

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205474Orig1s000

CHEMISTRY REVIEW(S)



NDA 205474

**Drug Name(Guaifenesin and Hydrocodone Bitartrate Oral
Solution)**

Sovereign Pharmaceuticals, Inc.

Ying Wang, PhD

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment III
Branch VIII**

CMC REVIEW OF NDA 205474

For the Division of Pulmonary, Allergy and Rheumatology Products

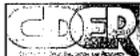


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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 205474
2. REVIEW #: 1
3. REVIEW DATE: 30-Sept-2014
4. REVIEWER: Ying Wang, PhD
5. PREVIOUS DOCUMENTS:N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	Jan 13, 2014
Correspondence (C)	
Amendment (BC)	May 19, 2014
Amendment (BC)	June 23, 2014

7. NAME & ADDRESS OF APPLICANT:

Name: Sovereign Pharmaceuticals, LLC
Address: 7590 Sand Street, Fort Worth, TX 76040, USA
Representative: Leonard Lawrence
Telephone:817-284-0429

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Pending
- b) Non-Proprietary Name: Guaifenesin and Hydrocodone Bitartrate Oral Solution
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5
 - Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: Cough suppressant and expectorant

11. DOSAGE FORM: Oral Solution

CMC Review Data Sheet

12. STRENGTH/POTENCY: 200 mg and 2.5 mg/5 mL
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

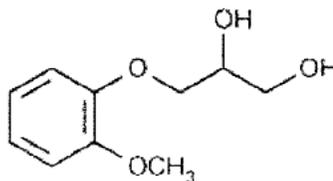
1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Compendial Name: Guaifenesin

Chemical Name(s):

IUPAC name: (+)-3-(o-Methoxyphenoxy)-1,2-propanediol

EP name: (2RS)-3-(2-Methoxyphenoxy)-propane-1,2-diol



Molecular Formula: C₁₀H₁₄O₄

Molecular weight: 198.22 g/mol

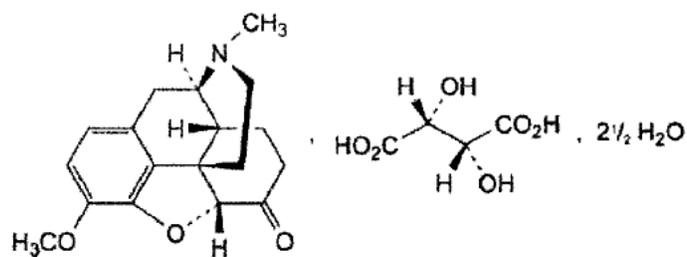
Compendial Name: Hydrocodone Bitartrate

Chemical Name(s):

USP name: Morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5 α)-, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5)

EP name: 4,5 α -Epoxy-3-methoxy-17-methylmorphinan-6-one Hydrogen (2R,3R)-2,3-dihydroxybutanedioate, 2.5 hydrate

CMC Review Data Sheet



Molecular Formula: $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2.5 H_2O$

Molecular Weight: 494.5 g/mol



CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Guaifenesin API	3	Adequate	10/06/2008	No significant change since last review that would impact use in this drug
	II		Hydrocodone Bitartrate API	1	Adequate	09/18/2014	
	III	(b) (4)		3	Adequate	10/04/2013	
	III			3	Adequate	09/10/2012	
	III			3	Adequate	06/07/2005	
	III			3	Adequate	0/24/2008	
	III			3	Adequate	07/16/2004	
	IV			4	N/A		See NDA review
	III			3	Adequate	09/10/2012	
	III			3	Adequate	08/07/2014	
	IV			1	Adequate	09/18/2014	
	IV			1	Adequate	09/18/2014	
	III			4	N/A		See NDA review
	III			3	Adequate	01/27/2014	
	III			3	Adequate	03/21/2012	
	III			3	Adequate	12/07/2004	
	III			3	Adequate	12/21/1998	
	III			3	Adequate	11/09/2012	
	III			3	Adequate	09/10/1999	



CMC Review Data Sheet

			(b) (4)			
--	--	--	---------	--	--	--

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	101683	

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	03/20/2014	
Pharm/Tox	Acceptable	Pending	
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
EA	Categorical exclusion (see NDA review)		Ying Wang

Executive Summary Section

The CMC Review for NDA 205474

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This drug product is recommended for approval from Chemistry, Manufacturing, and Control (CMC) perspective.*

The 24 month shelf life for the drug product when stored at room temperature of 20°C to 25°C (68°F to 77°F), with brief excursions permitted between 15°C and 30°C (between 59°F and 86°F), is proposed and granted.

* Some CMC (non-approvability) issues are in the process to be resolved.

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

N/A

II. Summary of CMC Assessments

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

(1) Drug Substance

Two drug substances (Guaifenesin USP and Hydrocodone Bitartrate USP) are used in this drug product.

Guaifenesin USP is a white powder and is soluble in water and slightly soluble in (b) (4). Information for Guaifenesin USP is referenced in DMF (b) (4) for which (b) (4) is the holder. Specification for Guaifenesin USP is provided in this NDA. It mostly follows USP, EP monographs, and ICH guidance. The Guaifenesin USP is stable with retest period of (b) (4).

Hydrocodone Bitartrate USP is a fine white (b) (4) powder. It is soluble in water and insoluble in (b) (4). Information for Hydrocodone Bitartrate USP is referenced in DMF (b) (4) for which (b) (4) is the holder. The proposed specification for Hydrocodone Bitartrate USP is provided in this NDA and it is (b) (4) than USP monograph with several additional tests. The Hydrocodone Bitartrate USP is stable with retest period of (b) (4).

Both drug substances have been used in several approved drug products.

Executive Summary Section

(2) Drug Product

Guaifenesin and Hydrocodone Bitartrate Oral Solution is a combination product containing hydrocodone bitartrate, a semisynthetic narcotic antitussive and analgesic, and guaifenesin, an expectorant. The oral solution is a clear, colorless to light yellow liquid and packaged in a 4 oz or 16 oz white HDPE bottle with a child resistant closure. Each 5 mL oral solution contains 200 mg Guaifenesin and 2.5 mg Hydrocodone Bitartrate.

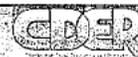
Stability data are provided in the submission for 4 batches at (b) (4) scale for orientations of both onside and upright. The drug product seems stable at the storage condition and there is no apparent trend for any parameter measured during stability. 24 month expiry is proposed and granted when stored at room temperature, 20°C to 25°C, with brief excursions within 15°C to 30°C.

Per current ONDQA review policy the risk assessment table is listed below. There is no high risk CMC issue that is associated with this drug product per risk assessment.



Executive Summary Section

Product attribute/CQA	Factors that can impact the CQA	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment, if any
Assay	<ul style="list-style-type: none"> incorrect amount of APIs purity of APIs pH (see below) incorrect amount of (b) (4) incorrect amount of water/propylene glycol incorrect amount of potassium sorbate (impact on solubility of API) 	3	2	1	6	<ul style="list-style-type: none"> The ratio of water/propylene glycol and the potassium sorbate content can impact drug solubility and since manufacturing includes a (b) (4) assay could potentially be impacted Amounts of formulation components controlled during dispensing (weighed and checked)
Appearance	<ul style="list-style-type: none"> incorrect amount water/propylene glycol 	1	1	1	1	<ul style="list-style-type: none"> Ratio of solvents could impact component solubility in formulation Amounts of formulation components controlled during dispensing (weighed and checked)
pH	<ul style="list-style-type: none"> incorrect amounts of buffer components (b) (4) 	1	3	1	3	<ul style="list-style-type: none"> Amounts of formulation components controlled during dispensing (weighed and checked) pH out of range could impact preservative/API content and appearance pH tested at release and solution is buffered Amounts of formulation components controlled during dispensing (weighed and checked)
Microbial limits	<ul style="list-style-type: none"> incorrect amount of (b) (4) incorrect water/propylene glycol lower: (b) (4) dissolution pH (for (b) (4) effectiveness; see above) incorrect amount of potassium sorbate (also has (b) (4)) 	1	1	Release (3) Stability (5)	3 (release) 5 (stability)	<ul style="list-style-type: none"> Amounts of formulation components controlled during dispensing (weighed and checked) pH is determined by quantities of buffer components (see above) Potassium sorbate found not to be necessary for (b) (4) (b) (4)



Executive Summary Section

	<ul style="list-style-type: none"> microbial contamination 					<ul style="list-style-type: none"> No routine ^{(b)(4)} testing proposed, but microbial testing at release/stability
Stability	<ul style="list-style-type: none"> incorrect amount of ^{(b)(4)} interaction of APIs interaction of APIs with excipients degradation of APIs 	3	2	Release (1) Stability (3)	6 (release) 18 (stability)	<ul style="list-style-type: none"> Guaifenesin and hydrocodone bitartrate are considered to be moderately stable drugs Degradants well known and not unusually toxic Amounts of formulation components controlled during dispensing (weighed and checked)
Palatability	<ul style="list-style-type: none"> incorrect amounts of saccharin and flavors 	1	3	5	15	No testing addresses this parameter upon release or during stability
Leachables	<ul style="list-style-type: none"> ^{(b)(4)} 	1	2	5	10	<ul style="list-style-type: none"> extractables studies in the submission represent the worst case scenario Applicant is currently not proposing leachables testing of drug product during stability.



Executive Summary Section

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

The drug product is indicated for the symptomatic relief of ^{(b) (4)} cough ^{(b) (4)}
^{(b) (4)} Measure Guaifenesin and
Hydrocodone Bitartrate Oral Solution with an accurate milliliter measuring device. Take ^{(b) (4)}

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Ying Wang, PhD

B. Endorsement Block:

(See appended electronic signature page)

Julia Pinto, PhD, Branch Chief, Branch VIII, ONDQA

C. CC Block: entered electronically in DFS

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/s/

CRAIG M BERTHA
09/04/2014

KAREEN RIVIERE
09/04/2014

TAPASH K GHOSH
09/04/2014

JULIA C PINTO
09/08/2014

Initial Quality Assessment (IQA) Addendum Pre-Marketing Applications

APPLICATION INFORMATION

1. NEW DRUG APPLICATION NUMBER: N205474

(b) (4) (alternate) are the trademarks proposed by the applicant for their guaifenesin and hydrocodone oral solution. The proposed indication is for the symptomatic relief of cough and (b) (4) mucu (b) (4)

There is a single strength of 200 mg guaifenesin/2.5 mg hydrocodone bitartrate per 5 mL (teaspoon). The proposed dose (b) (4)

(b) (4) The applicant proposes both a 4 and 16 oz. high-density polyethylene (HDPE) container for the drug product.

The applicant (Sovereign Pharmaceuticals, LLC) obtains guaifenesin from (b) (4) (b) (4) and reference DMF (b) (4). This DMF has been reviewed in the recent past and has been found acceptable for support of approved solid oral dosage form (SODF) drug products. However, various submissions (four quality amendments and three annual reports/updates) have been submitted to the DMF since the last review, thus a subsequent review of any important amendments is necessary to support this NDA.

Hydrocodone bitartrate drug substance is obtained from (b) (4) (b) (4) and the application references DMF (b) (4). This DMF was recently reviewed to support a solid oral dosage form and was found to be inadequate. The holder has responded to the resultant deficiency letter, and has also amended the file. These documents will need to be reviewed to determine if the file is adequate to support this NDA.

This addendum has been written to provide a more formal risk assessment to the reviewer regarding the drug product. The table below captures the associated risk analysis for each drug product CQA and is meant to help focus the reviewer on the higher risk aspects of the application during review.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205474

Received Date: 14-JAN-2014

Product attribute/CQA	Factors that can impact the CQA	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment, if any
Assay	<ul style="list-style-type: none"> incorrect amount of APIs purity of APIs pH (see below) incorrect amount of (b) (4) incorrect amount of water/propylene glycol incorrect amount of potassium sorbate (impact on solubility of API) 	3	2	Release (1) Stability (3)	6 (release) 18 (stability)	<ul style="list-style-type: none"> Stability data do show some degradation trend (moderate stability as formulated) The ratio of water/propylene glycol and the potassium sorbate content can impact drug solubility and since manufacturing includes a (b) (4) assay could potentially be impacted Amounts of formulation components controlled during dispensing (weighed and checked)
Appearance	<ul style="list-style-type: none"> incorrect amount water/propylene glycol 	1	1	1	1	<ul style="list-style-type: none"> Ratio of solvents could impact component solubility in formulation Amounts of formulation components controlled during dispensing (weighed and checked)
pH	<ul style="list-style-type: none"> incorrect amounts of buffer components (b) (4) 	1	3	1	3	<ul style="list-style-type: none"> Amounts of formulation components controlled during dispensing (weighed and checked) pH out of range could impact preservative/API content and appearance pH tested at release and solution is buffered Amounts of formulation components controlled during dispensing (weighed and checked)
Microbial limits	<ul style="list-style-type: none"> incorrect amount of (b) (4) incorrect 	1	1	Release (3) Stability (5)	3 (release) 5 (stability)	<ul style="list-style-type: none"> Amounts of formulation components controlled during dispensing (weighed and checked)

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205474

Received Date: 14-JAN-2014

	<ul style="list-style-type: none"> water/propylene glycol lowers (b)(4) dissolution pH (for (b)(4) effectiveness; see above) incorrect amount of potassium sorbate (also has (b)(4)) microbial contamination 					<ul style="list-style-type: none"> pH is determined by quantities of buffer components (see above) Potassium sorbate found not to be necessary for (b)(4) (b)(4) No routine (b)(4) testing proposed, but microbial testing at release/stability
Stability	<ul style="list-style-type: none"> incorrect amount of (b)(4) interaction of APIs interaction of APIs with excipients degradation of APIs 	3	2	Release (1) Stability (3)	6 (release) 18 (stability)	<ul style="list-style-type: none"> Guaifenesin and hydrocodone bitartrate are considered to be moderately stable drugs Degradants well known and not unusually toxic Amounts of formulation components controlled during dispensing (weighed and checked)
Palatability	<ul style="list-style-type: none"> incorrect amounts of saccharin and flavors (b)(4) 	1	3	5	15	No testing addresses this parameter upon release or during stability
Leachables	(b)(4)	3	2	5	30	<ul style="list-style-type: none"> Unclear that extractables studies are representative for formulation Applicant is currently not proposing leachables testing of drug product during stability studies

This document will be signed in DARRTS by the following:

Craig M. Bertha, PhD, Acting CMC Lead

Eric Duffy, PhD, Acting Branch Chief, Division Director

{See appended electronic signature page}

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

/s/

CRAIG M BERTHA
06/11/2014

ERIC P DUFFY
06/11/2014

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

I. Review Cover Sheet

1. OMPQ Reviewer: Linda Ng, Ph.D.
2. NDA/BLA Number: NDA 205-474
Submission Date: January 14, 2014
21st C. Review Goal Date: September 14, 2014
PDUFA Goal Date: November 14, 2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	(b) (4)
Established or Non-Proprietary Name (USAN) and strength:	(guaifenesin and hydrocodone bitartrate) Oral Solution, 2.5 mg, 200 mg/ 5mL
Dosage Form:	Oral Solution

4. SUBMISSION PROPERTIES:

Review Priority :	STANDARD
Applicant Name:	Sovereign Pharmaceuticals
Responsible Organization (OND Division):	DPARP

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

II. Application Detail

1. INDICATION: The symptomatic relief of cough (b) (4) loosen mucus (b) (4)
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: 2.5 mg, 200 mg/ 5mL
4. Rx/OTC DISPENSED: Rx OTC
5. ELECTRONIC SUBMISSION (yes/no)? yes
6. PRIORITY CONSIDERATIONS: no

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		x		
2.	Breakthrough Therapy Designation		x		
3.	Orphan Drug Designation		x		
4.	Unapproved New Drug		x		
5.	Medically Necessary Determination		x		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		x		
7.	Rolling Submission		x		
8.	Drug/device combination product with consult		x		
9.	Complex manufacturing		x		
10.	Other (e.g., expedited for an unlisted reason)		x		

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

III. FILING CHECKLIST

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

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
15.	Additional notes (non-filing issue)	X		
	1. Are all sites registered or have FEI #?			
	2. Do comments in EES indicate a request to participate on inspection(s)?		X	
	3. Is this first application by the applicant?		X	

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?		X	No statement made. None could be located

IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?	X		Claim to fit new dosage form, though all facilities have manufacturing history for the operations listed in the application
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	X		
19.	From a CGMP/facilities perspective, is the application fileable? If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			No
<input type="checkbox"/>	RTRT Proposal	PAT	Drug/Device Combo
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
PET	Design Space	Continuous Mfg	Naturally derived API
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other (explain):			

Manufacturing Highlights

1. Drug Substance

Parameter	Yes	No	Comment
Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	Two APIs in DMFs

Include process flow chart/diagram (see eCTD Section 2.3.S.1)

2. Drug Product

Parameter	Yes	No	Comment
Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	Oral solution

Include process flow chart/diagram (see eCTD Section 2.3.P.1)

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

3. Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues.

Not likely.

4. Drug Product Facility Inspectional History that could impact the manufacturing of this product

The two APIs facilities have been found acceptable based on profile.

The drug product manufacturer & tester had corrected GMP issues in the Warning Letter of [REDACTED] inspection. The [REDACTED] inspection was completed with 483 and VAI recommendation.

Additional information not covered above

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

For each EER, indicate PAI recommendation on the Manufacturing Facilities Chart above (e.g., PS, GMP, 10 Day, AC based on file review). This is the recommendation that will be entered into EES. **For PAI, include the reason for the PAI (i.e. PAI Trigger) in the comment section of the facilities chart.**

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) Yes
Based on Section IV, is a KTM warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart. No
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no) No
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL (DARRTS)

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/s/

LINDA L NG
03/14/2014

MAHESH R RAMANADHAM
03/14/2014

Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

APPLICATION INFORMATION

1. NEW DRUG APPLICATION NUMBER: N205474

(b) (4) (alternate) are the trademarks proposed by the applicant for their guaifenesin and hydrocodone oral so

(b) (4)

(b) (4)

ne
(HDPE) container for the drug product.

The applicant (Sovereign Pharmaceuticals, LLC) obtains guaifenesin from (b) (4) and reference DMF (b) (4). This DMF has been reviewed in the recent past and has been found acceptable for support of approved solid oral dosage form (SODF) drug products. However, various submissions (four quality amendments and three annual reports/updates) have been submitted to the DMF since the last review, thus a subsequent review of any important amendments is necessary to support this NDA.

Hydrocodone bitartrate drug substance is obtained from (b) (4) and the application references DMF (b) (4). This DMF was recently reviewed to support a solid oral dosage form and was found to be inadequate. The holder has responded to the resultant deficiency letter, and has also amended the file. These documents will need to be reviewed to determine if the file is adequate to support this NDA.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 205474

Received Date: 14-JAN-2014

2. Drug Name: (b)(4) (guaifenesin and hydrocodone bitartrate) Oral Solution

Although there is no formal policy, the chemistry classification codes for the drug product (see draft of MaPP 7500.3) would appear to be types 3, 4, and 5 (**New Dosage Form; New Combination; New Formulation or New Manufacturer, Same or New Indication**). Guaifenesin is currently available as extended release tablets both with and without an antitussive (dextromethorphan HBr) and decongestant (pseudoephedrine HCl), but not from Sovereign Pharmaceuticals.

3. RECEIVED DATE: 14-JAN-2014 (Applicant: Sovereign Pharmaceuticals, LLC)

4. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

	TYPE	ITEM	LOA DATE	COMMENTS
(b)(4)	3	(b)(4)	08-APR-2008	Last reviewed for SODF 04-OCT-2013; adequate
(b)(4)	3	(b)(4)	27-JUL-2012	Last reviewed for SODF 10-SEP-2012; adequate; recent amendments/updates not reviewed
(b)(4)	3	(b)(4)	27-JUL-2012	Last reviewed 07-JUN-2005; recent amendments/updates not reviewed
(b)(4)	3	(b)(4)	06-AUG-2012	Last reviewed 24-JUN-2008; adequate for aq. gel, recent amendments/updates not reviewed
(b)(4)	3	(b)(4)	06-MAY-2008	Last reviewed 16-JUL-2004; recent amendments/updates not reviewed
(b)(4)	4	(b)(4)	23-OCT-2013	Not reviewed for this

¹ The applicant has currently proposed two proprietary names for the drug product. OSE/OPDP has indicated that it does not have promotional issues with these proposed names.

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			Flavor PFC F-		flavor
(b) (4)	3	(b) (4)	(b) (4)	24-SEP-2007	Last reviewed for SODF 10-SEP-2012; adequate
	3		03-DEC-2012	Not reviewed	
	4		03-OCT-2013	Not reviewed	
	4		26-MAR-2013	Not reviewed	
	3		30-JUL-2012	Not reviewed	
	3		06-NOV-2009	Last reviewed for SODF 27-JAN-2014, adequate	
	2		02-JUL-2012	Last reviewed for SODF 28-SEP-2012, inadequate	
	2		09-JUL-2012	Last reviewed for SODF 06-OCT-2008, adequate; recent amendments/updates not reviewed	
	3		27-NOV-2012	Last reviewed for SODF 21-MAR-2012, adequate; recent amendments/updates not reviewed	
	3		30-JUL-2012	Last reviewed 07-DEC-2004; recent amendments/updates not reviewed	
	3		26-JUL-2012	Last reviewed 21-DEC-1998; recent amendments/updates not reviewed	
	3		08-APR-2008	Last reviewed for SODF 09-NOV-2012, adequate; recent amendments/updates not reviewed	
	3		28-NOV-2012	Last reviewed 10-SEP-1999; recent amendments/updates not reviewed	

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b. Recommended Consults

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	X	<input type="checkbox"/>	Request evaluation of stability data if trends in parameters appear to limit expiry and applicant's analysis is suspected of being deficient.
Clin Pharm	<input type="checkbox"/>	X	
EES	X	<input type="checkbox"/>	Draft entered into EES by acting CMC lead on 03-FEB-2014
Pharm/Tox	X	<input type="checkbox"/>	<p>After review of the three DMFs for the (b)(4) flavoring mixtures, it may be necessary to request that the pharmacologist evaluate any flavoring components that are not sanctioned for use in food or drugs (as per 21 CFR 172.510 and 172.515, etc.).</p> <p>The reviewer may need to consult the pharmacologist regarding the deficiencies identified in the last review of DMF (b)(4) from (b)(4) for the hydrocodone bitartrate drug substance, depending on the adequacy of the response (see 22-MAY-2013, amendment) that was provided but not reviewed.</p> <p>The P.7 section includes a toxicological assessment of container closure extractables (potential leachables). The adequacy of this report, from a toxicological perspective, should be assessed in order to determine the need for additional controls for the drug product container closure components or for routine leachables testing as part of the on-going stability protocol.</p>
Methods Validation	<input type="checkbox"/>	X	Left to reviewer discretion if any drug product methods are questionable, but guaifenesin and hydrocodone bitartrate are not NMEs so it is not mandatory that any methods be assessed by the Agency laboratory.
EA	<input type="checkbox"/>	X	Applicant claims a categorical exclusion under 21 CFR 25.31(a), and states that action on the application will not increase the use of the active moiety. Reviewer can evaluate if guaifenesin and hydrocodone bitartrate dosages proposed are the same or lower than other approved drug products containing these moieties.
New Drug Micro	<input type="checkbox"/>	X	The oral solution drug product is not sterile and the specification is consistent with recommendations of USP <1111> for aqueous preparations for oral use. The microbiology team has been notified (03-FEB-2014) of the application and will determine if any microbiology review is needed.

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CDRH	<input type="checkbox"/>	X	N/A
Other	<input type="checkbox"/>	X	N/A

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND	Submitted 11-FEB-2008, currently active	101683	Guaifenesin and hydrocodone bitartrate oral solution

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d. Previous Communications with the Applicant to note (see module 1.6.3 for complete detail):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
Type C Meeting Minutes	08-DEC-2011	IND 101683	Agency responds to regulatory, CMC, clinical, and non-clinical questions
Correspondence	04-JUN-2009	IND 101683	Non-Hold Comments from initial CMC review

OVERALL PRODUCT QUALITY CONCLUSIONS AND RECOMMENDATIONS

Is the Product Quality Section of the application fileable from a CMC perspective?

Yes	No	CMC Filing Issues
X	<input type="checkbox"/>	1.

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?

Yes	No	
<input type="checkbox"/>	X	

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?

Yes	No	Biopharmaceutics Filing Issues
<input type="checkbox"/>	<input type="checkbox"/>	To be separately assessed by the biopharmaceutics team

Are there potential biopharmaceutics review issues to be forward to the Applicant with the 74 day letter?

Yes	No	
<input type="checkbox"/>	<input type="checkbox"/>	See above

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Does the submission contain any of the following elements?

	Yes	No	Comments
Botanical Products	<input type="checkbox"/>	X	
Combination Products	<input type="checkbox"/>	X	
Nanotechnology	<input type="checkbox"/>	X	
PET	<input type="checkbox"/>	X	
QbD Elements	<input type="checkbox"/>	X	
SPOTS	<input type="checkbox"/>	X	

Is a team review recommended?

Yes	No	Suggested expertise for team
<input type="checkbox"/>	X	

CMC Summary: Critical Issues and Complexities

(This section is formatted to expand as far as needed by author.)

- Sovereign had submitted IND 101683 for the support of the development of the drug product of this NDA. A pre-NDA meeting was held with the sponsor on 09-NOV-2011, and there were several agreements met regarding CMC information for support of the NDA. First, the Agency agreed that it would accept 6 months of accelerated and 12 months of room temperature stability data for three batches of drug product to support the NDA. Second, the sponsor requested that they can support a formulation of the drug product with a new flavor by providing in the NDA, 3 months of accelerated and room temperature stability data for an additional 3 batches of the newly formulated drug product. The Agency agreed with the following stipulations: 1) that the sponsor provide a stability protocol and submit updated stability data during the course of the review; 2) that the sponsor commit to placing three lots on stability, collecting stability data and reporting the data post-approval in a CBE-0 supplement. The NDA stability section contains data for three batches (PB375, PB388 and RB2593) of drug product formulated with punch flavoring (cherry ^{(b)(4)}) and one batch (PB419) formulated with raspberry flavoring. All batches are packaged in both the 4 and 16 oz. bottle presentations and stability data are provided with bottles both upright and on their side. The applicant appears to have provided sufficient stability data as per the agreement, although there are some inconsistencies and data gaps

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noted (see table below). The applicant states in the stability and shelf-life report that they propose a **24 month** expiry for both formulations of the drug product. Note that the planned commercial production batch size is (b) (4). The following table summarizes the stability data provided:

Stability Data in Application²				
Batch	Size/Flavor	Pkg. Config./orient.	Accelerated (months) (40°C/25%RH)	Long term (months) (25°C/40%RH)
PB375	(b) (4)/punch ³	4 oz./side	6	12 + 42
		4 oz./upright	6	12 ⁴ + 42
		16 oz./side	6	12 + 42
		16 oz./upright	6	12 ³ + 42
PB388	(b) (4)/punch	4 oz./side	6	12 ³ + 35
		4 oz./upright	6	12 + 35
		16 oz./side	6	12 ³ + 35
		16 oz./upright	6	12 ³ + 35
RB2593	(b) (4)/punch	4 oz./side	6	24
		4 oz./upright	Initial + 6	Initial + 12+ 24
		16 oz./side	6	24
		16 oz./upright	None	None
PB419	(b) (4)/raspberry	4 oz./side	6	24
		4 oz./upright	Initial + 6	12 ³ + 24 (micro. only)
		16 oz./side	6	24
		16 oz./upright	Initial + 6	12 ³ + 24 (micro. only)

The applicant provides a stability summary and report and statistical-based prediction of shelf-life in terms of the assay and pH. Sufficient data have been provided to evaluate the proposed expiry period.

- There are several considerations regarding labeling for the drug product that will need to be addressed during the review. As evident from the above summary, the applicant currently proposes to market two distinct formulations with different flavors (punch and raspberry). The first has artificial raspberry flavoring and the second, artificial cherry (b) (4), which is called “punch” flavoring. Although this formulation difference is listed in the DESCRIPTION section of the labeling, it is not indicated on the carton labels. This issue

² Applicant is applying stability storage conditions typical for (b) (4) containers for liquid dosage forms.

³ Punch flavoring is obtained from a mixture of (b) (4) cherry flavors.

⁴ However, missing 9 month test-station.

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should be brought to the attention of the review team in case there is any concern if patients receive different formulations with flavoring differences unidentified.

The carton labels indicate that the product is (b) (4)

It is not typically desirable to list those compounds or materials that are not in the formulation due to limited space. This can be brought to the attention of the review team at the labeling meetings.

- The reviewer should consult the pharmacology/toxicology team regarding the deficiencies (see review in DARRTS) for the (b) (4) DMF (b) (4) for the hydrocodone bitartrate drug substance.
- Both drug substances and all of the excipients with the exception of the flavorings (cherry (b) (4) and raspberry) are of compendial grade. All of the compendial grade excipients have been used in oral solution or suspension drug products according to the inactive ingredient guide, however, it is not known how the concentrations translate and compare in terms of daily intake, or if the associated diseases might warrant different risk-benefit ratios to come into play with regard to the excipient daily intake. These evaluations are left for evaluation by the pharmacology/toxicology team as per 21 CFR 314.50(d)(2)(ii).
- The current procedure for the application of the degradant acceptance criteria is somewhat unique in that the unspecified (and unidentified) degradants are to be controlled relative to the hydrocodone standard. This is said to overestimate any degradants that are unspecified and due to guaifenesin, as the concentration of that drug is (b) (4) times that of the hydrocodone bitartrate (for details see specification justification report). Note that the ICH Q3B identification threshold based on the dose of hydrocodone bitartrate is 0.2% but for guaifenesin it is (b) (4) %.
- The formulation has a significant non-aqueous portion, consisting of (b) (4) % propylene glycol and (b) (4) % glycerin, with the remainder as purified water plus excipients (b) (4) and drug substances. Typically, if the information provided in support of the container closure components demonstrate that or assure that these components comply with the food contact regulations for packaging materials that could be used with aqueous based foods, this would be sufficient to justify the absence of any specific leachables testing for an aqueous based oral solution drug product. But since this solution contains substantial non-aqueous solvent components, the potential for leachables should be considered by the applicant. As per ICH Q6A, the applicant will need to provide evidence that leachables levels are sufficiently low (are safe) before dispensing with testing as a stability parameter. In P.7 the applicant has included an assessment of the

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extractables from the HDPE container closure system.

- The drug product is *not* packaged with a dose measuring device of any kind. Doses are to be taken in units of 5 mL (for each 200 mg guaifenesin and 2.5 mg of hydrocodone bitartrate). The current section 17 of the package insert indicates under 17.2 that “Patients should be advised to measure (b) (4) Oral Solution with an accurate milliliter measuring device. Patients should be informed that a household teaspoon is not an accurate measuring device and could lead to overdosage, especially when half a teaspoon is measured. Patients should be advised to ask their pharmacist to recommend an appropriate measuring device and for instructions for measuring the correct dose [see *Dosing and Administration (2) Warnings and Precautions (5.9)*].” It is recommended that the chemist ask the clinical team to consider this when they are making their safety evaluation of the application.

Description of Facility Related Risks or Complexities (i.e. foreign sites, large number of sites involved, etc.)

See EES for complete list of facilities related to this application.

The guaifenesin is manufactured internationally by (b) (4) and the hydrocodone bitartrate by (b) (4). Information for the manufacturer of the drug substances is provided in DMFs referenced in the application. The oral solution drug product is manufactured by Sovereign Pharmaceuticals at their Fort Worth, Texas facility. It is noted that the Sovereign facility (FEI 3003229412) was recently evaluated for the LIQ profile class 21-JUN-2013, and was found to be acceptable. The draft site information was entered into the EES by the acting CMC lead on 03-FEB-2014.

Biopharmaceutics Filing Review: Summary, Critical Issues and Complexities

(This section can expand as far as needed by author.)

Note: A separate filing review will be provided by the biopharmaceutics team if it is deemed necessary.

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FILING REVIEW CHECKLIST

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	N/A	Comment
1.	Is the CMC section organized adequately?	X	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X	<input type="checkbox"/>	<input type="checkbox"/>	
3.	Are all the pages in the CMC section legible?	<input type="checkbox"/>	<input type="checkbox"/>		All pages examined for production of this IQA were legible.
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X	<input type="checkbox"/>	<input type="checkbox"/>	The adequacy of the provided data will be determined during review.

B. FACILITIES*					
	Parameter	Yes	No	N/A	Comment
5	Is a single, comprehensive list of all involved facilities available in one location in the application?	X	<input type="checkbox"/>	<input type="checkbox"/>	See form 356h
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.	<input type="checkbox"/>	<input type="checkbox"/>	X	Note, however, that it is likely that precursor compounds in the synthesis of hydrocodone are derived from natural sources (e.g., from poppys).

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7	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X	<input type="checkbox"/>	<input type="checkbox"/>	
8	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X	<input type="checkbox"/>	<input type="checkbox"/>	

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

* 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	N/A	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	Exclusion requested as per 21 CFR 25.31(a); Applicant also claims that they know of no extraordinary circumstances regarding the EA.

D. MASTER FILES (DMF/MAF)					
	Parameter	Yes	No	N/A	Comment
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X	<input type="checkbox"/>	<input type="checkbox"/>	Refer to table of DMF information above.

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E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)					
	Parameter	Yes	No	N/A	Comment
13.	Does the section contain a description of the DS manufacturing process?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Reference is made to DMFs (b) (4) and (b) (4).
14.	Does the section contain identification and controls of critical steps and intermediates of the DS (in process parameters)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
15.	Does the section contain information on impurities?	X	<input type="checkbox"/>	<input type="checkbox"/>	
16.	Does the section contain information regarding the characterization of the DS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
17.	Does the section contain controls for the DS?	X	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above; the NDA contains the specification for the drug substances. The guaifenesin specification is the same as that in the USP monograph. The specification for hydrocodone bitartrate has additional test parameters beyond the USP monograph.
18.	Has stability data and analysis been provided for the drug substance?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
21.	Does the section contain container and closure information?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.

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F. DRUG PRODUCT (DP)					
	Parameter	Yes	No	N/A	Comment
22.	Does the section contain quality controls of excipients?	X	<input type="checkbox"/>	<input type="checkbox"/>	
23.	Does the section contain information on composition?	X	<input type="checkbox"/>	<input type="checkbox"/>	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X	<input type="checkbox"/>	<input type="checkbox"/>	
25.	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?	<input type="checkbox"/>	<input type="checkbox"/>	X	No critical steps are identified for the manufacturing process.
26.	Is there a batch production record and a proposed master batch record?	X	<input type="checkbox"/>	<input type="checkbox"/>	
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	<input type="checkbox"/>	X	<input type="checkbox"/>	The P.2 section does include the formulation development history, but it appears that a single formulation was chosen early on and carried forward, with the exception of the ^{(b) (4)} distinct flavors being proposed (raspberry flavor added later in development).
28.	Have any biowaivers been requested?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The biopharmaceutics team will address any biowaiver requests.
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	X	<input type="checkbox"/>	<input type="checkbox"/>	There are 4 and 16 oz. HDPE bottles with child-resistant closures.
30.	Does the section contain controls of the final drug product?	X	<input type="checkbox"/>	<input type="checkbox"/>	As noted above, there is currently no specification parameter for drug product leachables. An evaluation of the extractables report will be key to determining if such testing should be included as part of the routine stability protocol.

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31.	Has stability data and analysis been provided to support the requested expiration date?	X	<input type="checkbox"/>	<input type="checkbox"/>	As indicated above, the applicant has provided some analyses supporting their proposed drug product expiry period.
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	<input type="checkbox"/>	X	<input type="checkbox"/>	The applicant does not appear to be requesting any regulatory relief based on any QbD-related studies.
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	<input type="checkbox"/>	X	<input type="checkbox"/>	

G. METHODS VALIDATION (MV)

	Parameter	Yes	No	N/A	Comment
34.	Is there a methods validation package?	<input type="checkbox"/>	X	<input type="checkbox"/>	If the reviewer decides that the Agency should evaluate any of the methods, the applicant can be asked to provide sample and reference materials to the Agency laboratory.

H. MICROBIOLOGY

	Parameter	Yes	No	N/A	Comment
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	<input type="checkbox"/>	<input type="checkbox"/>		The microbiology team has been informed of the submission of this application and will make a determination of any review necessary, as per the pilot.

I. LABELING

	Parameter	Yes	No	N/A	Comment
36.	Has the draft package insert been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	
37.	Have the immediate container and carton labels been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	
38.	Does section contain tradename and established name?	X	<input type="checkbox"/>	<input type="checkbox"/>	The prominence of the drug established names is not presented on the label in accordance with 21 CFR 201.10(g).

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J. FILING CONCLUSION					
	Parameter	Yes	No	N/A	Comment
39.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X	<input type="checkbox"/>	<input type="checkbox"/>	
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	<input type="checkbox"/>	<input type="checkbox"/>	X	Describe filing issues here or on additional sheets
41.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	<input type="checkbox"/>	X	<input type="checkbox"/>	Describe potential review issues here or on additional sheets

REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

Craig M. Bertha, Ph.D., Acting CMC Lead

Prasad S. Peri, Ph.D., Branch Chief

{See appended electronic signature page}

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

/s/

CRAIG M BERTHA
02/04/2014

PRASAD PERI
02/09/2014
I concur