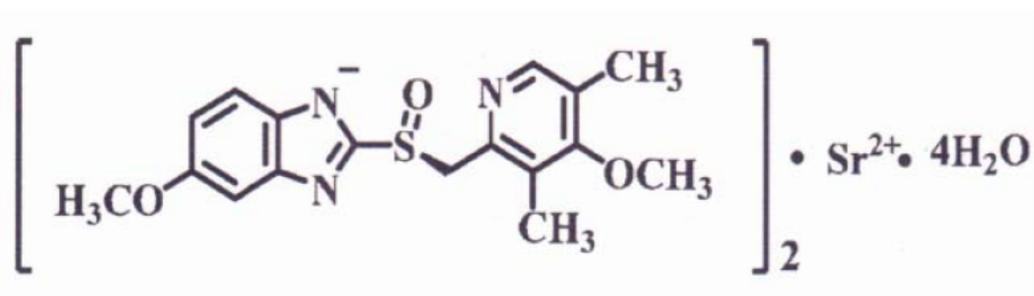
Not a SPOTS product

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776.44 (anhydrous)

17. RELATED/SUPPORTING DOCUMENTS:

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DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
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	III			1	Adequate	July 7, 2010	Review by C. Strasinger, Ph.D.
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¹ Action codes for DMF Table:

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Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
----------	--------------------	-------------

CMC Review Data Sheet

IND		
NDA		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	-	
EES	Pending (most recent recommendation: Inspection Scheduled for drug substance manufacturer (b) (4) All other facilities AC)	-	April C. Inyard (Coordinator), Elizabeth L. Johnson (Pre-approval Manager)
Pharm/Tox	N/A	-	
Biopharm	Acceptable	6/13/2011	Sandra Suarez Sharp, Ph.D
LNC	N/A	-	-
Methods Validation	N/A, according to the current ONDQA policy (see review)	-	-
DMETS-DMEPA	Trade name not acceptable	1/18/2011	Anne Crandall, Pharm.D.
EA	Claim for categorical exclusion is granted.	-	Raymond P. Frankewich, Ph.D.
Microbiology	N/A	-	-

Executive Summary Section

The CMC Review for NDA 202,342

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, quality, strength, and purity of the drug product.

However, a final “Acceptable” recommendation from Office of Compliance for the manufacturing facilities has *not* been made.

Also the information on the label/labeling is *not* considered acceptable from the CMC perspective (see p. 101).

Therefore, from the CMC perspective, this NDA is ***not recommended*** for approval at this time in its present form.

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

NA

II. Summary of CMC Assessments

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

(1) Drug Substance

The drug substance is esomeprazole strontium tetrahydrate. It is an alternate salt of esomeprazole, which is a drug substance that is marketed currently. The salt form of esomeprazole that is currently marketed is esomeprazole magnesium, which is the drug substance in Nexium[®] Capsules. Esomeprazole is the *S* enantiomer of omeprazole (*R*-omeprazole). Omeprazole is the active moiety in Prilosec[®] Capsules and several other currently marketed drug products.

Esomeprazole and omeprazole are both considered to be gastric acid secretion inhibitors. They act by inhibiting an enzyme in the gastric parietal (stomach wall) cell. Esomeprazole and omeprazole are both acid-labile substances. In order for these substances to reach the stomach wall, they must be protected from degradation by stomach acid, [REDACTED]

(b) (4)

Executive Summary Section

(b) (4). In the particular drug product formulation proposed in this NDA, the esomeprazole is contained in a small (b) (4) gelatin capsule.

Since this would be the first strontium salt of esomeprazole marketed commercially, a USAN name for the drug substance is necessary. A USAN name has been established. A letter dated April 27, 2011 from Gail Karet, Ph.D., Senior Scientist, USAN Program, USAN Council Associate, indicating the name esomeprazole strontium has been adopted by the USAN Council for the drug substance, was submitted in the amendment dated May 13, 2011.

Manufacturing process begins (b) (4)

The other raw materials (b) (4) appear to be adequately controlled. The manufacturing process (b) (4) appears to be adequately described and controlled.

The analytical procedures used to control esomeprazole strontium tetrahydrate drug substance appear to be acceptable for their intended purposes, and have been validated adequately. However, the drug substance specification provided in the original application contained several proposed acceptance criteria which were set too wide to assure quality of the drug substance. In their May 13, 2011 amendment, the applicant agreed to narrow many of the proposed acceptance criteria. The drug substance specification, as amended, is considered adequate to assure quality of the drug substance.

Considerable data has been submitted to establish the stability of the drug substance. The proposed retest period of (b) (4) is supported by (b) (4) stability data, and is considered acceptable.

Executive Summary Section

cGMP inspection of the proposed manufacturing site for the drug substance has been requested. The inspection was scheduled for (b) (4). As of the date of this review, the inspection report had not been filed.

(2) Drug Product

The drug product consists of capsules containing either 20 mg of esomeprazole (24.65 mg of esomeprazole strontium tetrahydrate) or 40 mg of esomeprazole (49.3 mg of esomeprazole strontium tetrahydrate). (b) (4)

All excipients used in the drug product conform to compendial standards. Adequate information has been submitted to describe the manufacturing process and process controls used to make HM70231 capsules. The analytical procedures used to control HM70231 capsules appear to be acceptable for their intended purposes, and have been validated adequately (in some cases, information is requested to clarify some validation aspects). However, the drug product specification provided in the original application contained several proposed acceptance criteria which were set too wide to assure quality of the drug product. At the agency's request, in their May 13, 2011 amendment, the applicant agreed to narrow many of the proposed acceptance criteria. The drug product specification including the dissolution test, as amended (amendment dated June 1, 2011), is now considered adequate to assure the identity, strength, purity and quality of the drug product.

The proposed container closure system for the drug product is adequately described as (b) (4)

For HM70231 capsules, stability data through twelve (12) months storage was provided in the amendment dated May 13, 2011. An expiration date of 12 months was requested by the applicant based on these data and it is granted. At this time, it is not recommended that the expiration dating period be set beyond 12 months (b) (4)

Labeling for the dosage form contains several errors, omissions, and deficiencies. These must be corrected before this NDA may be approved.

The proposed proprietary name for this drug ((b) (4)® capsules) been rejected (see review by DMEPA staff finalized January 18, 2011).

Executive Summary Section

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

The 20 and 40 mg capsules are intended to be taken orally. The drug product is intended as a delayed-release dosage form.

The Indications and Usage section of the proposed drug product labeling is almost identical to that of Nexium[®] Capsules. The only difference is that HM 70231 capsules are not indicated for Pediatric GERD for 1 to 11 year olds. All other indications are the same. The specific indications are:

- Gastroesophageal Reflux Disease (GERD). Includes Healing of Erosive Esophagitis; Maintenance of Healing of Erosive Esophagitis; Symptomatic Gastroesophageal Reflux Disease.
- (b) (4)
- Risk Reduction of NSAID-Associated Gastric Ulcer.
- *H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence.
- Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome.

The maximum daily dose of the drug product is 40 mg, twice daily (80 mg total) for Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome.

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided adequate information on the controls of the raw materials and manufacturing processes with adequate specifications for the drug substance and drug product. It also provided adequate stability data with proposed container/closure systems to support the expiration dating period of 12 months.

However, as of this review, no “Acceptable” recommendation from the Office of Compliance has been made for the cGMP compliance of the facilities involved.

Also deficient is the information on labels and labeling.

Therefore, from the CMC perspective, this NDA is *not* recommended for approval in its current form until the issues described above are satisfactorily resolved.

Executive Summary Section

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

(See appended electronic signature page)

Raymond P. Frankewich, Ph.D., Review Chemist, Branch II, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Moo Jhong Rhee, Ph.D., Branch Chief, Branch II, ONDQA

C. CC Block: entered electronically in DFS

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

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/s/

RAYMOND P FRANKEWICH
06/14/2011

MOO JHONG RHEE
06/14/2011
Chief, Branch IV

Initial Quality Assessment
Branch 3
Pre-Marketing Assessment Division 2

OND Division: Division of Gastroenterology Products
NDA: 202-342
Applicant: Hanmi USA, Inc
Stamp Date: 10/15/2010
Review Date: 11/26/2010
PDUFA Date: 8/15/2010
Filing Meeting: 12/2/2010
Proposed Trademark: (b) (4)
Established Name: esomeprazole strontium
Dosage Form: capsule
Route of Administration: oral
Indication: proton pump inhibitor

PAL: Marie Kowblansky, PhD

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	<input checked="" type="checkbox"/>

A. Summary

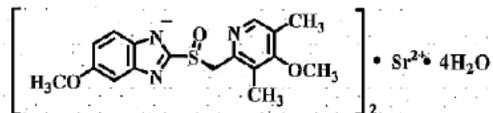
(b) (4) (esomeprazole strontium) Capsules is a delayed release product containing 20 or 40 mg of esomeprazole as the strontium salt. The product is intended for once daily administration (b) (4) Generally, the daily dose is 20 or 40 mg, (b) (4)

The current formulation, which was developed under IND 78,801, is submitted as a 505(b)(2) application, with Nexium (esomeprazole magnesium) Capsules as the reference drug. A bioequivalence study comparing the current product with Nexium was conducted for the 40 mg strength, but the application requests a biowaiver for the 20 mg strength since the product composition for the two strengths is dose proportional. Instead of a bioequivalence study for the 20 mg strength, comparative dissolution data with f2 analysis are provided.

Since strontium esomeprazole is a new salt of an approved drug this is a Type 2 application according to the Chemical Classification Code.

Drug Substance

The drug substance is the strontium salt of esomeprazole, where esomeprazole is the S-enantiomer of omeprazole



It is manufactured as the tetrahydrate at Hanmi Fine Chemical Co. in Korea (b) (4)

(b) (4)

(b) (4)

(b) (4)

Full characterization data for both the drug substance and related impurities are provided directly in the submission, without reference to any DMFs. This includes elemental analysis, UV spectrophotometry, IR, proton NMR, ¹³C-NMR, mass spectrometry, X-ray Diffraction, and differential scanning calorimetry (DSC). Specifications for esomeprazole strontium include testing for strontium content, impurities (b) (4) assay, residual solvents, particle size, optical rotation, and identification by IR.

Drug Product

The product is formulated in two strengths, as 20 mg and 40 mg omeprazole capsules (respectively containing 24.6 and 49.3 mg of esomeprazole strontium tetrahydrate). The capsules (b) (4)

(b) (4)

The composition of (b) (4) (b) (4)

All components are USP/NF materials. (The full composition is appended to this review.) The applicant explicitly states that pivotal trials were conducted with the same formulation for which approval is being sought.

Development efforts concentrated on making this product bioequivalent to Nexium, and primarily involved changes to the (b) (4)

The drug product will conform to the following specification

Test	Acceptance Criteria	method
Description		visual
Identification of esomeprazole	Retention time conforms to standard Spectrum conforms to standard	HPLC UV
Identification of strontium	White precipitate	In-house test based on chemical reaction
Assay (esomeprazole)	90% - 110% of label claim	HPLC with UV detection
Impurities (b) (4)	(b) (4)	HPLC
Enantiomeric purity (R-omeprazole)	(b) (4)	HPLC
(b) (4)		
Content uniformity	USP <905>	HPLC
Dissolution		
Acid stage (esomeprazole dissolved):	L ₁ : No individual determination exceeds (b) (4) L ₂ : Average of 12 units: (b) (4) individual: (b) (4) L ₃ : Average of 24 units: (b) (4) individual (b) (4)	In-house method based on USP monograph for omeprazole
Buffer stage: 20 mg 40 mg	(b) (4) dissolved in 30 min (b) (4) dissolved in 30 min:	
Microbial limits	Total aerobic microbial count: (b) (4) Total yeasts and molds count: (b) (4) <i>E. coli</i> : (b) (4)	USP < 1111> USP < 61> USP < 62>

- The proposed specification limits for related substances in the currently proposed products conform to ICH recommendations, and therefore, should be acceptable.
- (b) (4)
- The acid stage dissolution acceptance criteria warrant some clarification. The USP general chapter recommends that for delayed release dosage forms no more than 10% of the drug substance be dissolved at the completion of the two hour acid stage dissolution test. However, the USP monograph for omeprazole magnesium allows for two acid stage dissolution tests that may be used, both using 0.1N HCl as the dissolution medium, with stirring at 100 rpm, but Test 1 uses USP apparatus #2 and allows 15% of the drug substance

to be dissolved at the conclusion of the two hour test, and Test 2 calls for use of apparatus #1 and limits the amount dissolved to 10% after two hours. According to the USP monograph, if the product complies with Test 2, labeling should indicate that it *meets USP Dissolution Test 2*.

Six months of long term-, intermediate, and accelerated stability data have been submitted for three lots of product packaged in the proposed 30-count bottle (with desiccant). For the most part the data do not show any trends indicative of instability, with the exception of an increase in (b) (4). Currently, the applicant reasonably is requesting a (b) (4) expiration period for the product, but plans to submit 12 months of real time data by the mid-cycle of the review clock, at which time a 12 month expiration period will be requested.

In accordance with 21 CFR 25.31(b), the firm requests a claim for categorical exclusion from an environmental assessment on the basis that the estimated concentration of the drug substance at the point of entry into the aquatic environment will not exceed 1 ppb.

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES. (See appended list.)

Established name: The proposed name is "esomeprazole strontium delayed release tablets" with the labeled strength being listed in terms of esomeprazole content (not as the strontium salt). An equivalency statement, linking the expressed esomeprazole content to the esomeprazole strontium content is absent from the label.

Reviewers: The CMC review for this application has been assigned to Ray Frankewich, PhD; the Biopharmaceutics review has been assigned to Sandra Suarez-Sharp, Ph.D.

B. Critical issues for review

As a result of this initial overview of the application, the following items may need closer scrutiny during the course of the full review:

-- Esomeprazole strontium is not a USAN name; this application cannot be approved without a USAN name. In an April, 2009 meeting with FDA, the applicant was advised to apply for a USAN name because esomeprazole strontium is a new active ingredient. The applicant was further cautioned that the absence of a USAN name would be an approvability issue.

-- The product label expresses the product strength in terms of esomeprazole content. It does not have an equivalency statement relating the amount of esomeprazole to the amount of esomeprazole strontium that is present in the product.

-- (b) (4) This limit should probably be reduced to a level comparable to levels observed in batches on stability testing.

-- While the applicant explicitly states that pivotal trials were conducted with the same formulation for which approval is being sought, because of the numerous formulation changes that have been reported, this should be ascertained during the course of the full review.

-- The applicant's proposed (b) (4) limit for drug dissolution at the end of acid stage testing is unusual, particularly since the general USP requirement for delayed

release dosage forms is that not more than 10% be dissolved. However, the use of two different dissolution methods and acceptance criteria for the same product in a single USP monograph (as in the omeprazole monograph described above) is also unusual. This issue will be reviewed by the Biopharm reviewer.

-- The submission contains numerous unusual and unexpected statements, such as:

- Section 2.3.s.2.2 states that manufacturing changes for the drug substance will be reported in the DMF – there is no DMF, all drug substance information is submitted directly in the submission.

- The product is called (b) (4) (esomeprazole magnesium) in the highlights section, giving the established name as the magnesium salt, instead of the strontium salt. Also, Korean characters are used in some sections of the package insert.

- (b) (4) Other methods are marked as “Draft”, and yet others are marked “In-Progress”.

While some of these (and similar) statements appear to be careless mistakes in preparation of the submission, clarification may need to be obtained from the applicant regarding the use of “Draft” designation, or “expiration” of documents, if this is not clarified during the course of the full review.

C. Comments for 74-Day Letter --

1. In a pre-NDA meeting held April 27, 2009, you were advised that since esomeprazole strontium is a new active ingredient, you would need to apply for a USAN name for this drug substance. We repeat that request and remind you that your application cannot be approved without a USAN name.

2. Please provide justification as to why you believe that (b) (4) should be designated as the starting material, rather than any compound (b) (4) earlier in the synthesis scheme.

D. Recommendation – From the CMC perspective this application may be filed

Marie Kowblansky, PhD 11/26/2010
Pharmaceutical Assessment Lead

Moo-Jhong Rhee, PhD 11/26/2010
Branch Chief

Table P.1-1 Composition of the HM 70231 Capsules 20 mg and 40 mg

Component	Unit Quantity (mg/cap)		Function	Reference to Standards
	20 mg	40 mg		
API (b) (4)				
Active ingredient:				
Esomeprazole strontium tetrahydrate (as esomeprazole)	24.65 (20.0 mg)	49.3 (40.0 mg)	Active	In-house
Excipients:				
Sugar sphere (b) (4)		(b) (4)	(b) (4)	USP NF
Hypromellose (b) (4)				USP
Calcium carbonate				USP
Polysorbate 80				USP NF
Talc				USP
(b) (4)				USP
(b) (4)				USP NF
(b) (4)				
(b) (4)				USP
(b) (4)				USP
(b) (4)				USP
(b) (4)				USP NF
(b) (4)				
(b) (4)				USP NF
(b) (4)				USP NF
(b) (4)				USP NF
(b) (4)				USP
(b) (4)				
(b) (4)				USP
Total	(b) (4)	89.6	179.2	(b) (4)

NDA 201-342

Manufacturing Sites

The application includes a statement that all sites are ready for inspection

Drug Substance:

Hamni Fine Chemical Co.
1LA #603
Shiwha Industrial Complex
1248-8 Chongwang-dong
Shihung-city, Kyonggi-do
KOREA

Drug Product:

Name and address	Operations	Drug Establishment Registration Number	Contact
(b) (4)			

FILING CHECKLIST

NDA Number: **Supplement Number and Type:** **Established/Proper Name:**

NDA 201-342 original Esomeprazole strontium

Applicant: **Letter Date:**

Hamni Fine Chemical Co. October 15, 2010

Stamp Date:

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?	√		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	√		
3.	Are all the pages in the CMC section legible?	√		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?		√	USAN name has not been provided

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		
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.			Not applicable
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <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) 	√		

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) 	√		
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) 	√		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	√		

* 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.	Has an environmental assessment report or categorical exclusion been provided?	√		Claim of categorical exclusion

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	√		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	√		
14.	Does the section contain information regarding the characterization of the DS?	√		
15.	Does the section contain controls for the DS?	√		
16.	Has stability data and analysis been provided for the drug substance?	√		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not a filing issue

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?	√		
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?	√		
21.	Is there a batch production record and a proposed master batch record?	√		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	√		
23.	Have any biowaivers been requested?	√		
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	√		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		√	Not required

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?	√		

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

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	√		
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.			Not applicable
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	√		See IQA

{See appended electronic signature page}

Marie Kowblansky, Ph.D.
 CMC Lead
 Division of Pre-Marketing Assessment 2, Office of New Drug Quality Assessment

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
 Branch Chief
 Division of Pre-Marketing Assessment 2, Office of New Drug Quality Assessment

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/s/

MARIE KOWBLANSKY
12/02/2010

MOO JHONG RHEE
12/02/2010
Chief, Branch IV

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 18, 2011
FROM: Raymond P. Frankewich, Ph.D., Review Chemist, Branch II, ONDQA
THROUGH: Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV, DNDQA II/ONDQA
SUBJECT: Addendum to CMC Review #1 for NDA 202-342
TO: NDA 202-342

The previous CMC Review #1, dated 6-14-11, made a recommendation of not approval of this NDA because of the following unresolved issues:

1. There has been no “Acceptable” recommendation from the Office of Compliance.
2. Label/labeling issues were not considered acceptable from the CMC perspective.

As of the date of this memorandum, the Office of Compliance has issued an overall “Acceptable” recommendation (date: July 25, 2011) but the labeling has not been satisfactorily updated.

Therefore, from the CMC perspective, this NDA in its present form is not recommended for approval per 21CFR 314.125(6).

Attachment:

- 1) **EER reports**

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

Application:	NDA 202342/000	Sponsor:	HANMI USA
Org. Code:	180		4600 EAST WEST HWY STE 350
Priority:	2		BETHESDA, MD 20814
Stamp Date:	15 OCT 2010	Brand Name:	(b) (4) (Esomeprazole Strontium)
PDUFA Date:	15 NOV 2011	Estab. Name:	
Action Goal:		Generic Name:	
District Goal:	14 FEB 2011	Product Number; Dosage Form; Ingredient; Strengths	
			001; CAPSULE; ESOMEPRAZOLE; 20MG 002; CAPSULE; ESOMEPRAZOLE; 40MG
FDA Contacts:	C. TRAN ZWANETZ	Project Manager	(HFD 800) 301 796 3877
	R. FRANKEWICH	Review Chemist	301 796 1354
	M. KOWBLANSKY	Team Leader	301 796 1390

Overall Recommendation: ACCEPTABLE on 25 JUL 2011 by D. SMITH ()

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

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16 NOV 2010

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: CAPSULES EXTENDED RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22 APR 2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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/s/

RAYMOND P FRANKEWICH
10/21/2011

MOO JHONG RHEE
10/21/2011
Chief, Branch IV