CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203634Orig1s000

CHEMISTRY REVIEW(S)

M E M O R A N D U M

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

DATE: January 14, 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: CMC Review #1 for NDA 203-634

SUBJECT: Final Recommendation

The previous CMC Review #1, dated 11-9-2012, made a recommendation of not approval of this NDA because of the following unresolved issues:

1. Specification of the drug product has not been satisfactorily established due to unresolved issues on dissolution test.
2. Facility intended to (b) (4) budesonide drug substance has ***not*** yet been declared "Acceptable" by the Office of Compliance.
3. Label/labeling issues were not satisfactorily resolved from the CMC perspective.

The dissolution issues were satisfactorily resolved (Biopharm's Review dated 12/12/12) and the specification of the drug product has been amended with the revised dissolution acceptance criterion (**Attachment 1**). Revised dissolution acceptance criterion did not affect expiration dating period of 30 months established in CMC Review #1 (for details, see **Attachment 4**).

The Office of compliance has issued an overall "Acceptable" recommendation on **January 2, 2013** (**Attachment 2**).

Labels/labeling were revised according to our recommendations in CMC Review #1 (**Attachment 3**).

Recommendation:

Therefore, from the ONDQA's perspective, this NDA is now recommended for **APPROVAL**.

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/s/

RAYMOND P FRANKEWICH
01/14/2013

MOO JHONG RHEE
01/14/2013
Chief, Branch IV

NDA 203634

Uceris® (budesonide) Extended-Release Tablets 9 mg

Santarus, 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 Division of Gastroenterology and Inborn Errors Products (CDER/ODEIII/DGIP, HFD-180)

Table of Contents

CMC Review Data Sheet

1. NDA 203634

2. REVIEW #: 1

3. REVIEW DATE: November 8, 2012

4. REVIEWER: Raymond P. Frankewich, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	December 14, 2011
Correspondence (C)	
Amendment (BC)	February 9, 2012
Amendment (BC)	February 10, 2012
Amendment	March 20, 2012
Amendment (BC)	April 10, 2012
Amendment	May 16, 2012
Amendment	June 27, 2012
Amendment (Labeling)	July 20, 2012
Amendment	September 11, 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Santarus, Inc.
Address:	3721 Valley Centre Drive, Suite 400 San Diego, CA 92130
Representative:	Maria Bedoya – Toro, Ph.D., MBA
Telephone:	(858) 314 – 5715

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Uceris
b) Non-Proprietary Name (USAN):	Budesonide
c) Code Name/# (ONDQA only):	(b) (4) ((b) (4) code for (b) (4) form of

CMC Review Data Sheet

budesonide

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

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anti-inflammatory

11. DOSAGE FORM: Tablet (extended-release)

12. STRENGTH/POTENCY: 9 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

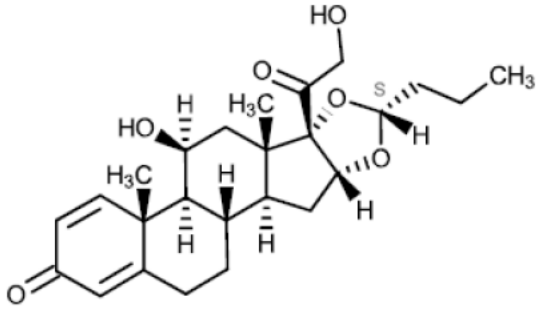
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: Pregna-1,4-diene-3,20-dione, 16,17-butylidenebis(oxy)-11,21-dihydoxy-,[11β,16α(R)]

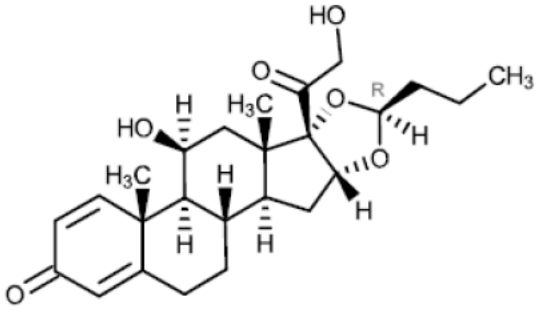
16α, 17-[(S)-butylidenebis(oxy)]-11β, 21-dihydroxypregna-1,4-diene-3,20-dione

Structural formula (drug substance has two epimers):

CMC Review Data Sheet



Epimer A



Epimer B

Molecular formula: $C_{25}H_{34}O_6$

Molecular weight: 430.53

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II						(b) (4)
	III						
	III						
	III						
	III						
	III						
	III						
	III						
	III						
	III						
	III						

[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:

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending	November 8, 2012	
Pharm/Tox	NA		
Biopharm	Pending	November 8, 2012	Elsbeth Chikale, Ph.D.
LNC	NA		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	NA		
EA	Request for claim for the Categorical Exclusion is granted.	February 9, 2012	Raymond P. Frankewich, Ph.D.
Microbiology	NA		

The CMC Review for NDA 203-634

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has ***not*** submitted sufficient information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has ***not*** issued an overall "Acceptable" recommendation for the facilities involved in this application.

Also, issues on labels/labeling are ***not*** satisfactorily resolved yet.

Therefore, from the ONDQA perspective, this NDA is not recommended for approval per 21 CFR314.125(b),(6) and (13) in its present form until the above issues are satisfactorily resolved.

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

Not applicable

II. Summary of CMC Assessments

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

(1) Drug Substance

The drug substance is budesonide. Budesonide is an anti-inflammatory substance. It is described in the labeling of this NDA as a synthetic corticosteroid. The indication of the drug product is the induction of remission in patients with active, mild to moderate ulcerative colitis. In this drug product, budesonide is intended to act as an anti-inflammatory agent in the ileum and/or ascending colon.

Budesonide is the active ingredient in fifteen (15) different currently marketed drug products, according to the Orange Book (this includes different strengths of the same dosage form). The dosage forms include oral capsules, metered powder inhalations, inhalation suspensions, and metered aerosol inhalations.

Budesonide used for this drug product is sourced from [redacted] (b) (4) and manufactured at a facility in [redacted] (b) (4). The description of the

manufacture of budesonide is described in DMF [redacted] held by [redacted] DMF [redacted] was evaluated in support of this review. DMF [redacted] currently is considered adequate to support this NDA.

The applicant's specification for budesonide drug substance is the same as the USP monograph for budesonide, with two more tests added: one for residual solvents; [redacted]; the other for particle size.

(2) Drug Product

The drug product is formulated as a delayed and extended release tablet. It is intended to deliver budesonide directly into the colon and then slowly disperse the budesonide over a period of time. The tablet is coated with an acid-resistant polymer film which breaks down at or above pH 7.0, which is the normal pH in the terminal ileum, which is the distal (remote) part of the small intestine. The acid-resistant coating allows the tablet to pass through the acidic condition of the stomach without significant decomposition. It is in the ileum where budesonide is released from the tablet core. The tablet core contains budesonide with specific polymers that provide for the extended release of budesonide throughout the colon.

The manufacturing process is a [redacted]

Drug product specification includes tests for Appearance, Identification, Assay, Content Uniformity, and Degradants of the drug substance. Also included are compendial microbial tests (USP <61>, including the test for *E. Coli*), and tests for Dissolution and [redacted]. The Dissolution test includes both in an acid and buffer stages, and the buffer stage includes three time points (1, 4, and 8 hrs.) to evaluate the extended-release properties of the drug product. However, the acceptability of the dissolution test has not been established yet, pending completion of Biopharm's Review.

Two packaging presentations are proposed: a 30-count HDPE bottle and a physician sample blister pack.

Stability data through 24 months storage is provided for samples of three (3) commercial batches of drug product, Data are provided for storage at both the ICH Controlled Room Temperature conditions (CRT) (25 °C / 60% RH) and ICH Accelerated conditions (40 °C / 75% RH). Statistical analysis was performed for the CRT storage condition for Assay, three of the four specified degradation products, Total Impurities, and Buffer Stage Dissolution at two time points (4 hrs. and 8 hrs.). Based on the submitted data, the proposed expiration dating period of 30 months for both proposed package presentations is granted.

The drug product is described as a delayed and extended release tablet in the Description section of the labeling, which is correct, but it will be designated as extended-release tablets in the labeling per ONDQA policy.

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

According to the Dosage and Administration section of the package insert, one 9 mg tablet is to be taken once daily in the morning for up to 8 weeks. The indication is for induction of remission of active, mild to moderate ulcerative colitis in adult patients. Repeated 8 week courses can be given for active disease.

C. Basis for Not-Approval Recommendation

21 CFR 314.125(b)(1)

- Specification of the drug product has not been satisfactorily established due to unresolved issues on dissolution test.

21 CFR314.125(b)(13)

- Facility intended to (b) (4) budesonide drug substance has ***not*** yet been declared "Acceptable" by the Office of Compliance.

21 CFR314.125(b)(6)

- The proposed label/labeling need to be revised (see the **List of Deficiencies**, p. 92)

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Raymond P. Frankewich, Ph.D., Review Chemist, ONDQA, DNDQAII Branch IV

B. Endorsement Block:

(See appended electronic signature page)

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

C. CC Block: entered electronically in DFS

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/s/

RAYMOND P FRANKEWICH
11/09/2012

MOO JHONG RHEE
11/09/2012
Chief, Branch IV

Initial Quality Assessment
Branch IV
Division of New Drug Quality Assessment II

OND Division:	**Division of Gastroenterology and Inborn Error Products**
NDA:	203-634
Applicant:	Santarus, Inc.
Stamp Date:	12/14/2011
Review Date:	2/6/2011
PDUFA Date:	10/14/2012
Filing Meeting:	1/25/2012
Proposed Trademark:	Uceris
Established Name:	budesonide
Dosage Form:	tablet
Route of Administration:	oral
Indication:	ulcerative colitis
CMC Lead:	Marie Kowblansky, PhD

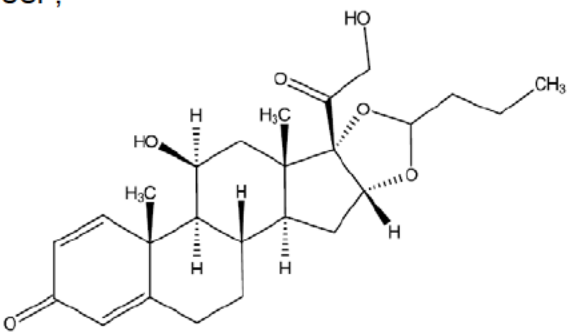
	YES	NO
ONDQA Fileability:	☒	
Comments for 74-Day Letter		☒

A. Summary

The proposed product is a delayed and extended release tablet formulation intended for once daily administration in the treatment of ulcerative colitis. This product, which was developed under IND 74,882 has been submitted as a 505 (b)(2) application with Entocort EC (budesonide) capsules as the reference listed drug. It is a topically active product, containing 9 mg of budesonide per tablet.

Drug Substance

The drug substance, budesonide, USP,



is manufactured by (b) (4) (a subsidiary of (b) (4), and (b) (4). Complete CMC information regarding preparation and control of this drug substance is provided in (b) (4) DMF# (b) (4). It will conform to all USP requirements, including control of Epimer (b) content between (b) (4)

A retest period of (b) (4) months is proposed for drug substance stored at the recommended long-term storage condition of (b) (4)

Drug Product

The proposed tablet, which contains 9 mg of budesonide, is white to off white, round, biconvex, enteric-coated, and debossed with "MX9" on one side. Its composition will be

Components	Amount (mg)	Function	Reference to Standards
		(b) (4)	
Budesonide	9.0	Active Ingredient	USP
Stearic Acid	(b) (4)	(b) (4)	NF
Lecithin			NF
Microcrystalline cellulose			NF
Hydroxypropylcellulose			NF
Lactose (b) (4)			NF
Silicon Dioxide			NF
Magnesium Stearate			NF
(b) (4)			NF
		(b) (4)	
Methacrylic Acid Copolymer, Type A	(b) (4)		NF
Methacrylic Acid Copolymer, type B			NF
Talc			NF
Titanium Dioxide			NF
Triethylcitrate			NF
(b) (4)			NF
Tablet Weight:			

(b) (4)

This is the same as the formulation used in pivotal trials. The delayed release coating is formulated to not dissolve below pH 7, thereby protecting the budesonide from degradation in the acidic gastric environment; the mixture of (b) (4) are responsible for the extended release characteristics of the drug substance once the enteric coating has dissolved in the colon.

The manufacturing process consists of (b) (4) (as reproduced from the submission below)

(b) (4)

The above processes are followed by (b) (4)

The finished product specification includes testing for appearance, identification (HPLC, UV), assay, related substances, dual stage dissolution testing, microbial testing, [redacted], and dye identification testing. The last two tests will only be conducted on every [redacted] batch.

Impurity limits are in accord with ICH qualification recommendations and should be considered acceptable, although the need for a [redacted] limit for total impurities should be further evaluated. Dissolution limits of [redacted] (after 4 hours at pH 7.2) appear somewhat liberal to this reviewer, but the decision regarding their acceptability will be made by the ONDQA Biopharmaceutics reviewer.

Stability data for tablets stored up to 18 months at controlled room temperature in the proposed commercial container/closure are provided, with the observation that all data have met the proposed specification requirements. A [redacted] month expiration dating period is proposed based on the data. The dissolution data (4 hours at pH 7.2) show a trend that should be further scrutinized. While all three stability batches start with dissolution of [redacted] at the 4-hour point, at the 18 month point the percent dissolved ranges between [redacted]

The application repeatedly refers to the combination of [redacted] coupled with the enteric coating, as a novel patented "MultiMatrix" (MMX) delivery system. The application further claims that MMX technology has been used in various products such as Lialda and refers to the current product name as "Uceris (budesonide MMX) Extended Release tablets" throughout the submission. In fact, Lialda did indeed use a formulation that contained [redacted] along with an enteric coating; that application also claimed that it was formulated with the "unique MMX" technology. However, based on the data, the review decision was that Lialda could only be labeled as delayed release (not extended) and the term "MMX" could not be used in the label, as it was promotional in nature and did not achieve the targeted performance with regard to extended release properties. To the present reviewer's knowledge, there are no other approved products that claim the use of "MMX technology".

The full CMC review of this NDA will be done by Dr. Ray Frankewich; the Biopharmaceutics information will be reviewed by Dr. Elsbeth Chikale.

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 one part per billion with approval of this product.

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES.

Established name: Uceris (budesonide) extended release tablets. Budesonide is a USAN name, and sequently acceptable. The acceptability of the extended release designation will depend on the data and will be decided at the conclusion of the NDA review.

B. Critical issues for review

This application does not appear to have any extraordinary issues that need to be evaluated.

-- The dissolution stability data should be evaluated for any trends indicative of instability (as discussed above).

-- The package insert states: [redacted] that statement needs to be clarified.

-- The Description section of the product label will need to be closely scrutinized to determine that there are no misrepresentations or promotional information regarding “MMX technology” included.

C. Comments for 74-Day Letter -- None

D. Recommendation – From the CMC perspective this application is fileable

Marie Kowblansky, PhD
CMC Lead

2/13/2012
Date

Moo-Jhong Rhee, PhD
Branch Chief

NDA Number:	Supplement Number and Type:	Established/Proper Name:
203,634	original	Uceris® (budesonide) Tablets, 9 mg
Applicant:	**Letter Date:**	**Stamp Date:**
Santarus, Inc.	December 14, 2011	December 16, 2011

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?	√		

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: • 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.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • 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.	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: • 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.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	√		

- 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?	√		The exclusion request provided references 21 CFR §25.31(a), which excludes action on an NDA if the action does not increase use of the active moiety. However, since this drug product is proposed to address a different indication than any of the currently marketed dosage forms containing budesonide, this claim does not appear to be appropriate. Before the filing date, the applicant should either clarify their exclusion request or submit a EA. This drug is indicated for Ulcerative Colitis; Entocort (NDA 21-324) is indicated for Crohn's Disease.

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?		√	Referenced to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		√	Referenced to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?		√	Referenced to DMF (b) (4)
15.	Does the section contain controls for the DS?		√	Reference is provided to DMF (b) (4)
16.	Has stability data and analysis been provided for the drug substance?		√	Referenced to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	

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?	√		18 months provided; (b) (4) months requested. Real-time 24 month data should be available during review period (stability start date was 9/7/09)
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not required
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not required

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?		√	Although no separate validation package has been submitted, there appears to be sufficient methods validation information in the body of this electronic submission

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?	√		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III	(b) (4)			
	III				
	III				
	III				
	III				
	III				
	III				
	II				

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?	√		Provided 2/9/2012 as amendment to original submission

{See appended electronic signature page}

Ray Frankewich, PhD
CMC Reviewer
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Moo-Jhong Rhee, PhD
Branch Chief
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

Date

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/s/

MARIE KOWBLANSKY
02/14/2012

MOO JHONG RHEE
02/14/2012
Chief, Branch IV