CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204553Orig1s000

PRODUCT QUALITY REVIEW(S)

MEMORANDUM

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

DATE: September 26, 2013

TO: Review #1 of NDA 204553

FROM: Jane Chang, Ph.D.
Review Chemist, ONDQA

SUBJECT: Final ONDQA Recommendation on NDA 204553
Sodium sulfate, potassium sulfate and magnesium sulfate powder for oral solution

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SUMMARY

In NDA 204553 CMC Review #1 dated 01-Aug-2013, it was recommended that the NDA was not ready for approval in its present form because labeling issues were not resolved.

Subsequently, the applicant provided a revised container label as well as carton and package insert labeling. Revisions were made to sections 'Highlights', 'Dosage Forms and Strengths', 'Description' and 'How Supplied/Storage and Handling' per this reviewer's recommendation. The revised label and labeling are satisfactory from the ONDQA perspective.

Updated information on the mixing cup for reconstitution was provided. The information is acceptable.

RECOMMENDATION
This NDA is now recommended for approval from the ONDQA perspective with an expiration dating period of 24 months.

Review Notes

Labeling issues were identified in CMC Review #1 (see pages 9 and 75-84) dated 01-Aug-2013. Subsequently, the applicant provided a revised package insert labeling via email to Project Manager, Mr. Matthew Scherer, on September 25, 2013. The revised labeling incorporated this reviewer's recommendations for sections 'Dosage Forms and Strengths', 'Description' and 'How Supplied/Storage and Handling'.

Updated information on the mixing cup for reconstitution was provided in the September 18, 2013 amendment.

The updated information is summarized below.

I. PACKAGE INSERT

1. *"Highlights" Section*

TRADENAME sodium sulfate, potassium sulfate and magnesium sulfate powder for oral solution

Initial U.S. Approval: 2010

----------**DOSAGE FORMS AND STRENGTHS**----------

(b) (4)

Reviewer's Assessment:

Item	*Comments on the Information Provided in NDA*	*Conclusions*
Product Title, including proprietary name, established name, dosage form, and route of administration	*There is no approved proprietary name as of the date of this review. The established name "sodium sulfate, potassium sulfate and magnesium sulfate", dosage form and route of administration "powder for oral solution" are provided.*	***Satisfactory***
Dosage forms and strengths	*The dosage form "powder" is provided, the strength of each drug substance is adequately provided.*	***Satisfactory***

Conclusion: The "Highlights" section is satisfactory.

2. Prescribing Information

a. Section 3 Dosage Forms and Strengths

(b) (4)

Each bottle contains: sodium sulfate 17.5 g, potassium sulfate 3.13 g, and magnesium sulfate 1.6 g.

Reviewer's Assessment:

Item	*Comments on the Information Provided in NDA*	*Conclusions*
Dosage form and strength	*The correct dosage form (powder) and strengths (17.5 g for sodium sulfate, 3.13 g for potassium sulfate, 1.6 g for magnesium sulfate) are provided.*	***Satisfactory***

Conclusion: This section is satisfactory.

b. Section 11 Description

(b) (4)

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name and established name	*There is no approved proprietary name as of the date of this review.* *The established name "sodium sulfate, potassium sulfate and magnesium sulfate" is provided.*	***Satisfactory***
Dosage form and route of administration	*The dosage form and route of administration "powder for oral solution" is provided.*	***Satisfactory***
Inactive ingredient information	*The inactive ingredients, including citric acid anhydrous USP, sucralose NF, and lemon flavor, are listed*	***Satisfactory***
Pharmacological/ therapeutic class	*The pharmacological/ therapeutic class "osmotic laxative" is provided.*	***Satisfactory***
Chemical name, structural formula, molecular weight	*Chemical name, structural formula and molecular weight are correctly described in this section.*	***Satisfactory***

Conclusion: The revised labeling reflects additional recommendation, including structural formula of each drug substance, provided by this reviewer since the completion of Review #1. The information is acceptable.

c. Section 16 How Supplied/Storage and Handling

TRADENAME NDC 10702-083-23

How Supplied:

Each TRADENAME contains:

- Two 200 cc bottles of white to off-white powder. Each bottle contains sodium sulfate 17.5 g, potassium sulfate 3.13 g, and magnesium sulfate 1.6 g.
- One (b) (4) oz mixing container with a 16 oz fill line.

Storage:

Store at 20° to 25°C (68° to 77°F). Excursions permitted between 15° and 30°C (59° and 86°F). See USP controlled room temperature.
Keep out of reach of children.

Reviewer's Assessment: This section has been revised per this reviewer's recommendation (see Review #1, page 79).

Item	Comments on the Information Provided in NDA	Conclusions
Strength of dosage form in metric system	*Strengths "17.5 g for sodium sulfate, 3.13 g for potassium sulfate, and 1.6 g for magnesium sulfate" are provided.*	***Satisfactory***
Units of dosage form	*Two bottles per kit are correctly described.*	***Satisfactory***
Identification of dosage forms, shape, color, coating, scoring, imprinting, NDC number	*NDC Number is stated: 10702-083-23*	***Satisfactory***
Storage condition	*Storage condition "Store at 20 to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [See USP Controlled Room Temperature]" is provided.*	***Satisfactory***

Conclusion: ***Satisfactory***

d. Manufacturer's or Distributor's name

Manufactured by KVK-TECH, Inc. Newtown, PA 18940

Reviewer's Assessment: The information in this section, which is provided at the end of Patient Counseling, remains the same as that provided in the original submission.

Conclusion: ***Satisfactory***

II. CONTAINER LABEL

The revised container label was provided in the 9/18/2013 amendment. The label is shown below.

Reviewer's Assessment: The previous proposed proprietary name (b) (4) *which was denied, has been deleted. Revisions for "Directions" have been made per DMEPA reviewer, Lisa Khosla's request. All other pertinent information remains unchanged. From CMC perspective, the container label remains acceptable.*

III. CARTON LABELING

The revised carton labeling was provided in the 9/18/2013 amendment. The labeling is shown below.

(b) (4)

Reviewer's Assessment: The issues identified in Review #1 (page 83) regarding the route of administration and the font size of established name have been addressed in the revised carton labeling. Route of administration, i.e. oral, has been included and the font size of the established name is at least half as large as that of the proprietary name. The information is acceptable.

IV. (b) (4)

The manufacturer and dimension for (b) (4) for reconstitution have been revised in the 9/18/2013 amendment. The information is summarized below.

Description	Manufacturer	Components	Reference
(b) (4)			

Drawings (see Figure 1), specification, and certificate of analysis (COA) for the mixing cup are provided. The specification includes testing for description (acceptance criteria: 20 ounce (b) (4) indicating "16oz Fill Line") and identification by infrared spectroscopy. The COA shows that the

(b) (4) meets the requirements of USP <661> (b) (4). The (b) (4) is used in non-product contact surface.

Figure 1: (b) (4) Drawing and Dimensions

(b) (4)

Reviewer's Assessment: The information is acceptable. The mixing cup that has direct contact with the drug product meets the FDA requirement for contact with food products.

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

/s/

JANE L CHANG
09/26/2013

MOO JHONG RHEE
09/27/2013
Chief, Branch IV

NDA 204553

Sodium Sulfate, Potassium Sulfate, and Magnesium Sulfate Powder for Oral Solution

GATOR PHARMACEUTICALS, INC.

Jane L. Chang, Ph.D.

Review Chemist

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

For Division of Gastroenterology and Inborn Errors Products
HFD-180

Table of Contents

Chemistry Review Data Sheet

1. NDA 204553

2. REVIEW #: 1

3. REVIEW DATE: 01-Aug-2013

4. REVIEWER: Jane L. Chang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	02-Aug-2012
Withdrawal Request- General Information/Application	26-Sep-2012
Acknowledge Withdrawal- Pending NDA (including communication of CMC deficiencies)	03-Oct-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	02-Aug-2012
Resubmission/After Withdrawal (SD-6)	30-Nov-2012
Amendment (SD-8)	01-Apr-2013
Amendment (SD-10)	24-May-2013
Amendment (SD-12)	14-Jun-2013
Amendment (SD-13)	28-Jun-2013
Amendment (SD-14)	28-Jun-2013
Amendment (SD-15)	23-Jul-2013
Amendment (SD-16)	23-Jul-2013

7. NAME & ADDRESS OF APPLICANT AND CONTACT:

Name	Gator Pharmaceuticals, Inc.
Address	194 Inlet Drive St. Augustine, FL 32080
Representative	Paul Burlaga, Director
Telephone	(215) 579-1842

Chemistry Review Data Sheet

Contact Information:

Name	KVK-Tech, Inc.
Address	110 Terry Dr, Suite 200 Newtown, PA 18940
Representative	Ashvin Panchal, Director-Quality
Telephone	(215) 579-1842
Fax	(215) 579-0746

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None (see page 8)
b) Non-Proprietary Name (USAN): sodium sulfate, potassium sulfate, magnesium sulfate
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3 (New Dosage Form)
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: osmotic laxative

11. DOSAGE FORM: Powder

12. STRENGTH/POTENCY: Each 6 oz bottle contains 17.5 g of sodium sulfate, 3.13 g of potassium sulfate, and 1.6g of magnesium sulfate

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: __Y__Rx ___OTC

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

_____SPOTS product – Form Completed

__Y___Not a SPOTS product

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

Chemistry Review Data Sheet

Chemical Name	Molecular Formula	Molecular Weight
Sodium sulfate	Na_2SO_4	142.04
Potassium sulfate	K_2SO_4	174.26
Magnesium sulfate	$MgSO_4$	120.37

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	3/29/2013	By J. Chang
	II			1	Adequate	3/27/2013	By J. Chang
	II			1	Adequate	6/13/2013	By J. Chang
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	III			4	N/A	N/A	Non-product contact surface
	III			4	N/A	N/A	

[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	113084	(b) (4) (sodium sulfate, potassium sulfate, magnesium sulfate) for Solution Kit

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	1/23/2013	T. Sharp
Pharm/Tox	N/A		
Biopharm	Approval	6/28/2013	Mark Seggel
Methods Validation	N/A, according to the current ONDQA IQP 5105		
Office of Drug Safety	The proposed proprietary name (b) (4) was denied because it is overly fanciful and implies superiority to other products that contain the same active ingredient.	4/24/2013	Lisa V. Khosla
	The proposed proprietary name (b) (4) was denied because it implies superiority to other products and minimizes the risks associated with its use.	7/22/2013	Lisa V. Khosla
EA	Categorical exclusion (see page 85 of this review)		
Microbiology	N/A		

Chemistry Review for NDA 204553

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. The Office of Compliance has made an overall "Acceptable" recommendation for the facilities involved in this NDA. However, labeling issues are still pending as of the date of this review. Therefore, from the ONDQA perspective, this NDA is not ready for approval per 21 CFR 314.125(b)(6) in its present form until the labeling issues are satisfactorily 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)

(1) Drug Product

Sodium sulfate, potassium sulfate, and magnesium sulfate powder for solution is an osmotic laxative indicated for cleansing of the colon in preparation for colonoscopy in adults. The drug product is packaged in white 200 cc HDPE round bottles with white (b) (4) plastic caps. Each drug product kit contains two bottles of powder for reconstitution. Each bottle contains 22.7 g of powder, including 17.5 g of sodium sulfate, 3.13 g of potassium sulfate, and 1.6 g of magnesium sulfate. The inactive ingredients include: citric acid anhydrous USP, sucralose NF, and lemon flavor.

The manufacture of sodium sulfate, potassium sulfate, and magnesium sulfate powder for solution involves the following units of operation: (b) (4)

(b) (4)

The proposed specification (see page 52) for sodium sulfate, potassium sulfate, and magnesium sulfate powder for solution are acceptable. The specification include

description, identification (sodium, potassium, magnesium, and sulfate), assay (sodium, potassium, magnesium, and sulfate), uniformity of dosage units, (b) (4) (b) (4) pH of the dissolved product solution, and elemental impurities. The analytical procedures and their method validations were reviewed and found to be adequate to support their intended purpose.

Supporting stability data of the drug product support the proposed expiration dating period of 2 years when stored at 20° to 25°C (68° to 77°F), excursions permitted between 15° and 30°C (59° and 86°F).

(2) Drug Substance

The drug substances are sodium sulfate (b) (4), potassium sulfate (b) (4), and magnesium sulfate (b) (4). Sodium sulfate (b) (4) is manufactured by (b) (4) Details of the manufacturing process and control of materials for sodium sulfate anhydrous are provided in DMF# (b) (4) This DMF has been reviewed by this reviewer and found to be adequate to support the NDA. The drug substance complies with the USP monograph requirements. Additional tests, including (b) (4), particle size, and microbial limits, are included in the drug substance specification.

Potassium sulfate (b) (4) is manufactured by (b) (4) Details of the manufacturing process and control of materials for potassium sulfate (b) (4) are provided in DMF# (b) (4) This DMF has been reviewed by this reviewer and found to be adequate to support the NDA. The drug substance complies with the FCC requirements. Additional tests, including sulfate identification, solubility, (b) (4) pH, (b) (4), acidity/alkalinity, particle size, and microbial limits, are included in the drug substance specification.

Magnesium sulfate (b) (4) is manufactured by (b) (4) CMC information is referenced to DMF (b) (4) This DMF has been reviewed by this reviewer and found to be adequate to support this NDA. The drug substance complies with the USP monograph requirements. An additional test, i.e. particle size, is included in the drug substance specification.

A retest date of (b) (4) is established by the applicant for each drug substance.

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

Split Dose (2-Day) Regimen

- Evening before colonoscopy: Take one bottle containing 22.7 g sodium sulfate, potassium sulfate, magnesium sulfate powder for solution and add water up to the neck of the bottle. Shake well and mix thoroughly. Pour the contents of one bottle of reconstituted solution into the mixing container provided. Fill the container with water to the 16 oz fill line, and drink the entire amount.
- Drink 32 oz water over the next hour.

- Next morning: repeat both steps using the second bottle.
- Complete preparation at least 2 hours before colonoscopy.

C. Basis for Approval or Not-Approval Recommendation

Not-Approval:

- 21 CFR 314.125 (b)(6)
  Labeling issues are not resolved.

III. Administrative

A. Reviewer's Signature

See appended electronic signature page

B. Endorsement Block

See appended electronic signature page

C. CC Block

Entered electronically in DARRTS

A APPENDICES

A.1 Facilities and Equipment (biotech only)
N/A

A.2 Adventitious Agents Safety Evaluation
N/A

A.3 Novel Excipients
N/A

R REGIONAL INFORMATION

R.1 Executed Batch Records
Representative executed batch records as well as the respective in-process controls data were provided for batches D0374, D0375, and D0376.

R.2 Comparability Protocols
N/A

R.3 Methods Validation Package
See section I.P.5.2 on page 53 of this review for the analytical procedures. The analytical procedures and their validation were reviewed and found to be adequate. Methods validation packages will not be sent to FDA laboratories because the methods do not meet the "method validation request criteria" according to the current ONDQA IQP 5105 effective 3/31/2012.

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

A. LABELING & PACKAGE INSERT

1. Physician's Labeling Rule Prescription Drug Labeling

The information provided in the 4/1/2013 amendment is summarized below.

1) "Highlights" Section

Product title was not included.

----------**DOSAGE FORMS AND STRENGTHS**----------

- Two bottles containing 22.7 g of Powder

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Product Title, including proprietary name, established name, dosage form, and route of administration	Not provided. Because both proposed proprietary names, (b) (4) and (b) (4), were denied, only the established name should be used for the product title.	**Unsatisfactory**
Dosage forms and strengths	The dosage form "powder" was provided, but the strength of each drug substance was not provided.	**Unsatisfactory**

Conclusion: The "Highlights" section is unsatisfactory.

This reviewer made the following revisions to the labeling posted in the eroom, which was provided by the applicant on May 6, 2013 via email to the Project manager, Mr. Matthew Scherer:

1. *Add the product title as the following:*

(b) (4)

2. *Revise "DOSAGE FORMS AND STRNGTHS" section as the following:*

(b) (4)

2) *"Full Prescribing Information" Section*

a. *Section 3 Dosage Forms and Strengths*

(b) (4)

Each 22.7 g bottle contains: contains: sodium sulfate 17.5 g, potassium sulfate 3.13 g, magnesium sulfate 1.6 g.

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Dosage form and strength	The correct dosage form (powder) and strengths (sodium sulfate 17.5 g, potassium sulfate 3.13 g, magnesium sulfate 1.6 g) were provided. However, there is typographical error (repetition of (b) (4)) and unnecessary information (22.7 g).	**Unsatisfactory**

Conclusion: This section is unsatisfactory.

This reviewer made revisions to the 06-May-2013 labeling posted in the eroom

as shown below:

(b) (4)

Each (b) (4) bottle contains: (b) (4) sodium sulfate 17.5 g, potassium sulfate 3.13 g, and magnesium sulfate 1.6 g.

b. *Section 11 Description*

(b) (4)

Reviewer's Assessment:

Chemistry Assessment Section

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name and established name	The proprietary name (b) (4) was provided. Two proprietary names, (b) (4) and (b) (4) that the applicant proposed were both denied (see DMEPA reviews by Lisa Khosla dated 4/24/2013 and 7/22/2013). The established name of the drug product was not provided.	**Unsatisfactory**
Dosage form and route of administration	The dosage form (powder for reconstitution) was not provided correctly. Route of administration was not provided.	**Unsatisfactory**
Inactive ingredient information (quantitative, if injectables)	The inactive ingredients are not listed correctly. The formulation (b) (4) (b) (4) used is lemon flavor.	**Unsatisfactory**
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	Not provided	**Unsatisfactory**
Chemical name, structural formula, molecular weight	Chemical name, structural formula and molecular weight are correctly described in this section.	**Satisfactory**
If radioactive, statement of important nuclear characteristics	N/A	
Other important chemical or physical properties (such as pKa or pH)	None	

<u>Conclusion:</u> The "Description" section is unsatisfactory.

This reviewer made revisions to the 06-May-2013 labeling posted in the eroom as shown below:

(b) (4)

c. ***Section 16 How Supplied/Storage and Handling***

Each (b) (4) contains:

(b) (4)

- One (b) (4) oz mixing container with a 16 oz fill line.

Storage:
Store between 20º to 25°C (68º to 77°F). Excursions permitted between 15º to 30°C (59º to 86°F). See USP controlled room temperature.
Keep out of the reach of children.
(b) (4)
NDC 10702-083-23

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Strength of dosage form in metric system	Strengths are not provided.	**Unsatisfactory**
Units of dosage form e.g. bottles of 30 tablets	Two bottles per kit are correctly described.	**Satisfactory**
Identification of dosage forms, shape, color, coating, scoring, imprinting, NDC number	NDC Number is stated: 10702-083-23	**Satisfactory**
Special handling (e.g., protect from light)	None	
Storage condition	Minor modification to the proposed storage condition "Store between 20 to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature] is recommended (see below).	**Satisfactory**

Conclusion: The "How Supplied/Storage and Handling" section is unsatisfactory. This reviewer made revisions to the 06-May-2013 labeling posted in the eroom as shown below:

NDC 10702-083-23
How Supplied:
Each (b) (4) (b) (4) contains:

- Two (b) (4)-200 cc bottles (b) (4) white to off-white powder. Each bottle contains sodium sulfate 17.5 g, potassium sulfate 3.13 g, and magnesium sulfate 1.6 g.
- One (b) (4) (b) (4) oz mixing container with a 16 oz fill line.

Storage:
Store (b) (4) at 20° to 25°C (68° to 77°F). Excursions permitted between 15° (b) (4) and 30°C (59° (b) (4) and 86°F). See USP controlled room temperature.
Keep out of the reach of children.
(b) (4)
(b) (4)

d. *Manufacturer's or Distributor's name per 21 CFR 201.1(h)(5)*

Manufactured by KVK-Tech, Inc. Newtown, PA 18940

Reviewer's Assessment: The information was provided at the end of labeling.
Conclusion: ***Satisfactory***

2. Labels

The container label and carton labeling provided in the 4/1/2013 amendment are shown below.

1) Immediate Container Label

(b) (4)

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence)	The established name is presented incorrectly. Dosage form and route of administration should be included in the established name of the drug product. Conflicting established names were presented in the resubmission. The established name of the drug product presented in the container label is "sodium sulfate, potassium sulfate, and magnesium sulfate" whereas in "Request for Proprietary Name Review", it was presented as "Sodium Sulfate, Potassium Sulfate, Magnesium Sulfate for Oral Solution Kit". The font size of established name is **less** than 50% of the proprietary name.	**Unsatisfactory**
Strength	Strengths (17.5 g for sodium sulfate, 3.13 g for potassium sulfate, and 1.6 g for magnesium sulfate) are correctly expressed.	**Satisfactory**
Net contents	The net content (22.7 g of powder) is described	**Satisfactory**
Lot number	There is a space allocated for this information.	**Satisfactory**
Expiration date	There is a space allocated for this information.	**Satisfactory**
"Rx only" statement	The statement is prominently displayed.	**Satisfactory**
Storage (not required)	A minor revision is recommended as following. "Store at 20° - 25°C (68° - 77°F); excursions permitted between 15° and 30 °C (59° and 86°F) [see USP Controlled Room Temperature]"	**Satisfactory**
NDC number (requested, but not required for all labels or labeling)	NDC number (10702-083-23) is indicated.	**Satisfactory**
Bar Code	Barcode is indicated.	**Satisfactory**
Name of manufacturer/distributor	The name of manufacturer is correctly described per 21CFR 201.1(h)(5).	**Satisfactory**
Others		

Conclusion: The immediate container label provided in the 4/1/2013 amendment is unsatisfactory.

The following comments were conveyed to the applicant on 4/11/2013:

Address the following issues for the container and carton labels and provide the updated container and carton labels:

- *Revise the established name of your drug product, which should include names of drug substances, dosage form, and route of administration. For example, the proprietary name and established name may be expressed as:*

  (b) (4)

  (sodium sulfate, potassium sulfate, and magnesium sulfate) Powder for Oral Solution

  Furthermore, the font size of the established name should be at least half as large as that of the proprietary name per 21 CFR 201.10(g)(2).

- *Revise the storage condition from* (b) (4) *to "Store at 20° - 25°C (68° - 77°F); excursions permitted between 15° and 30 °C (59° and 86°F) [see USP Controlled Room Temperature]".*

In the 6/28/2013 amendment (SD-13), revised container label was provided as shown below.

(b) (4)

The information is acceptable. The established name, the font size of the established name, and storage condition have been revised per this reviewer's recommendation. It should be noted that the proposed proprietary name (b) (4) *was denied (see DMEPA review dated 7/22/2013 by Lisa Khosla).*

2) Carton Labeling

(b) (4)

Reviewer's Assessment:

Chemistry Assessment Section

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence)	The established name is presented incorrectly. See comments on page 80. The font size of established name is greater than 50% of the proprietary name.	**Unsatisfactory**
Strength	Strengths (17.5 g for sodium sulfate, 3.13 g for potassium sulfate, and 1.6 g for magnesium sulfate) are correctly provided.	**Satisfactory**
Net contents	This carton contains: 2 Bottles containing 22.7 g powder (22.7 g of powder in one bottle) 1 16-ounce mixing container 1 Patient booklet.	**Satisfactory**
Lot number	There is a space allocated for this information.	**Satisfactory**
Expiration date	There is a space allocated for this information.	**Satisfactory**
Name of all inactive ingredients (except for oral drugs)	Since this is an oral dosage form, it is not required.	**Satisfactory**
Sterility Information (if applicable)	Since this is an oral dosage form, it is not applicable.	
"Rx only" statement	The statement is prominently displayed on the main panel.	**Satisfactory**
Storage Conditions	A minor revision is recommended as following. "Store at 20° - 25°C (68° - 77°F); excursions permitted between 15° and 30 °C (59° and 86°F) [See USP Controlled Room Temperature]"	**Satisfactory**
NDC number	NDC number is indicated.	**Satisfactory**
Bar Code	Barcode is indicated.	**Satisfactory**
Name of manufacturer/distributor	The name of manufacturer is correctly described per 21CFR 201.1(h)(5).	**Satisfactory**
"See package insert for dosage information"	The following statements are present. "Please read full prescribing information in this kit." "Read patient booklet contained in kit at least 2 days before scheduled procedure. Reconstitute powder with drinking water. Dilute the reconstituted solution as directed prior to use." However, the following statement is also present above the graphic presentation on reconstitution of the powder: "NOTE: Dilute the solution concentrate as directed prior to use". This statement may cause unnecessary confusion as the drug product is a powder. This issue has been communicated via email to DMEPA reviewer, Lisa Khosla, on 4/4/2013.	**Satisfactory (from CMC perspective)**
"Keep out of reach of children" (optional for Rx, required for OTC)	Since this is Rx drug, it is optional.	
Route of Administration (not required for oral)	Since the drug product is a powder for oral solution. The route of administration should be included as part of the drug product established name.	**Unsatisfactory**

Conclusion: The carton labeling submitted in the 4/1/2013 amendment is unsatisfactory. The same issues (see page 81) as those identified for the container label are also present. These issues should be addressed.

In the 6/28/2013 amendment (SD-13), a revised carton labeling was provided. The established name and storage condition have been revised per this reviewer's recommendation (see page 81). ***However, the fond size of the established name is less than 50% of the proprietary name.*** *Furthermore, the statement "NOTE: Dilute the solution concentrate as directed prior to use" remained in the labeling. As the proposed proprietary name, (b) (4), was denied, the font size of the established name may not be an issue once the proprietary name is deleted.* ***In conclusion, the carton labeling provided in the 6/28/2013 amendment is not acceptable.***

3. Product Data Elements in Structured Product Labeling

The information for Product Data Elements in Structured Product Labeling, which is presented only in the original submission, is summarized below.

Labeling Item	Information Provided		
Trade name	Not provided. The following information was provided: (b) (4)		
Established name (active ingredient)	Not provided. The following information was provided: (b) (4)		
Product Code	10702-083		
Route of Administration	oral		
DEA Schedule	N/A		
Active and Strength	**Name (Active Moiety)** SODIUM SULFATE (SODIUM SULFATE) POTASSIUM SULFATE (POTASSIUM SULFATE) MAGNESIUM SULFATE (MAGNESIUM SULFATE)	**Basis of Strength** SODIUM SULFATE POTASSIUM SULFATE MAGNESIUM SULFATE	**Strength** 17.5 g 3.13 g 1.6 g
Inactive Ingredients Name	SUCRALOSE CITRIC ACID MONOHYDRATE		
Product Characteristics Color flavor	 WHITE (TO OFF WHITE) lemon		
Packaging			
#	**Item Code**	**Package Description**	
1	NDC: 10702-083-23	22.7 g in bottle	
Marketing Information			
Marketing Category	Application Number or Monograph Citation		
ANDA	ANDA 204553		

Labeler - KVK-Tech, Inc. (173360061)			
Establishment			
Name	**Address**	**ID/FEI**	**Operations**
KVK-Tech, Inc.		173360061	Manufacture

Reviewer's Assessment: Except for issues identified below, the information is acceptable. All inactive ingredients (except for lemon flavor, which is listed under "Product Characteristics") are listed and the names of inactive ingredients are consistent with those in the FDA database for Substance Registration System – Unique Ingredient Identifier (UNII). The established name should not include route of administration. The dosage form "powder, for solution" is consistent with the nomenclature listed in http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. The following comments were conveyed to the applicant on 4/11/2013:

> *Address the following issues for Product Data Elements in Structured Product Labeling:*
>
> - *Provide proprietary name.*
> - *Revise the established name of the drug substances and dosage form from* (b) (4) *to "sodium sulfate, potassium sulfate, and magnesium sulfate powder, for solution".*
> - *Revise* (b) (4) *in Product Characteristics from* (b) (4) *to "white".*
> - *Revise marketing category and application number from* (b) (4) *to "NDA".*

The following additional follow-up comments were conveyed to the applicant on 7/10/2013 email (DARRTS NDAIR dated 7/12/2013):

> *To date, you have not provided any response to address Items 7 and 8 described in the FDA Information Request Letter dated April 11, 2013. Please provide an updated mock-up container label and carton labeling to address issues described in Item 7of the letter. Please either provide an updated Structured Product Labeling (SPL) or commit to address the issues described in Item 8 of the letter. Please note that proprietary name should be included in Product Data Elements in SPL only if an approved one is available.*

In the 6/28/2013 amendment (SD-13), updated container label and carton labeling were provided (see pages 81 and 84). In the 7/23/2013 amendment (SD-16), the applicant commits to provide updated Product Data Elements for SPL once the proposed proprietary name is approved to address Item 8 of the 4/11/2013 Information Request. The response is acceptable.

B. ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION

In the original submission, a categorical exclusion from the preparation of an environmental assessment (EA) was requested under 21 CFR 25.31. The basis of this exclusion is the fact that the proposed drug product in all significant characteristics is similar to several other products already manufactured and marketed by others.

Reviewer's Assessment: The claim of categorical exclusion is acceptable.

III. List Of Deficiencies

Except for the highlighted item in **bold** type regarding the carton labeling (see page 90) and the recommended revisions of the package insert (see pages 75 - 79), all other deficiencies have been addressed adequately. Revision of the package insert is still under discussion as of the date of this review.

The following comments were conveyed to the applicant in the 10/3/2012 FDA Acknowledge Withdrawal letter. Except for Items 4b) and 9, the applicant has responded adequately in the 11/30/2012 resubmission. A follow-up information request regarding Item 4b and 9 was made on 4/11/2013 (see page 87).

The resubmitted application should address the following deficiencies identified during our preliminary review of the withdrawn application. Note that this is a list of issues identified to date. It does not necessarily represent a complete list of all issues.

1. Provide the following missing information for all three drug substances:
   a) Description of manufacturing process and process control
   b) Control of materials (starting materials, reagents, solvents, and auxiliary materials)
   c) Control of critical steps and intermediates
2. Provide data for two additional batches of the drug product. Data of only one batch of the drug product were submitted.
3. Revise the drug substance specifications:
   a) Potassium sulfate:
      i. Add an identification test for sulfate
      ii. Revise the sample size and acceptance criterion (b) (4) to (b) (4) g and NMT (b) (4) mg/kg, respectively, per the current FCC8 monograph.
   b) For magnesium sulfate, add USP <733> loss on ignition with acceptance criteria of loses (b) (4) % - (b) (4) %
4. Revise the drug product specification:
   a) Revise tests for assay and uniformity of dosage units for sodium sulfate, potassium sulfate, and magnesium sulfate to sodium, potassium, and magnesium, respectively. The proposed analytical procedures provide measurements only for the metal contents.
   b) Include testing for metal impurities, including (b) (4) (b) (4), with acceptance criteria of (b) (4) ppm, (b) (4) ppm, (b) (4) ppm, and (b) (4) ppm, respectively. Based on an oral daily dose of 45.4 g, these limits correspond to permitted daily exposure of 15 µg, 25 µg, 10 µg, and 15 µg, respectively, per USP Draft Chapter <232> Metals and Limits published in Pharmacopeial Forum 36 (1). Provide analytical procedure and method validation data for the test.

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IV. Attachments

A. Attachment 1 - EES Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 204553/000	**Sponsor:**	GATOR PHARMS
Org. Code:	180		194 INLET DR
Priority:	3		ST AUGUSTINE, FL 32080
Stamp Date:	03-AUG-2012	**Brand Name:**	(b) (4)
PDUFA Date:	04-OCT-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	05-AUG-2013	**Product Number; Dosage Form; Ingredient; Strengths**	001; POWDER, FOR ORAL SOLUTION; SODIUM SULFATE ANHYDROUS; 17.5GM/1BOT 001; POWDER, FOR ORAL SOLUTION; POTASSIUM SULFATE; 3.13GM/1BOT 001; POWDER, FOR ORAL SOLUTION; MAGNESIUM SULFATE ANHYDROUS; 1.6GM/1BOT

FDA Contacts:	C. TRAN-ZWANETZ	Project Manager	(HFD-800)	3017963877
	J. CHANG	Review Chemist		3017961973
	M. KOWBLANSKY	Team Leader		3017961390

Overall Recommendation:	ACCEPTABLE	on 23-JAN-2013	by T. SHARP	()	3017963208
	PENDING	on 16-JAN-2013	by EES_PROD		
	PENDING	on 16-JAN-2013	by EES_PROD		
	PENDING	on 27-SEP-2012	by EES_PROD		
	PENDING	on 17-SEP-2012	by EES_PROD		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	(b) (4)		
Profile:		**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	17-JAN-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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

DMF No: **AADA:**

Responsibilities: (b) (4)

Profile: **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-JAN-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

DMF No: **AADA:**

Responsibilities: (b) (4)

Profile: **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-JAN-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** **FEI:** 3005117563
KVK-TECH INC

NEWTOWN, , UNITED STATES 189403427

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: POWDERS (INCLUDES ORAL AND TOPICAL) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-JAN-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	CFN: (b) (4) (b) (4)	FEI: (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	(b) (4)		
Profile:		**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	17-JAN-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	CFN:	FEI: (b) (4)	
	(b) (4)		
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	(b) (4)		
Profile:		**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	17-JAN-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

B. Attachment 2 – Email Communication

Chang, Jane

From: Chakraborti, Tamal K
Sent: Tuesday, July 16, 2013 12:36 PM
To: Chang, Jane
Cc: Kowblansky, Marie; Rhee, Moo Jhong; Chakder, Sushanta K
Subject: RE: NDA 204553 Elemental Impurities

Hi Jane,

I have discussed this with Sushanta. We will follow the USP limit. The estimated exposure to (b) (4) from two doses of the drug product at NMT (b) (4) ppm would be about (b) (4) microgram, which is close to the USP limit of 25 microgram/day. In addition, drug product will be administered in just two doses (22.7 g/dose) as a preparation for colonoscopy. Therefore, the proposed specification of (b) (4) at NMT (b) (4) ppm in the drug product does not appear to raise any safety concern from the nonclinical perspective and is acceptable.

Thanks!

Tamal

From: Chang, Jane
Sent: Monday, July 15, 2013 3:48 PM
To: Chakraborti, Tamal K
Cc: Kowblansky, Marie; Rhee, Moo Jhong
Subject: NDA 204553 Elemental Impurities

Hi Tamal,

I would like to seek your input on the limit of cadmium for NDA 204553.

Previously, we told the applicant to set the limits per USP <232>. However, recently USP announced that the implementation of USP <232> was postponed. I noticed that the limits for several elemental impurities do not align between USP <232> and ICH Q3D. Except for (b) (4) all other elemental impurities by USP are equal or tighter than those of ICH Q3D.

Elemental Impurities	*Oral PDE, mcg/day*		*Recommended Limit for NDA (b) (4) ppm**		*Limits in the pending NDA, ppm*
	USP	*ICH Q3D*	*per USP*	*Per ICH Q3D*	
(b) (4)	25	5.0	0.6	0.1	(b) (4)

Is the proposed limit for (b) (4), i.e. (b) (4) ppm, acceptable? Thanks.

Jane

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/s/

JANE L CHANG
08/01/2013

MOO JHONG RHEE
08/01/2013
Chief, Branch IV

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204553	**Reviewer:** Mark R. Seggel	
Submission Date:	Original: 03-AUG-2012 Resubmission: 04-DEC-2012		
Division:	DGIEP	**Team Leader:** Angelica Dorantes, Ph.D.	
Applicant:	Gator Pharmaceuticals Inc.	**Supervisor:** Rik Lostritto, Ph.D.	
Trade Name:	*TBD*	**Date Assigned:**	-
Generic Name:	sodium sulfate, potassium sulfate, magnesium sulfate for oral solution	**Date of Review:**	17-JUN-2013
Indication:	Osmotic laxative for cleansing of the colon in preparation for colonoscopy in adults	**Type of Submission:**	505(b)(2) NDA; RLD is N22372
Formulation / strengths	sodium sulfate 17.5 gm, potassium sulfate 3.13 gm, and magnesium sulfate 1.60 gm per bottle diluted to 16 oz.	**GRMP Goal:**	13-SEP-2013
Route of Administration	Oral	**PDUFA Goal:**	04-OCT-2013
Type of Review	Biowaiver Request		

SUMMARY:

This new drug application describes an alternative presentation of magnesium sulfate anhydrous, potassium sulfate, and sodium sulfate for preparing a bowel cleansing solution. The currently approved product containing these osmotic laxatives is marketed as an oral solution which requires only further dilution before administration (Braintree's NDA 22-372 for Suprep). The alternative presentation proposed by Gator Pharmaceuticals is a blend of dry powders that requires reconstitution with water, and further dilution, before administration.

The applicant notes that per the Orange Book, there is no requirement of in-vivo bioequivalence study for the RLD. They therefore request a waiver for in-vivo bioequivalence. The Applicant intends to rely on FDA's prior determination that the reference listed drug, Suprep (NDA 22-372) is safe and effective. It also intends to rely on the Agency's finding of safety and effectiveness data for the listed drug.

In support of the request for a biowaiver, Gator Pharmaceuticals provided a quantitative comparison of the active components of the proposed product and the approved formulation. The active ingredients, magnesium sulfate, potassium sulfate and sodium sulfate are present, after reconstitution and/or dilution at the same levels (and concentrations). The compositions are compared below. There are minor differences (b) (4); these would not be expected to impact the performance of the osmotic laxative. Note that the applicant does not cite 21 CFR 320.22(b)(3).

There are no significant new impurities in the proposed product. No clinical pharmacology or clinical studies were conducted in support of the new product; the clinical review team has not identified any new safety concerns.

RECOMMENDATION:

The proposed product delivers the same active ingredients at the same levels and concentrations to the colon as the RLD. Both the proposed product and the RLD are administered as aqueous solutions and systemic absorption is not required for activity. The equivalence of the products is self-evident. A waiver of the *in vivo* bioequivalence study requirement is granted. From the Biopharmaceutics perspective, NDA 204553 for sodium sulfate, potassium sulfate, magnesium sulfate for oral solution is recommended for approval.

Signature
Mark R. Seggel
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: R.Lostritto, J.Chang, M.Kowblansky

REVIEW NOTES

The components and composition of the proposed product and the RLD are compared in Table 1.

Table 1. Quantitative Composition of Proposed Product and RLD

Ingredients	NDA 204553		Suprep® NDA 22-372*
	Amount Per Bottle (gm)	Quantity %	Amount Per Bottle (gm)
Sodium Sulfate, USP (b) (4)	17.50	(b) (4)	17.50
Potassium Sulfate, FCC (b) (4)	3.13		3.13
Magnesium Sulfate, US	1.60		1.60
Citric Acid Anhydrous, USP	(b) (4)		
Sucralose (b) (4)			
(b) (4)			
Lemon Flavor			
(b) (4)			
	-	-	(b) (4)
Theoretical weight	22.7 gm	100.00	-

*from NDA 22-372 Chemistry Review #1

Orange Book Listing of the RLD:

Appl No	TE Code[4]	RLD[5]	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N022372		Yes	MAGNESIUM SULFATE ANHYDROUS; POTASSIUM SULFATE; SODIUM SULFATE	SOLUTION; ORAL	1.6GM/BOT;3.13GM/BOT;17.5GM/BOT	SUPREP BOWEL PREP KIT	BRAINTREE LABS

Active Ingredient: MAGNESIUM SULFATE ANHYDROUS; POTASSIUM SULFATE; SODIUM SULFATE
Dosage Form; Route: SOLUTION; ORAL
Proprietary Name: SUPREP BOWEL PREP KIT
Applicant: BRAINTREE LABS
Strength: 1.6GM/BOT;3.13GM/BOT;17.5GM/BOT
Application Number: N022372
Product Number: 001
Approval Date: Aug 5, 2010
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code: -

Reviewer's Assessment:

According to CFR 320.22(b)(3), for certain drug products the in vivo bioavailability (BA) or bioequivalence (BE) of the drug product may be self-evident and the Agency can waive the

requirement for the submission of in vivo BA/BE data of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident if the drug product meets the following:
(i) Is a solution for application to the skin, an oral solution, elixir, syrup, tincture, a solution for aerosolization or nebulization, a nasal solution, or similar other solubilized form; and
(ii) Contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application or abbreviated new drug application; and
(iii) Contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application or abbreviated new drug application that may significantly affect absorption of the active drug ingredient or active moiety for products that are systemically absorbed, or that may significantly affect systemic or local availability for products intended to act locally.

The proposed drug product is an aqueous salt solution for oral administration. Absorption is not required, as the drug acts as an osmotic laxative. It has the same dosage form (after reconstitution and dilution), route of administration, and indication as the RLD.

The proposed drug product has the same concentration of active ingredient as the RLD. The inactive ingredients are not expected to affect the local action of the dissolved salts. In section 3.2.P.2, the applicant states that, "based on the common scientific information about pH of electrolyte solutions, the final pH of the reconstituted solution should be acidic in the range of (b) (4)*." However the current drug product specification does not include a test and acceptance criterion for (reconstituted solution) pH. The pH of Suprep has a limit of 2.5 – 3.5. Any potential differences in product pH are expected to be inconsequential. As solutions administered orally, neither product has a test for osmolarity.*

Therefore, the in vivo BA/BE of the proposed drug product is self-evident, and the Applicant's request for a biowaiver for their proposed 'sodium sulfate, potassium sulfate, magnesium sulfate for oral solution' is acceptable and the biowaiver is granted.

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/s/

MARK R SEGGEL
06/26/2013

ANGELICA DORANTES
06/28/2013

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

NDA Number:	Supplement Number:	Established/Proper Name:
204553 (Type 5 application: new formulation)	Original Application	(b) (4) (sodium sulfate, potassium sulfate, magnesium sulfate)
Applicant:	**Letter Date:**	**Stamp Date:**
Gator Pharmaceuticals	30-November-2012 *	04-December-2012

* This application was originally submitted August, 2012, it was withdrawn 9/27/2012 and resubmitted as indicated here.

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?	√		This NDA is poorly organized, but sufficient to be filed
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?			No IND associated with this NDA

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 yet determined if the drug substances are purified from natural sources or synthesized

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?	√		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?	√		By reference to DMFs [redacted] (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	√		By reference to DMFs [redacted] (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	√		By reference to DMFs [redacted] (b) (4)
15.	Does the section contain controls for the DS?	√		
16.	Has stability data and analysis been provided for the drug substance?	√		By reference to DMFs [redacted] (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not required; not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not required; 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?	√		Manufacturing description is provided in Section 3.2.P.2. Master batch record is provided in Section 3.2.P.3.3.
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?		√	Single formulation is discussed. Optimization of manufacturing process is presented.
23.	Have any biowaivers been requested?	√		Biopharmaceutics reviewer has been assigned
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?	√		

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

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?	√		The package insert does not follow the PLR format.
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.			
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		√	

{See appended electronic signature page}

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

Date

{See appended electronic signature page}

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

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/s/

MARIE KOWBLANSKY
01/31/2013

MOO JHONG RHEE
01/31/2013
Chief, Branch IV