CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203595Orig1s000

CHEMISTRY REVIEW(S)

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

Date: **January 17, 2013**
From: **Gene W. Holbert, Ph.D.**
Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch IV/Division of New Drug Quality Assessment II/ONDQA
To: **CMC Review #1 of NDA 203595**
Subject: **Final Recommendation**

CMC review #1 noted the following outstanding items:

A. Drug Substance:
- Inadequate specification for assuring the purity of PEG 3350, which is not controlled for the presence of toxic (b) (4) and (b) (4) Revised specification with a test and acceptance criterion of less than (b) (4) for these two impurities is needed.

B. Drug Product:
- Batch analysis data for unflavored SUCLEAR Part 2 is absent. The information submitted in section 3.2.P.5.4 Batch Analysis is for the lemon-lime flavored product.
- Identity of manufacturer of the flavor packets and a copy of the flavor packet labeling are needed.
- Clarification of the purpose/use of (b) (4) purchased from (b) (4) is needed.
- Absence of the expiration dating period of the flavor packets.
- Absence of a batch record for the unflavored drug product.
- Changes to the dosing cup.

C. Label/labeling issues were not resolved.

On **September 7, 2012**, the applicant ***satisfactorily*** responded to the drug product deficiencies, and on **January 8, 2013** the applicant also ***satisfactorily*** responded to the issues concerning (b) (4) and (b) (4) in the PEG3350 drug substance.

On **January 11, 2013**, the applicant submitted batch analysis data for PEG3350 sourced from (b) (4) (6 lots) and (b) (4) (8 lots). All lots from (b) (4) failed the revised acceptance criterion of NMT (b) (4) for the sum of (b) (4). Consequently, we have requested that the applicant amend their application to withdraw (b) (4) as a supplier of PEG3350. On **January 17, 2013**, Braintree deleted (b) (4) as a supplier of PEG33350 via an amendment. **(see Attachment 1)**

On January 17, 2013, the final label and labeling were submitted and they were revised ***satisfactorily*** from the ONDQA perspective. (see **Attachment 2**)

Recommendation: This NDA is now recommended for **Approval** from the ONDQA perspective.

Attachments:

Attachment 1:

1) **The applicant responded on September 7 to the CMC information requests sent on August 9, 2012.**

   - Provide batch analysis data for unflavored SUCLEAR Part 2. The information submitted in section 3.2.P.5.4 Batch Analysis is for the lemon-lime flavored product.

     Applicant submitted batch analysis data for lot # RD 1050. Satisfactory.

   - The supplier of the flavoring in the flavor packets has been identified as (b) (4) Identify the manufacturer of the flavor packets and submit a copy of the flavor packet labeling.

     Applicant stated that the flavor packets are manufactured in-house at the Braintree Laboratories manufacturing facility. Draft flavor packet labeling was included in the submission. Satisfactory.

   - Clarify the purpose/use of (b) (4) purchased from (b) (4) and submit a COA for (b) (4) The page inserted at tab #5 (b) (4) is blank.

     Applicant stated that (b) (4) is used to package the flavorings. Satisfactory.

   - Specify the expiration dating period of the flavor packets.

     Applicant states that the flavor packets have an expiration dating period of two years and "is supported by long-term stability data presented in Module 3, Volume 2.3, Tabs 73-80 inclusive." (Those tabs contain blank forms.)

     The applicant further states that this is the same flavoring packaged as part of the currently approved HalfLytely product (NDA 21-551). Satisfactory.

   - The executed batch record submitted pertains to the Lemon-Lime PEG-ELS flavored finished product. The current application is for a formulation with favoring to be added by the patient as desired. Submit a batch record for a batch of unflavored drug product with the attached flavor packs.

     The applicant submitted a copy of the executed batch record for batch RD 1050. Satisfactory.

2) **Modifications to the dosing cup:**

DMEPA expressed concern about the prominence of the fill line on the dosing cup (the same cup is supplied in approved NDA 22-372). The applicant has proposed a different cup with the fill line emphasized in red and with a slightly different shape. The materials of construction (b) (4) are unchanged and meet the requirements for materials in contact with food (21 CFR 177.1520). The volume will remain the same (16 oz). On January 14, 2013, the applicant submitted revised specifications and a drawing of the new cup. From the CMC perspective, the newly proposed cup is **acceptable**.

3) Revision of the specification for Polyethylene Glycol (PEG) 3350 drug substance including the analytical method for the determination of (b) (4) and (b) (4)

A revised drug substance specification sheet for PEG 3350 was submitted on January 4, 2013. The pharmacology/toxicology review team has found the revised limits for (b) (4) to be acceptable. The information is reproduced below.

Test	Method	Specification	Result
Description	Visual	Fine, free flowing or waxy white/off white powder or granules	
Completeness and Color of Solution	Current NF	Clear to slightly hazy, colorless solution	Manufacturer's COA
Viscosity at 98.9 ºC	SOP0431	76-110 cSt	Manufacturer's COA
Average Molecular Weight	SOP 0185	3015-3685	
pH at 25 ºC	Current NF	4.5-7.5	Manufacturer's COA
(b) (4)			Manufacturer's COA Manufacturer's COA Manufacturer's COA Manufacturer's COA **
Identification	SOP 0110	Infrared Absorption: the IR absorption spectrum of the preparation sample exhibits maxima at the same wavelengths as that of the standard.	
Assay	SOP 0110	Minimum 95%	Manufacturer's COA

* Specification of Total Combined NMT (b) (4) for Limit of (b) (4) only applies to Suclear Product

** To be performed only if Limit of (b) (4) and (b) (4) test results exceeds (b) (4)

Note: USP <467> Residual Solvents specifically states that it does not apply to (b) (4) or other residual solvents with (b) (4)

(b) (4)

[redacted]

The [redacted] procedure in this analytical method appears to be based in part on the USP/NF monograph for Polyethylene Glycol [redacted] The method appears to be adequate for the determination of [redacted] and [redacted] in PEG3350.

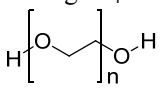
Summary of the Validation of a Chromatographic Method for the Limit Determination of [redacted] and [redacted] Impurities in [redacted] Peg 3350 Raw Material (Protocol 693) was submitted on January 8, 2013, and deemed to be adequate.

On January 11, 2013, the applicant submitted batch analysis data for PEG3350 sourced from [redacted] (6 lots) and [redacted] (8 lots). All lots from [redacted] failed the revised acceptance criterion of NMT [redacted] for the sum of [redacted] and [redacted] Consequently, we have requested that the applicant amend their application to withdraw [redacted] as a supplier of PEG3350. Braintree deleted [redacted] as a supplier of PEG33350 in the submission dated January 17, 2013.

Attachment 2: Final Labeling/Labels

Item 11. Description

Suclear (sodium sulfate, potassium sulfate and magnesium sulfate; and PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride) is an osmotic laxative that includes one 6-oz bottle of oral solution and one 2-L bottle of powder for oral solution.

Component	Molecular Formula	Molecular Weight
Sodium Sulfate	Na_2SO_4	142.04
Potassium Sulfate	K_2SO_4	174.26
Magnesium Sulfate	$MgSO_4$	120.37
Polyethylene Glycol 3350 (PEG-3350)		3350
Sodium Chloride	NaCl	58.44
Sodium Bicarbonate	$NaHCO_3$	84.01
Potassium Chloride	KCl	74.55

The 6-oz bottle of oral solution contains 17.5 g of sodium sulfate, 3.13 g of potassium sulfate, and 1.6 g of magnesium sulfate. Inactive ingredients include sodium benzoate, NF, sucralose, malic acid, FCC, citric acid, USP, flavoring ingredients and purified water, USP. The solution is a clear to slightly hazy liquid. The solution is clear and colorless when diluted to a final volume of 16-oz with water. Each kit also contains a 16-oz mixing container.

The 2-L bottle contains a white powder for oral solution containing 210 g of PEG 3350, NF, 5.6 g of sodium chloride, USP, 2.86 g of sodium bicarbonate, USP and 0.74 g of potassium chloride, USP. Inactive ingredients include 1 g of an optional flavor ingredient. Flavor packs are available in Cherry, Lemon-Lime, Orange and Pineapple. The preparation can be used with or without the addition of a flavor pack. When dissolved in water to a volume of 2 L, the solution is isosmotic, clear and colorless.

Item 16. How Supplied/Storage and Handling

Each Suclear kit contains:

- One 6-oz (177-mL) bottle of oral solution
- One 16-oz mixing container
- One 2-L bottle with powder for oral solution
- Four flavor packs (1 gram each Cherry, Lemon-Lime, Orange and Pineapple flavors)

Storage:
Store at 20º to 25°C (68º to 77°F). Excursions permitted between 15º to 30°C (59º to 86°F). See USP controlled room temperature.

Suclear NDC 52268-901-01

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

GENE W HOLBERT
01/17/2013

MOO JHONG RHEE
01/17/2013
Chief, Branch IV

NDA 203-595

SUCLEAR

(sodium sulfate, potassium sulfate and magnesium sulfate oral solution; and PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)

Braintree Laboratories, Inc.

Gene W. Holbert, Ph.D.

Senior 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

Table of Contents

Chemistry Review Data Sheet

1. NDA 203-595

2. REVIEW #: 1

3. REVIEW DATE: 8-10-2012

4. REVIEWER: Gene W. Holbert, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	12/16/2011
Communication	01/24/2012
Communication	03/09/2012
Communication	03/23/2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Braintree Laboratories, Inc.
Address:	60 Columbian Street West P.O. Box 850929 Braintree, MA 02185
Representative:	Vivian A, Caballero Director, Regulatory Affairs
Telephone:	(781) 843-2202

8. DRUG PRODUCT NAME/CODE/TYPE:

   a) Proprietary Name: SUCLEAR
   b) Non-Proprietary Name (USAN): sodium sulfate, potassium sulfate and magnesium sulfate oral solution/PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride powder for solution
   c) Code Name/#: BLI 850, (b) (4)
   d) Chemical Type/Submission Priority:

- Chemical Type: 4
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Laxative/cathartic

11. DOSAGE FORM: Two dosage forms; Oral solution, and powder for solution

12. STRENGTH/POTENCY: 17.5 g sodium sulfate, 3.13 g potassium sulfate and 1.6 g magnesium sulfate per 6 oz bottle; 210 g PEG 3350, 5.6 g sodium chloride, 2.86 g sodium bicarbonate and 0.74 g potassium chloride per 2 L bottle

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
____SPOTS product – Form Completed

_x_ Not a SPOTS product

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

Name	Formula	Molecular Weight
Sodium Sulfate, USP	Na_2SO_4	142.04
Potassium Sulfate, (b) (4)	K_2SO_4	174.26
Magnesium Sulfate, USP	$MgSO_4$	120.37
Polyethylene Glycol 3350, NF	$H(OCH_2CH_2)_nOH$	3350
Sodium chloride, USP	NaCl	58.44
Sodium Bicarbonate, USP	$NaHCO_3$	84.01
Potassium Chloride, USP	KCl	74.55

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW DATE	COMMENTS
(b) (4)	IV (II)	(b) (4)		3	Adequate	02/28/2011 N. Takiar	Reviewed as Type II LOA: 03/18/2009
	II			3	Adequate	06/24/2011 B. Wu	LOA: 03/25/2009
	II			3	Adequate	03/30/2011 M. Ahmed	LOA: 03/25/2009

(b) (4)		(b) (4)				
	II		3	Adequate	12/02/2008 T. Mehta	LOA: 09/02/2010
	IV		1	Adequate	01/25/2012 G. Holbert	LOA: 10/08/2007
	IV			Adequate	04/18/2012 G. Holbert	LOA: 03/06/2012
	III		1	Adequate	01/18/2012 G. Holbert	LOA: 08/06/2009
	III		1	Adequate	03/02/2012 G. Holbert	LOA: 08/06/2008
	III		3	Adequate	09/07/2010 A. Banerjee	LOA: 09/02/2010
	III		1	Adequate	01/26/2012 G. Holbert	LOA: 07/02/2009
	III		1	Adequate	02/02/2012 G. Holbert	LOA: 04/15/2009
	III		1	Adequate	12/15/1998 A. Mueller	LOA: 09/06/2007
	III		3	Adequate	01/24/2012 B. Zarabi	LOA: 04/16/2009
	III		1	Adequate	01/31/2012 G. Holbert	LOA: 09/22/2007
	III		1	Adequate	02/13/2012 G. Holbert	LOA: 09/18/2007
	III		1	Adequate	02/13/2012 G. Holbert	LOA: 11/24/2009
	III		1	Adequate	02/16/22012 G. Holbert	LOA: 11/24/2009
	III		1	Adequate	01/18/2012 G. Holbert	LOA: 05/04/2009
	III		1	Adequate	02/14/2012 G. Holbert	LOA: 04/17/2009
	III		1	Adequate	02/03/2012 G. Holbert	LOA: 04/22/2009
	III		1	Adequate	02/01/2012 G. Holbert	LOA: 12/31/2007
	III		1	Adequate	01/24/2012 G. Holbert	LOA: 03/10/2011
	III		1	Adequate	01/31/2012 G. Holbert	LOA: 02/23/2006

[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)

Note: All packaging components have been approved in the NDAs referenced below.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	57,673	Half Lytely Bowel Prep. (b) (4)
IND	74,808	BLI-850 Oral Sulfate Solution (Magnesium/Sodium/Potassium)
IND	102,894	BLI-850 Oral Sulfate Solution (Magnesium/Sodium/Potassium) and PEG-ELS Solution Kit
NDA	21-551	Half Lytely Bowel Preparation Kit
NDA	22-372	Suprep Bowel Preparation Kit
NDA	22-015	Miralax

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	03/20/2012	D. Smith
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Not required	05/18/2012	G. Holbert
DMETS	N/A		
EA	Categorical exclusion is granted.	04/26/2012	G. Holbert
Microbiology	N/A		

The Chemistry Review for NDA 203595

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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

Labeling issues are still ***pending*** as of the date of this review as well.

The Office of Compliance has made an overall "Acceptable" site recommendation.

Therefore, from the CMC perspective, this NDA is ***not*** recommended for approval in its present form per 21 CFR 314.125(b)(1),(6) until the above issues are resolved.

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

None

II. Summary of Chemistry Assessments

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

Each SUCLEAR kit contains one 6 oz bottle of an oral solution and one 2 liter bottle of powder for solution. The package also contains one 16 oz mixing container.

The 6 oz bottle contains 17.5 g sodium sulfate, 3.13 g potassium sulfate and 1.6 g magnesium sulfate. Inactive ingredients include Sodium Benzoate, NF, Sucralose, Malic Acid, FCC, Citric Acid, USP, flavoring ingredients and Purified Water, USP.

Each 2 liter bottle contains a white powder for solution containing 210 g polyethylene glycol (PEG) 3350, 5.6 g sodium chloride, 2.86 g of sodium bicarbonate, 0.74 g potassium chloride and 1 g of optional flavor ingredient. Flavor Packs are available in Cherry, Lemon-Lime, Orange and Pineapple.

The Polyethylene Glycol (PEG) 3350 contains [redacted] (b) (4) and [redacted] (b) (4) as impurities, both of which are known to be toxic. They are not adequately controlled. The ICH PDE limit is [redacted] (b) (4) and, to meet this requirement, their limits should be less than [redacted] (b) (4) based on the 210g daily dose of this drug product. This concern was

conveyed to the applicant on July 16, 2012 through a telephone conference, and resolution of this issue is still pending as of this review.

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

SUCLEAR should be taken as a 1 day or 2 day (split-dose) oral regimen as detailed in the package insert.

The dose for colon cleansing requires administration of both bottles of SUCLEAR: One 6 oz bottle diluted to 16 oz with water followed by a 2 liter jug of powder reconstituted with water taken orally prior to the colonoscopy.

No solid food or milk (clear liquids only) should be consumed prior to colonoscopy.

C. Basis for Not-Approval Recommendation

21 CFR 314.125(b)(1)

- Specification of the drug substance, polyethylene glycol (PEG) 3350, is inadequate for assuring the purity of the drug substance due to the lack of controlling the amount of toxic (b) (4) and (b) (4) in the PEG 3350 with a limit of less than (b) (4)

21 CFR 314.125(b)(6)

- Label/labeling issues are still unresolved.

(See the **List of Deficiencies**, p. 87.)

III. Administrative

A. Reviewer's Signature

Signed electronically in DARRTS

B. Endorsement Block

Gene W. Holbert, Ph.D./16-AUG-2012
Moo-Jhong Rhee, Ph.D./17-AUG-2023

C. CC Block

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/s/

GENE W HOLBERT
08/17/2012

MOO JHONG RHEE
08/17/2012
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:	203-595
Applicant:	Braintree
Stamp Date:	12/19/2011
Review Date:	2/16/2012
PDUFA Date:	10/19/2012
Filing Meeting:	2/2/2012
Proposed Trademark:	(b) (4)
Established Name:	sodium sulfate, potassium sulfate, magnesium sulfate, PEG-3350 and (b) (4) for oral soln
Dosage Form:	Liquid solution/powder for reconstitution
Route of Administration:	Oral
Indication:	Colon cleansing prior to colonoscopy
CMC LEAD:	Marie Kowblansky, PhD

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

A. Summary

(b) (4) is intended for bowel cleansing prior to colonoscopy. It is supplied as a kit consisting of two components (plus optional flavoring) that are to be taken sequentially either two hours apart, or over a two day period:

- 6 oz bottle of liquid concentrate containing sodium sulfate, potassium sulfate, and magnesium sulfate, which requires dilution with water before consuming
- 2 L bottle containing polyethylene glycol (PEG), sodium bicarbonate, sodium chloride, potassium chloride as a powder for reconstitution with 2 liters of water.
- One gram flavor packs for optional use with the reconstituted PEG solution.

This product, which was developed under IND 102,894 is being filed as a 505 (b)(1) application. The sulfates solution is the same composition as the sulfates solution that was recently approved for Suprep Bowel Prep Kit (NDA 22-372, approved in 2010). The PEG solution is one of the solutions approved for the HalfLytely® and Bisacodyl Tablet Bowel Prep Kit (NDA 21-551 approved in 2004). Both components are identical in composition to their respective approved products and are the same as used in pivotal clinical studies. The compositions of the two components of this product are given below (s reproduced from submission).

Sulfates Component:

Raw Material and Grade Quality	Method	Quantity per Dose (6 oz bottle)	Function
Sodium Sulfate, USP	USP	17.510 g	Active ingredient
Potassium Sulfate, (b) (4)	(b) (4)	3.130 g	Active ingredient
Magnesium Sulfate Anhydrous, USP	USP	1.600 g	Active ingredient
Sodium Benzoate, NF	NF		(b) (4)
Sucralose (b) (4) (b) (4)	In-house method		
Malic Acid, FCC	FCC		
Citric Acid, USP	USP		
(b) (4) Flavor	FCC		
			(b) (4)
Purified Water, USP	USP		(b) (4)

PEG Component:

Raw Material and Grade Quality	Method	Quantity per Dose (2L bottle)	Function
Polyethylene Glycol 3350, NF	NF	210 g	Active ingredient
Sodium Chloride, USP	USP	5.60 g	Active ingredient
Sodium Bicarbonate, USP	USP	2.86 g	Active ingredient
Potassium Chloride, USP	USP	0.074 g	Active Ingredient
Flavor Ingredients (optional)	In-house method	1.00 g	Flavoring agent

The firm requests a claim for categorical exclusion from an environmental assessment on the basis that approval of this product would not increase the use of the active moieties. This product would substitute for other currently used (approved) products that contain the same active moieties.

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

Proposed Established name: (sodium sulfate, potassium sulfate, magnesium sulfate, PEG-3350 (b) (4) for oral solution).

The full CMC review of this NDA will be done by Dr. Gene Holbert.

B. Critical issues for review

--Since the two components of this product (the sulfates solution and PEG powder for reconstitution) are already FDA-approved as components of other colon cleansing products, there should be few, if any, deficiencies.

--Although stability data were not evaluated as part of this cursory review, the stability of the two currently proposed product components should be the same as in the approved products if the same container/closures were used.

(b) (4)

C. Comments for 74-Day Letter --

Submit a copy of the Letter of Authorization (LOA) to reference DMF (b) (4) for PEG 3350 (b) (4)

(b) (4) DMF (b) (4), which you have referenced is not available for review. Please verify that you have provided the correct DMF number and submit a new LOA.

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

Marie Kowblansky, PhD
CMC Lead

2/17/2012
Date

Moo-Jhong Rhee, PhD
Branch Chief

(b)
)

NDA Number:	Supplement Number and Type:	Established/Proper Name:
203595	Original	Sodium Sulfate, Potassium Sulfate and Magnesium Sulfate, and PEG-3350 and Electrolytes for Oral Solution
Applicant:	**Letter Date:**	**Stamp Date:**
Braintree Laboratories	December 16, 2011	December 19, 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?	√		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	√		

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 DMFs
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		√	Referenced to DMFs
14.	Does the section contain information regarding the characterization of the DS?		√	Referenced to DMFs
15.	Does the section contain controls for the DS?		√	
16.	Has stability data and analysis been provided for the drug substance?		√	Referenced to DMFs
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not require
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not required

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?		√	Not required. Components of this application have been included in Braintree applications for similar products (NDAs 19-797, 21-551 and 22372)
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 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?		√	No separate validation package has been submitted, but there appears to be sufficient methods validation information in the body of the 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)	IV (II)		(b) (4)	Undated	Reviewed as Type II
	II			3/25/2009	
	II			9/2/2010	
	II			9/21/2010	
	IV			10/8/2007	
	IV			8/10/2009	DMF Closed 10/10/2007
	III			8/6/2009	
	III			8/6/2008	
	III			9/2/2010	
	III			7/2/2009	
	III			4/15/2009	
	III			9/6/2007	
	III			4/16/2009	
	III			9/22/2007	
	III			9/18/2007	
	III			11/24/2009	
	III			11/24/2009	
	III			5/4/2009	
	III			4/17/2009	

(b) (4)		(b) (4)		
	III		4/22/2009	
	III		12/31/2007	
	III		3/10/2011	
	III		2/23/2006	

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 appended electronic signature page}

Gene W. Holbert, Ph.D.
CMC Reviewer
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

January 23, 2012
Date

{See appended electronic signature page}

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

Date

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

/s/

MARIE KOWBLANSKY
02/17/2012

MOO JHONG RHEE
02/17/2012
Chief, Branch IV