CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205474Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205474 SUPPL # HFD #

Trade Name Obredon

Generic Name: Hydrocodone Bitartrate & Guaifenesin

Applicant Name Sovereign Pharmaceuticals, LLC

Approval Date, If Known November 14, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The primary assessment of this submission pertained to the evaluation of the pharmacokinetic characteristics of hydrocodone and guaifenesin after administration of the proposed product compared to a reference. Apart from the pharmacokinetic information and safety information from the BE study, no additional efficacy and safety information was obtained.

If it is a supplement requiring the review of clinical data but it is not an effectiveness

Reference ID: 3658432

supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

Reference ID: 3658432

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 22-442

NDA# 19-111

NDA# 22-439

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer

Reference ID: 3658432

to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

Reference ID: 3658432

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

Reference ID: 3658432

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Laura Musse
Title: Regulatory Health Project Manager
Date: November 14, 2014

Reference ID: 3658432

OND/DPARP Deputy Director signing form: Lydia Gilbert-McClain, M.D.
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12;

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

/s/

LAURA MUSSE
11/14/2014

LYDIA I GILBERT MCCLAIN
11/14/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 205474 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Obredon Established/Proper Name: Hydrocodone Bitartrate & Guaifenesin Dosage Form: Oral Solution		Applicant: Sovereign Pharmaceuticals, LLC Agent for Applicant (if applicable):
RPM: Laura Musse		Division: DPARP

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: November 14, 2014

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is _____	☐ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)* Waiver granted, expiration date:12/2015	☐ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 5
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Reference ID: 3658519

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval-November 14, 2014
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included November 13, 2014
• Original applicant-proposed labeling	☒ Included January 14, 2014
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)* *January 14, 2014, November 6 and 13, 2014*	
• Most-recent draft labeling	☒ Included November 13, 2014
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Non-acceptability April 9, 2014 and September 15, 2014 Reviews-4/7/14 and 8/18/14, November 10, 2014 Acceptability -November 12, 2014
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ April 22, 2014 DMEPA: ☒ September 29, 2014, November 10, 2014 DMPP/PLT (DRISK): ☒ None OPDP: ☒ October 3, 2014 SEALD: ☒ None CSS: ☒ None Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ March 27, 2014 October 22, 2014
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC If PeRC review not necessary, explain: _____	May 7, 2014
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	January 23, 2014 , February 24,2014 March 6, 13, 14, and 27, 2014, May 16 and 30, 2014, June 5, 2014, July 21, 2014, October 16, 2014, November 3, 4, 5, 6, 13, 2014
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	PeRC-March 25, 2014
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ November 9, 2011
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	May 30, 2014
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division (Deputy) Director Summary Review *(indicate date for each review)*	☒ November 14, 2014
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ October 27, 2014
	☐ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
• Clinical review(s) *(indicate date for each review)*	March 27, 2014 October 3, 2014 October 9 , 2014
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	April 29, 2014
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A

Version: 8/27/2014

❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ July 23, 2014
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ September19, 2014, February 28, 2014
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None requested April 2, 2014
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ October 17, 2014
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ January 14, October 10, 2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page59
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☒ February 9, 2014 and March 15, 2014
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ July 23, 2014
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	October 8, 2014
☐ Review & FONSI *(indicate date of review)*	
☒ Review & Environmental Impact Statement *(indicate date of each review)*	October 8, 2014
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: March 14, 2014 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ None
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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

/s/

LAURA MUSSE
11/14/2014

NDA 205474



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 13, 2014

To: Leonard Lawrence, BS, MBA,RAC Manager, Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Sovereign Pharmaceuticals, LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 817-284-0531	**Fax number:** (301) 796-9728
Phone number: 817-284-0429	**Phone number:** (240) 402-3720

Subject: NDA 205474 (hydrocodone and guaifenesin)- Labeling Information Request

Total no. of pages including cover: 3

Comments:

Document to be mailed: **YES** **X- NO**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 240-402-3720. Thank you.

Your original NDA application 205474, dated January 14, 2014 is under review. We have the following request for information:

1. Submit an updated draft of the package insert, carton and container labels with the approved proprietary name: Obredon.

Respond to by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by 4 pm, Thursday, November 13, 2014. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Health Project Manager, at 240-402-3720.

Review/History Clearance From

(To be used/added as a third page to faxed, electronic, or other correspondence, where applicable)

Drafted by:	LMusse	Date: 11/12/14
Revised by:	SBarnes	Date: 11/13/14
	ADurmowicz	Date: 11/13/14
Clearance:	SBarnes	Date: 11/13/14
Finalized:	LMusse	Date: 11/13/14
File Name:	Update Label with Pro Name	Date: 11/13/14

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

/s/

LAURA MUSSE
11/13/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205474

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Sovereign Pharmaceuticals, LLC
7590 Sand Street
Fort Worth, TX 76118

ATTENTION: Leonard Lawrence, BS, MBA, RAC
Manager, Regulatory Affairs

Dear Mr. Lawrence:

Please refer to your New Drug Application (NDA) dated January 13, 2014, received January 14, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate and Guaifenesin Oral Solution, 2.5 mg/200 mg per 5 mL.

We also refer to your October 24, 2014, correspondence, received October 24, 2014, requesting review of your proposed proprietary name, Obredon.

We have completed our review of the proposed proprietary name, Obredon and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your October 24, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact Laura Musse, Regulatory Project Manager in the Office of New Drugs, at (240) 402-3720.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
11/12/2014

NDA 205474



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 6, 2014

To: Leonard Lawrence, BS, MBA,RAC Manager, Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Sovereign Pharmaceuticals, LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 817-284-0531	**Fax number:** (301) 796-9728
Phone number: 817-284-0429	**Phone number:** (240) 402-3720

Subject: NDA 205474 (guaifenesin and hydrocodone)- Information Request for PMR/PMC Commitment

Total no. of pages including cover: 3

Comments:

Document to be mailed: **YES** **X- NO**

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Your original NDA 205474, dated January 14, 2014, is under review. We request written confirmation of your agreement to conduct the following post-marketing required studies and to the scheduled milestone.

1. Conduct a study to assess the pharmacokinetics of each drug component of TRADENAME in children 6 to 17 years with symptoms of the common cold.

Final Protocol Submission:	March, 2015
Study Completion:	September, 2015
Final Report Submission:	March, 2017

2. Conduct a study to assess the safety of TRADENAME in children 6 to17 years with symptoms of the common cold. The dose used in this study will be based upon the results of the pharmacokinetic study in children ages 6 to 17 years. .

Final Protocol Submission:	September, 2018
Study Completion:	March, 2019
Final Report Submission:	September, 2022

Respond to these Information Requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by Friday November 7, 2014. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Health Project Manager, at 240-402-3720.

Review/History Clearance From

Drafted by:	LMusse	Date: 11/4/14
Revised by:	ADurmowicz	Date: 11/6/14
	SBarnes	Date: 11/4/14
Clearance:	SBarnes	Date: 11/4/14
Finalized:	LMusse	Date: 11/6/14
File Name:	PMC/PMR Commitment	Date: 11/6/14

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/s/

LAURA MUSSE
11/11/2014

NDA 205474



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 6, 2014

To: Leonard Lawrence, BS, MBA,RAC Manager, Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Sovereign Pharmaceuticals, LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 817-284-0531	**Fax number:** (301) 796-9728
Phone number: 817-284-0429	**Phone number:** (240) 402-3720

Subject: NDA 205474 (guaifenesin and hydrocodone)- Information Request for PMR/PMC Commitment

Total no. of pages including cover: 3

Comments:

Document to be mailed: **YES** **X- NO**

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Final Protocol Submission:	March, 2015
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Final Report Submission:	March, 2017

2. Conduct a study to assess the safety of TRADENAME in children 6 to17 years with symptoms of the common cold. The dose used in this study will be based upon the results of the pharmacokinetic study in children ages 6 to 17 years. .

Final Protocol Submission:	September, 2018
Study Completion:	March, 2019
Final Report Submission:	September, 2022

Respond to these Information Requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by Friday November 7, 2014. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Health Project Manager, at 240-402-3720.

Review/History Clearance From

Drafted by:	LMusse	Date: 11/4/14
Revised by:	ADurmowicz	Date: 11/6/14
	SBarnes	Date: 11/4/14
Clearance:	SBarnes	Date: 11/4/14
Finalized:	LMusse	Date: 11/6/14
File Name:	PMC/PMR Commitment	Date: 11/6/14

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/s/

LAURA MUSSE
11/06/2014

NDA 205474



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 6, 2014

To: Leonard Lawrence, BS, MBA,RAC Manager, Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Sovereign Pharmaceuticals, LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 817-284-0531	**Fax number:** (301) 796-9728
Phone number: 817-284-0429	**Phone number:** (240) 402-3720

Subject: NDA 205474 (Guaifenesin and Hydrocodone)- Labeling (additional) Comment to- # 2

Total no. of pages including cover: 12

Comments:

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205474
hydrocodone /Guaifenesin bitrate oral solution

Dear Mr. Lawrence:

Your NDA submission dated, August 22, 2014, for hydrocodone/Guaifenesin Bitrate, is currently under review. This information request is in response to your October 24, 2014 submission, which contained your revised label. We have an additional labeling comment in the attached marked up labeling. Please use this version, it includes the comments and recommendations from the comments sent to you on November 4, 2014 and the additional labeling comment, which can be found in the adverse reaction section -6. The proposed insertion is underlined. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

Submit revised labeling incorporating the changes shown in the attached marked up label via email to Laura.Musse@fda.hhs.gov by 12 noon on Friday, November 7, 2014, followed by an official submission to the NDA. If there are any questions, contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

Review/History Clearance From
(To be used/added as a third page to faxed, electronic, or other correspondence, where applicable)

Drafted by:	LMusse	Date: 11/5/14
Revised by:	SBarnes	Date: 11/6/14
Clearance:	SBarnes	Date: 11/X/14
Finalized:	LMusse	Date: 11/X/14
File Name:	Label Revision Round 3	Date: 11/X/14

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

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/s/

LAURA MUSSE
11/06/2014

NDA 205474



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 5, 2014

To: Leonard Lawrence, BS, MBA,RAC Manager, Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Sovereign Pharmaceuticals, LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 817-284-0531	**Fax number:** (301) 796-9728
Phone number: 817-284-0429	**Phone number:** (240) 402-3720

Subject: NDA 205474 (hydrocodone bitrate and guaifenesin)
Carton and Container Label Comments # 1

Total no. of pages including cover: 3

Comments:

Document to be mailed: **YES** **X- NO**

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NDA 205474
hydrocodone bitrate and guaifenesin oral solution

Dear Mr. Lawrence:

Your NDA submission dated, August 22, 2014, for hydrocodone bitrate/guaifenesin, is currently under review. We are providing our comments for the carton and container labeling. Note that currently you do not have an acceptable trade name so that your product will be labeled using the established names. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

1. **Container Labels:**

   a. Revise the statement on the side panel that begins with, 'KEEP THIS AND ALL…'to title case and decrease the font size. As presented, it competes for prominence with the other information listed.

   b. Revise the statement [(b) (4)] to read 'Each 5 mL contains:' to improve readability.

   c. Revise the statement '[(b) (4)]' to 'raspberry flavor' or 'cherry punch flavor' (depending on the formulation) and relocate it to the bottom of the principal display panel above 'Rx Only'.

   d. Remove the statement [(b) (4)] to decrease clutter and increase readability of the label.

   e. Relocate the statement 'Warning: May be habit forming' to the side panel to decrease clutter and increase readability of the label.

   f. Charge [(b) (4)] to CII anywhere it appears on the carton or container label.

Submit revised labeling incorporating the changes listed above via email to Laura.Musse@fda.hhs.gov by 12 noon on Monday, November 10, 2014, followed by an official submission to the NDA. If there are any questions, contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

Review/History Clearance From
(To be used/added as a third page to faxed, electronic, or other correspondence, where applicable)

Drafted by:	LMusse	Date: 11/5/14
Revised by:	A Durmowicz	Date: 11/5/14
	SBarnes	Date: 11/5/14
Clearance:	SBarnes	Date: 11/5/14
Finalized:	LMusse	Date: 11/5/14
File Name:	Carton and Container Rev	Date: 11/5/14

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/s/

LAURA MUSSE
11/05/2014

NDA 205474



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 4, 2014

To: Leonard Lawrence, BS, MBA,RAC Manager, Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Sovereign Pharmaceuticals, LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 817-284-0531	**Fax number:** (301) 796-9728
Phone number: 817-284-0429	**Phone number:** (240) 402-3720

Subject: NDA 205474 (Guaifenesin and Hydrocodone)- Labeling Comments # 2

Total no. of pages including cover: 13

Comments:

Document to be mailed: **YES** **X- NO**

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NDA: 205474
Product: Guaifenesin/hydrocodone Bitrate Oral Solution
Applicant: Sovereign Pharmaceuticals, LLC

Dear Mr. Lawrence:

Your NDA submission dated, August 22, 2014, for Guaifenesin/hydrocodone Bitrate, is currently under review. This information request is in response to your October 24, 2014 submission, which contained your revised label. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are (underlined) and deletions are in (strike-out). Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

Submit revised labeling incorporating the changes shown in the attached marked up label via email to Laura.Musse@fda.hhs.gov by 12 noon on Friday, November 7, 2014, followed by an official submission to the NDA. If there are any questions, contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

Review/History Clearance From
(To be used/added as a third page to faxed, electronic, or other correspondence, where applicable)

Drafted by:	LMusse	Date: 11/3/14
Revised by:	SBarnes	Date: 11/3/14
Clearance:	SBarnes	Date: 11/3/14
Finalized:	LMusse	Date: 11/3/14
File Name:	Label Revision Round 2	Date: 11/3/14

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

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/s/

LAURA MUSSE
11/04/2014

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

MEETING DATE: October 24, 2014
TIME: 12:30 PM -1 PM
LOCATION: FDA White Oak, Bldg 22, Room 4440, Teleconference
APPLICATION: NDA 205474
DRUG NAME: (b) (4) (Guaifenesin and Hydrocodone Bitartrate)
TYPE OF MEETING: Proposed Proprietary Name

APPLICANT: Sovereign Pharmaceuticals, LLC.

MEETING CHAIR: Lubna Merchant, Associate Director, DMEPA

MEETING RECORDER: Nichelle Rashid, Safety Regulatory Project Manager

FDA ATTENDEES:

Lubna Merchant, Associate Director, DMEPA
Kendra Worthy, Team Leader, DMEPA
Lissa Owens, Safety Evaluator, DMEPA
Nichelle Rashid, Safety Regulatory Project Manager (SRPM), OSE

SOVEREIGN PHARMACEUTICALS, LLC ATTENDEES:

David Brown, Owner
Miles Davis, President/CEO
Paul Hafey, VP R&D
Len Lawrence, Manager, Regulatory Affairs
Ruth Collins, Senior Specialist, Regulatory Affairs

Background:

DMEPA requested a teleconference to inform Sovereign Pharmaceuticals, LLC of preliminary concerns identified during the review of the proposed proprietary name, (b) (4) and the alternate name, (b) (4)

Discussion

DMEPA discussed their findings:

DMEPA stated that the teleconference was to notify Sovereign of their findings and safety concerns with regards to the proposed name, (b) (4) and the alternate name, (b) (4)

It is the FDA's policy to review only the primary name submission; however, considering the timelines associated with the NDA, DMEPA conducted a preliminary evaluation of the alternate name. A concern was identified for the primary proposed name, [redacted] as well as the alternate name, [redacted] DMEPA review identified that both names are unacceptable for the following reasons:

1. [redacted] contains the United States Adopted Name (USAN) [redacted] which is reserved for positive inotropic agents [redacted] type).
2. [redacted] has orthographic similarity and overlapping product characteristics with the name Zonatuss (Benzonatate Capsules, USP 150 mg 1 TID for Cough). The safety concern is that a patient could receive [redacted] instead of [redacted]

DMEPA discussed the following regulatory options.

1. Given the approaching NDA PDUFA date, Sovereign may withdraw the proposed proprietary name "[redacted] and resubmit a new request. [redacted]
2. DMEPA can continue their analysis and work to finalize the proprietary name review for [redacted] at which point DMEPA will issue a denial letter for the USAN stem.

Sponsor:

Q: Sovereign asked for additional clarification on the USAN stem.

Agency:

A: DMEPA restated that [redacted] contains the USAN [redacted]

Sponsor:

Q: Sovereign clarified that if they change the [redacted] of the proposed proprietary name by changing the [redacted] new proposed proprietary name would be acceptable.

Agency:

A: DMEPA stated that change the [redacted] (b) (4) . However, Sovereign would have to resubmit a new proposed proprietary name request and it would have to be reevaluated. It was also stated that other divisions within the Agency provide input in the evaluation of the name.

Sponsor:

Q: Sovereign inquired about [redacted] (b) (4), to the proposed proprietary name.

Agency:

A: DMEPA indicated that [redacted] (b) (4) included in the established name on the labeling. [redacted] (b) (4) DMEPA did not recommend [redacted] (b) (4) the proposed proprietary name.

Sponsor:

Q: Sovereign inquired about [redacted] (b) (4) of their proposed proprietary name.

Agency:

A: DMEPA explained the [redacted] (b) (4) of proprietary names.

Sponsor:

Q: Sovereign indicated that they have had numerous issues using the proprietary name software, POCA and inquired how they could receive technical assistance.

Agency:

A: DMEPA stated that information to assist with POCA concerns would be forwarded to Sovereign by the SRPM.

Conclusions:

Sovereign withdrew their submission for Request for Proposed Proprietary Name Review for (b) (4) on October 24, 2014.

Sovereign submitted a request for Proposed Proprietary Name Review for Obredon on October 24, 2014.

The email address for POCA concerns was sent to Sovereign on October 24, 2014. CDEROSETRACKING@fda.hhs.gov

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/s/

NICHELLE E RASHID
11/03/2014

NDA 205474



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: October 16, 2014

To: Leonard Lawrence, BS, MBA,RAC Manager, Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Sovereign Pharmaceuticals, LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 817-284-0531	**Fax number:** (301) 796-9728
Phone number: 817-284-0429	**Phone number:** (240) 402-3720

Subject: NDA 205474 (Guaifenesin and Hydrocodone)- Labeling Comments # 1

Total no. of pages including cover: 23

Comments:

Document to be mailed: **YES** **X- NO**

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NDA: 205474
Product: Guaifenesin/hydrocodone Bitrate Oral Solution
Applicant: Sovereign Pharmaceuticals, LLC

Dear Mr. Lawrence:

Your NDA submission dated, August 22, 2014, for Guaifenesin/hydrocodone Bitrate, is currently under review. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are (underlined) and deletions are in (strike-out). Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

Additionally, we note that the product name lists Guaifenesin first and Hydrocodone second. For consistency with other hydrocodone-containing cough and cold products, please change the product name throughout the label to have the Hydrocodone component listed first.

Submit revised labeling incorporating the changes shown in the attached marked up label via email to Laura.Musse@fda.hhs.gov by close of business today, Friday, October 24, 2014, followed by an official submission to the NDA. If there are any questions, contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

Annotated:
FDA proposed and clean label

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

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/s/

LAURA MUSSE
10/16/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205474

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Sovereign Pharmaceuticals, LLC
7590 Sand Street
Fort Worth, TX 76118

ATTENTION: Leonard Lawrence, BS, MBA, RAC
Manager, Regulatory Affairs

Dear Mr. Lawrence:

Please refer to your New Drug Application (NDA) dated January 13, 2014, received January 14, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Guaifenesin and Hydrocodone Bitartate Solution, 200 mg/2.5 mg per 5 mL.

We also refer to your July 18, 2014, correspondence, received July 18, 2014, requesting review of your proposed proprietary name, (b) (4)

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary name " (b) (4) as proposed, misleadingly overstates the drug's efficacy. (b) (4)

Please note that the Federal Food Drug and Cosmetic Act (FD&C Act) provides that labeling or advertising can misbrand a product if misleading representations are made (See 21 U.S.C. 321(n)). The FD&C Act also provides that a drug is misbranded if its labeling is false or misleading in any particular (21 USC 352(a)). A proprietary name, which appears in labeling,

could result in such misbranding if it is false or misleading, such as by making misrepresentations with respect to safety or efficacy.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact Laura Musse, Regulatory Project Manager in the Office of New Drugs, at (240) 402-3720.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
09/05/2014

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 21, 2014

To: Leonard Lawrence, BS, MBA, RAC Manager, Regulatory Affairs	**From:** Sadaf Nabavian (for Laura Musse) Regulatory Project Manager
Company: Sovereign Pharmaceuticals, LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 817-284-0531	**Fax number:** 301-796-9718
Phone number: 817-284-0429, x152	**Phone number:** 301-796-2777

Subject: NDA 205474; Information Request

Total no. of pages including cover: 2

Comments: Please confirm receipt.

Document to be mailed: **YES** **xNO**

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NDA 205474
Guaifenesin and Hydrocodone Bitartrate
Sovereign Pharmaceuticals, LLC

Dear Mr. Lawrence:

Your NDA submission dated January 13, 2014, for guaifenesin and hydrocodone bitartrate oral solution is currently under review and we have the following request for information:

- Table 1 of the extractables study report for the HDPE container closure system (HDPE Container Closure System: Safety of Extractable and Leachables report from [redacted] (b) (4)) lists extractables study results for 12 identified extractables on a mg/kg basis. Provide an estimate of the maximum daily exposure (e.g. amount/day) for each of the identified extractables at the maximum daily dose of the proposed combination product.

Submit the requested information via email to Laura.Musse@fda.hhs.gov by COB, Friday, August 1, 2014, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabvian, Senior Regulatory Project Manager (if before July 28, 2014) or Laura Musse, Regulatory Project Manager, at 240-402-3721.

Initiated by: Nikunj Patel/Marcie Wood/7.21.2014
Cleared by: Sandy Barnes/7.21.2014
Finalized by: SNabavian/7.21.2014

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/s/

SADAF NABAVIAN
07/21/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205474

ADVICE/INFORMATION REQUEST

Sovereign Pharmaceuticals, LLC
7590 Sand Street
Fort Worth, TX 76118

Attention: Leonard Lawrence, BS, MBA,RAC
Manager, Regulatory Affairs

Dear Mr. Lawrence:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for guaifenesin and hydrocodone bitartrate for symptomatic (b) (4).

We also refer to your submission dated, February 28, 2014 containing the Initial Pediatric Study Plan (iPSP) for guaifensin and hydrocodone and to your amendments dated March 11, and 18, 2014. We acknowledge receipt of your April 4, 2014 amendment containing your Agreed iPSP.

We have completed our review of the submission, and we confirm our agreement to your Agreed iPSP. A clean copy of the Agreed iPSP is attached for your reference. We have the following additional comment:

We encouraged you to make additional attempts to reduce the time of your pediatric development program.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

  If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

If your IND is not in eCTD format:

- you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;

- if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);

- if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as "Duplicate."

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

If you have any questions, contact Laura Musse, Regulatory Health Project Manager, at (240) 402-3720

Sincerely,

{See appended electronic signature page}

Lydia Gilbert-McClain, M.D.
Deputy Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Agreed iPSP

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/s/

LYDIA I GILBERT MCCLAIN
06/06/2014

Liu, Youbang

From: Leonard Lawrence <llawrence@sovpharm.com>
Sent: Thursday, June 05, 2014 1:52 PM
To: Liu, Youbang
Subject: RE: Information Request for NDA 205474, 03MAY14
Attachments: emfalert.txt

Youbang,

I was out of the office earlier this week and now acknowledge the receipt of this request of information.

Sincerely,

Len Lawrence, BS, MBA, RAC
Regulatory / Clinical Affairs Manager
Sovereign Pharmaceuticals, LLC
7590 Sand Street
Fort Worth, Texas 76118
(O) 817-284-0429 x152
(F) 817-284-0531
llawrence@sovpharm.com

From: Liu, Youbang [mailto:Youbang.Liu@fda.hhs.gov]
Sent: Tuesday, June 03, 2014 10:15 AM
To: Leonard Lawrence
Subject: Information Request for NDA 205474, 03MAY14

Sovereign Pharmaceuticals, LLC
Attention: Leonard Lawrence, BS, MBA, RAC
Manager, Regulatory Affairs
7590 Sand Street
Fort Worth, TX 76118

Dear Mr. Lawrence:

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 205474, Guaifenesin and Hydrocodone Bitartrate Oral Solution, 200 mg and 2.5 mg/5 mL. We have the following comments and information requests:

- In your summary technical report for the execution of (b) (4) study, there are noticeable extractable and leachable impurities found in the drug product for some of the materials used in your drug manufacturing system. Specifically, the study indicated that with (b) (4) materials the leachable level can be as high as (b) (4), respectively. In addition, the study also indicated that extractable can be as high as (b) (4) material. Provide justification along with the data to support the safe use (identification and toxicity of the impurities) of these materials in your drug manufacturing system. Alternately, replace these materials with other more compatible materials.

Please acknowledge the receipt of this email and provide the amendment submission by July 2, 2014.

Reference ID: 3519652

Reference ID: 3662307

Regards,

Youbang Liu, Ph.D.
Regulatory Project Manager
Division III, ONDQA/OPS/CDER/FDA
10903 New Hampshire Avenue
Building 21, Room 2525
Silver Spring, MD 20993
Phone: (301) 796-1926

Reference ID: 3519652

Reference ID: 3662307

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/s/

YOUBANG LIU
06/05/2014

Liu, Youbang

From: Leonard Lawrence <llawrence@sovpharm.com>
Sent: Friday, May 30, 2014 11:40 AM
To: Liu, Youbang
Subject: RE: Information Request for NDA 205474
Attachments: emfalert.txt

Youbang,

I acknowledge the receipt of your request. We will submit a response as soon as possible.

Sincerely,

Len Lawrence, BS, MBA, RAC
Regulatory / Clinical Affairs Manager
Sovereign Pharmaceuticals, LLC
7590 Sand Street
Fort Worth, Texas 76118
(O) 817-284-0429 x152
(F) 817-284-0531
llawrence@sovpharm.com

From: Liu, Youbang [mailto:Youbang.Liu@fda.hhs.gov]
Sent: Friday, May 30, 2014 10:38 AM
To: Leonard Lawrence
Subject: Information Request for NDA 205474

Sovereign Pharmaceuticals, LLC
Attention: Leonard Lawrence, BS, MBA, RAC
Manager, Regulatory Affairs
7590 Sand Street
Fort Worth, TX 76118

Dear Mr. Lawrence:

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 205474, Guaifenesin and Hydrocodone Bitartrate Oral Solution, 200 mg and 2.5 mg/5 mL. We have the following comments and information requests:

- The extractable study in your application used [redacted] (b) (4) as extractants while the drug formulation has propylene glycol and glycerin [redacted] (b) (4). Provide justification as why your extractable study is adequate to support the safe use of the container closure system (no leachable impurity is above the safety level). Alternately, provide relevant extractable/leachable data to support the safe use of the container closure system for this drug product formulation.

Please acknowledge the receipt of this email and provide the amendment submission by July 2, 2014.

Regards,

Reference ID: 3515745

Reference ID: 3662307

Youbang Liu, Ph.D.
Regulatory Project Manager
Division III, ONDQA/OPS/CDER/FDA
10903 New Hampshire Avenue
Building 21, Room 2525
Silver Spring, MD 20993
Phone: (301) 796-1926

Reference ID: 3515745

Reference ID: 3662307

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/s/

YOUBANG LIU
05/30/2014

NDA 205474



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: May 16, 2014

To: Leonard Lawrence, BS, MBA,RAC Manager, Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Sovereign Pharmaceuticals, LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 817-284-0531	**Fax number:** (301) 796-9728
Phone number: 817-284-0429	**Phone number:** (240) 402-3720

Subject: NDA 205474 (Guaifenesin and Hydrocodone)- Information Request

Total no. of pages including cover: 3

Comments:

Document to be mailed: **YES** **X- NO**

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 240-402-3720. Thank you.

Your original NDA application 205474, dated January 14, 2014 is under review. We have the following request for information: Your proposed drug product has been marketed in the United States since 2006 as an unapproved drug product. We request you provide following information:

1. Total doses being distributed, from 2006 to present time.

2. Post-marketing experience, including all adverse event reports received from any source for the drug. The data should be presented as a descriptive summary. For deaths or serious adverse events, if any, case reports should be attached.

Respond to these Information Requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by Wednesday, May 28, 2014. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Health Project Manager, at 240-402-3720.

Review/History Clearance From

(To be used/added as a third page to faxed, electronic, or other correspondence, where applicable)

Drafted by:	LMusse	Date: 5/15/14
Revised by:	SBarnes	Date: 5/15/14
Clearance:	SBarnes	Date: 5/15/14
Finalized:	LMusse	Date: 5/16/14
File Name:	FDA IR #5	Date: 5/16/14

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/s/

LAURA MUSSE
05/16/2014

PeRC PREA Subcommittee Meeting Minutes
May 7, 2014

PeRC Members Attending:
Lynne Yao
George Greeley
Hari Cheryl Sachs
Tom Smith
Karen Davis-Bruno
Andrew Mosholder
Lily Mulugeta
Robert “Skip” Nelson
Dianne Murphy
Daiva Shetty
Peter Starke
Susan McCune
Coleen LoCicero

PREA

10:30	NDA	205474	Hydrocodone Bitartrate and Guaifenesin iPSP Partial Waiver/Deferral/Plan	Symptomatic relief of (b) (4) . (b) (4)

Hydrocodone Bitartrate and Guaifenesin Partial Waiver/Deferral/Plan

- NDA 205474 seeks review of Hydrocodone Bitartraate and Guaifenesin for the symptomatic relief (b) (4)
- The application has a PDUFA goal date of November 14, 2014.
- *PeRC Recommendations:*
  - The PeRC agreed with the Division to grant a partial waiver in patients <6 years of age because the product would be ineffective and/or unsafe. A deferral was also agreed to because additional efficacy and/or safety of the product in pediatric patients 6-17 years of age.
  - The PeRC continues to note that scientifically, pediatric studies to establish the effectiveness of cough suppressants should not rely on

extrapolation because efficacy in adults have not been clearly established for product approved under the OTC monograph for cough and cold products. (b) (4) In the interim, the PeRC recognizes that cough and cold products under the monograph are considered safe and effective. In this circumstance pediatric studies may rely on extrapolation of effectiveness as long as appropriate dosing and safety are established. The PeRC agrees with the Division's plan to ask for additional efficacy information as part of the safety study as this may help to establish the efficacy of this product as well as additional products in the future

- The PeRC also recommends that the timelines for study be moved up and that the sponsor consider studies that require less time.

(b) (4)

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

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/s/

GEORGE E GREELEY
05/20/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205474

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Sovereign Pharmaceuticals, LLC
7590 Sand Street
Fort Worth, TX 76118

ATTENTION: Leonard Lawrence, BS, MBA, RAC
Regulatory Affairs Manager

Dear Mr. Lawrence:

Please refer to your New Drug Application (NDA) dated January 13, 2014, received January 14, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Guaifenesin and Hydrocodone Bitartrate Oral Solution, 2.5 mg/200 mg.

We also refer to your January 14, 2014, correspondence, received January 14, 2014, requesting review of your proposed proprietary name, (b) (4)

We have completed our review of the proposed proprietary name, (b) (4) and have concluded that this name is unacceptable because (b) (4) is similar in spelling to other (b) (4). Each of these products contains active ingredients that are different from your proposed Guaifenesin and Hydrocodone product.

We note that your proposed name, (b) (4) is an extension of your cough/cold product line. However, we are concerned that there are other (b) (4) marketed as oral solutions. For these products, we have concerns that the similarity in spelling along with shared dosage form may lead (b) (4) to be confused with (b) (4) A safety concern associated with this potential confusion is that (b) (4) would contain different active ingredients from (b) (4)

Although brand name extensions are used in the marketplace, brand name extensions for products (b) (4) that contain inconsistent active ingredients can present a safety issue. The (b) (4) product line does not contain a consistent active ingredient, yet they have similar indications, may be used in the same patient population, and share overlapping product characteristics such as oral route of administration. Brand name extension products have

been associated with patient and practitioner confusion about the product's ingredients, strength, and concentration[1].This confusion has led to errors in which the wrong product or dose was administered or the product was administered when contraindicated. Published literature suggests the risk of administering the wrong product because of brand name extension may be increased when the products do not share at least one common active ingredient.[2] Additionally, the proposed proprietary name, (b) (4) is similar in spelling and pronunciation to the product (b) (4) . The pair share (b) (4)

Furthermore, FDA's Phonetic and Orthographic Computer Analysis (POCA) calculates a 76% orthographic and phonetic match for this name pair.

We acknowledge that (b) (4) has been discontinued; however, postmarketing experience has shown that although a drug product has been discontinued, some prescribers may continue to use the proprietary name when prescribing.

Therefore based on the spelling of (b) (4) to these other products, we find your proposed name unacceptable based on 21 CFR 201.10(c)(5), which states "The labeling of a drug may be misleading by reason of designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient."

(b) (4)

We note that your secondary name, (b) (4) also uses an extension of a product line (b) (4) and therefore would likely present the same safety concerns.

[1] ISMP Medication Safety Alert! Acute Care Edition, October 22, 2009, Vol. 14 (Issue 21): 1-2

[2] ISMP Medication Safety Alert! Acute Care Edition. April 8, 2004: Vol. 9 (issue 7): 1-2.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact Jessica Lee, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
04/09/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205474

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Sovereign Pharmaceuticals, LLC
7590 Sand Street
Fort Worth, TX 76118

Attention: Leonard Lawrence, BS, MBA, RAC
Manager, Regulatory Affairs

Dear Mr. Lawrence:

Please refer to your New Drug Application (NDA) dated January 13, 2014, received January 14, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Guaifenesin and Hydrocodone Bitartrate Oral Solution, 200 mg/2.5 mg/5mL.

We also refer to your amendments dated February 28 and March 17, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 24, 2014

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. Submit a 120-day safety update as required per 21 CFR 314.50(d)(5)(vi)(b).

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

General Comment

1. Submit the label in portrait orientation format.

Highlights (HL)

2. Remove the header from the first page.

3. Remove references using section titles in the Dosage and Administration section. Present references using only numerical identifiers.

4. Reconfigure the margins to ½ inch on all sides and in-between the columns.

5. Edit the length of HL to the ½ page or less requirement.

6. The HL must be in two- column format and not be presented within a box. The use of a box is reserved for Boxed warnings.

7. Insert a horizontal line to separate the HL from the TOC.

8. Major headings within the HL must be presented in the center of the horizontal line.

9. Insert a white space before each major heading.

10. Insert numerical reference identifiers after each statement in the HL.

11. Edit the product name within the Limitations Statement of the HL to appear in UPPERCASE letters.

Table of Contents (TOC)

12. Remove the packaging configuration information from the TOC.

13. Insert a horizontal line to separate the TOC from the FPI

Full Prescribing information (FPI)

14. At the beginning of the FPI, insert the heading bolded and in UPPERCASE letters: **FULL PRESCRIBING INFORMATION**

15. All cross references within the FPI must use the major heading and the numerical identifier of the subsection heading. For example, revise the reference in the INDICATIONS AND USAGE in subsection 1.1 as follows. Insertions are underlined and deletions are strikethrough.

    "…Not indicated for pediatric patients under 6 years of age [~~see~~ See ~~Pediatric Use~~ Use In Specific Populations (8.4]."

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by April 11, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Pulmonary, Allergy and Rheumatology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request March 18, 2014 for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

This drug product may be appropriately labeled for use in pediatric patients 6 - 17 years of age. We will notify you if the current pediatric labeling for that age group is not adequate.

If you have any questions, call Laura Musse, Regulatory Health Project Manager, at (240) 402-3720.

Sincerely,

{See appended electronic signature page}

Lydia Gilbert-McClain, M.D., Deputy Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

LYDIA I GILBERT MCCLAIN
03/27/2014

NDA 205474



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 14, 2014

To: Leonard Lawrence, BS, MBA,RAC Manager, Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Sovereign Pharmaceuticals, LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 817-284-0531	**Fax number:** (301) 796-9728
Phone number: 817-284-0429	**Phone number:** (240) 402-3720

Subject: NDA 205474 (Guaifenesin and Hydrocodone)- Information Request

Total no. of pages including cover: 3

Comments:

Document to be mailed: **YES** **X- NO**

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We have reviewed your initial Pediatric Study Plan (iPSP) received by email on March 11, 2014 for hydrocodone bitartrate and guaifenesin Oral Solution and have the following information request:

1. In your iPSP, the required timelines for the two studies deferred (PK and safety study), are missing. You must clarify the timelines in a month/year format for protocol submission, study completion, and final report submission for the deferred studies.

2. Clarify if your product has ever been marketed in a foreign country(ies) and indicate if the product has ever received any regulatory actions from foreign countries.

Respond to these Information Requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by Wednesday, March 17, 2014. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Health Project Manager, at 240-402-3720.

Review/History Clearance From

(To be used/added as a third page to faxed, electronic, or other correspondence, where applicable)

Drafted by:	LMusse	Date: 3/12/14
Revised by:	SBarnes	Date: 3/15/14
Clearance:	SBarnes	Date: 3/15/14
Finalized:	LMusse	Date: 3/15/14
File Name:	FDA IR #4	Date: 3/15/14

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/s/

LAURA MUSSE
03/14/2014

NDA 205474



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 13, 2014

To: Leonard Lawrence, BS, MBA,RAC Manager, Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Sovereign Pharmaceuticals, LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 817-284-0531	**Fax number:** (301) 796-9728
Phone number: 817-284-0429	**Phone number:** (240) 402-3720

Subject: NDA 205474 (Guaifenesin and Hydrocodone)- Information Request

Total no. of pages including cover: 3

Comments:

Document to be mailed: **YES** **X- NO**

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Your original NDA application 205474, dated January 14, 2014 is under review. We have the following request for information:

In the body of the file report-403.pdf, we noted that:

1. The units of hydrocodone concentration-time plots on page 50 are pg/ml, however, the unit of hydrocodone C_{max} in in Table 6 on page 37 is in ng/ml; the unit of AUC in the Table 6 is hr*ng/ml. Please reconcile those units to make the report consistent.

2. The units of AUC and C_{max} are missing in most of the tables, such as the tables on page 7, 8, 36, 37, and 38. Units to those parameters must be provided.

Respond to these Information Requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by Wednesday, March 20, 2014. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Health Project Manager, at 240-402-3720.

Review/History Clearance Form

(To be used/added as a third page to faxed, electronic, or other correspondence, where applicable)

Drafted by:	LMusse	Date: 3/12/14
Revised by:	SBarnes	Date: 3/12/14
Clearance:	SBarnes	Date: 3/12/14
Finalized:	LMusse	Date: 3/12/14
File Name:	FDA IR #3	Date: 3/12/14

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/s/

LAURA MUSSE
03/13/2014

NDA 205474



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 6, 2014

To: Leonard Lawrence, BS, MBA,RAC Manager, Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Sovereign Pharmaceuticals, LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 817-284-0531	**Fax number:** (301) 796-9728
Phone number: 817-284-0429	**Phone number:** (240) 402-3720

Subject: NDA 205474 (Guaifenesin and Hydrocodone)- Information Request

Total no. of pages including cover: 3

Comments:

Document to be mailed: **YES** **X- NO**

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 240-402-3720. Thank you.

Reference ID: 3466461
Reference ID: 3662307

We have reviewed your initial Pediatric Study Plan (iPSP) submitted on February 28, 2104 for Hydrocodone Bitartrate and Guaifenesin Oral Solution, and we do NOT agree with your iPSP.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), your proposed drug product, a new combination of active ingredients, is required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients (currently defined as <18 years old) unless this requirement is waived, deferred, or inapplicable. Under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an iPSP containing outline of the pediatric study or studies that fulfill the requirement of the PREA. We have following request:

1. Submit a proposal to request a partial waiver for pediatric studies in patients <6 years of age because the use of opioids in children less than 6 years of age has been associated with fatal respiratory depression.

2. Submit a plan to conduct 2 studies to assess the pharmacokinetics and safety of the proposed drug product in pediatric patients 6 to 17 years of age. The pediatric study plan should be submitted with timelines for protocol submission, study completion, and final report submission for the 2 studies listed below.

    a. Conduct a study to assess the pharmacokinetics of each active component in proposed drug product in (b) (4) children ages 6-17 years with symptoms of (b) (4). The results of this study will be used to determine the appropriate dose of the proposed drug product to evaluate in a safety study in children ages 6 -17 years.

    b. Conduct a study to assess the safety of the proposed drug product in (b) (4) children 6 -17 years of age with symptoms (b) (4). The dose used in this study will be based upon the results of the pharmacokinetic study in children ages 6 -17 years.

Response to these Information Requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by Wednesday, March 12, 2014. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Health Project Manager, at 240-402-3720.

Review/History Clearance Form

(To be used/added as a third page to faxed, electronic, or other correspondence, where applicable)

Drafted by:	LMusse	3/6/14	Date: 3/6/14
Revised by:	SBarnes		Date: 3/6/14
Clearance:	SBarnes		Date: 3/6/14
Finalized:	LMusse		Date: 3/6/14
File Name:	FDA IR RESP		Date: 3/6/14

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/s/

LAURA MUSSE
03/06/2014

NDA 205474



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 24, 2014

To: Leonard Lawrence, BS, MBA,RAC Manager, Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Sovereign Pharmaceuticals, LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 817-284-0531	**Fax number:** (301) 796-9728
Phone number: 817-284-0429	**Phone number:** (240) 402-3720

Subject: NDA 205474 (Guaifenesin and Hydrocodone)- Information Request

Total no. of pages including cover: 3

Comments:

Document to be mailed: **YES** **X- NO**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Reference ID: 3459659
Reference ID: 3662307

Your original NDA application 205474, dated January 14, 2014 is under review. We have the following request for information:

1. **PREA Requirements:**

   Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

   Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP). The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

   For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

Please provide a response to the information requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by Friday, February 28, 2014. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

Reference ID: 3459659
Reference ID: 3662307

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/s/

LAURA MUSSE
02/24/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205474

NDA ACKNOWLEDGMENT

Sovereign Pharmaceuticals, LLC
7590 Sand Street
Fort Worth, TX 76118

Attention: Leonard Lawrence, BS, MBA, RAC
Manager, Regulatory Affairs

Dear Mr. Lawrence:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Guaifenesin and Hydrocodone Bitartrate Oral Solution, 200 mg; 2.5 mg/5mL

Date of Application: January 13, 2014

Date of Receipt: January 14, 2014

Our Reference Number: NDA 205474

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 15, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-3720.

Sincerely,

{See appended electronic signature page}

Laura Musse, R.N., M.S., C.R.N.P.
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JESSICA K LEE
01/23/2014
Signing on behalf of Laura Musse

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 101683

MEETING MINUTES

Sovereign Pharmaceuticals, LLC
7590 Sand Street
Fort Worth, TX 76118

Attention: Leonard Lawrence, BS, MBA, RAC
Manager, Regulatory/Clinical Affairs

Dear Mr. Lawrence:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for guaifenesin and hydrocodone bitartrate Oral Solution.

We also refer to the meeting between representatives of your firm and the FDA on November 9, 2011. The purpose of the meeting was to discuss clinical studies 92001 and 92002 to verify your belief that these study results satisfy FDA's requirements for submission of an NDA under 505(b)(2).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Wayne Amchin
Senior Consumer Safety Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

Reference ID: 3055769
Reference ID: 3062307

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Pre-NDA

Meeting Date and Time: November 9, 2011, 1-2pm
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1417
Silver Spring, Maryland 20903

Application Number: 101683
Product Name: guaifenesin and hydrocodone bitartrate oral solution
Indication: Symptomatic relief (b) (4)

Sponsor/Applicant Name: Sovereign Pharmaceuticals, LLC

Meeting Chair: Lydia I. Gilbert-McClain, M.D., Deputy Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), Office of Drug Evaluation II
Meeting Recorder: Wayne Amchin, Senior Consumer Safety Officer, DPARP

FDA ATTENDEES

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), Office of Drug Evaluation II
Lydia I. Gilbert-McClain, M.D., Deputy Director, DPARP
Peter R. Starke, M.D., Clinical Reviewer, DPARP
Suresh Doddapaneni, Ph.D., Clinical Pharmacology Team Leader, Office of Clinical Pharmacology
Lokesh Jain, Ph.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology
Arun Agrawal, Ph.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology
Alan C. Schroeder, Ph.D., CMC Lead, Division of New Drug Quality Assessment III, Office of New Drug Quality Assessment
Wayne Amchin, M.Intn'l Affairs, M.P.A, Cert. Drug Development and Regulatory Science, Regulatory Project Manager

Reference ID: 3053769
Reference ID: 3662207

SPONSOR ATTENDEES

Miles Davis, Ph.D., R.Ph., President, Sovereign Pharmaceuticals, LLC
Paul Hafey, B.S., Vice President, Research and Development
Leonard Lawrence, B.S., M.B.A., R.A.C., Manager, Regulatory/Clinical Affairs
(b) (4), Consultant (Statistician) to Sovereign Pharmaceuticals, LLC

1.0 BACKGROUND

A pre-IND meeting was held with the sponsor on April 14, 2008. At the time of the November 9, 2011, Type C meeting request, the sponsor believed they were following FDA's most current advice on development of its product. However, in correspondence dated June 3, 2009, FDA provided the sponsor with additional information related to bioequivalence (BE) requirements of combination products containing hydrocodone. Specifically, the June 3, 2009 correspondence stated that the BE study should compare the proposed combination product to each of the individual components. This BE study should be designed to meet the BE criteria of 90% confidence interval of geometric mean ratio of Cmax and AUC being contained within 80 and 125%. In our November 3, 2011, preliminary meeting comments to the sponsor for the November 9, 2011, meeting, DPARP referenced the comments from the June 3, 2009, correspondence. The sponsor responded to the preliminary meeting comments via November 7, 2011, email in which the sponsor indicated that it wanted to discuss questions 1 and 2 at the meeting and that they were unaware of the June 3, 2009, comments because its lead contact with the FDA at that time did not convey that information to the sponsor. This is important background for the November 9, 2011, meeting because, based on the data provided in the sponsor's meeting package, it appears that the BE criteria were met for the hydrocodone component only, but not for the guaifenesin component of the proposed combination product.

Based on the sponsor's meeting questions, which were pre-NDA meeting type questions, the sponsor appeared to have expectations that their development program had sufficiently progressed to be near the point that it could submit a fileable NDA. With the failure to meet the BE criteria set forth in the June 3, 2009, correspondence, the meeting would focus on what the sponsor could do to address the shortcomings in its development program.

Any discussion that took place at the meeting is captured in section 2.0, including any changes in our original position. Sovereign's original questions are included below in normal font; DPARP's responses are included below in *italicized* font; and the discussion is in ***bold italicized*** font.

2. QUESTIONS AND DISCUSSION

2.1. Regulatory/Medical

Question #1: Does the Agency agree that based upon the results presented for Hydrocodone Bitartrate bioequivalence requirement set forth in the Pre-IND meeting (April 14, 2008) for the proposed drug product Guaifenesin and Hydrocodone Bitartrate Oral Solution, 200 mg /2.5 mg per 5 mL, that it appears that no further Hydrocodone Bitartrate studies would be required for the Agency to accept the NDA filing [505(b)(2) of the Act]?

Response: *No, we do not agree. We remind you that in the Agency's correspondence to you dated June 3, 2009, additional information related to* ***bioequivalence (BE)*** *requirements of combination products* ***containing*** *hydrocodone was provided. Among other things, it was stated that the BE study should compare the proposed combination product to each of the*

Reference ID: 3662207
Reference ID: 3055769

individual components. This BE study should be designed to meet the BE criteria of 90% confidence interval of geometric mean ratio of Cmax and AUC being contained within 80 and 125%. It appears that for your proposed drug product, BE criteria, as outlined above, were met for the hydrocodone component only. Overall, since BE criteria for guaifenesin component ***were not*** *met, you do not have data demonstrating bioequivalence of your product with respect to the reference products of individual components.*

Discussion: ***Sovereign indicated that it based its clinical studies on the advice FDA provided at the Pre-IND meeting in April 2008, the results of which demonstrated higher bioavailability from the guaifenesin component from their product than the comparator reference product. Sovereign further stated that there were some formulation issues with the reference guaifenesin product, as they observed precipitation sometime after the completion of the study. Sovereign indicated that they had experienced some solubility challenges with guaifenesin during preparation of its reference product at their site, which were overcome with sonication, and specific instructions were provided for preparation of reference guaifenesin solution at the study site. However, the product stayed in solution during the dosing period and there were no signs of precipitation at the time of administration. Sovereign indicated that they believed their results did not indicate a drug-drug interaction (DDI) issue. Given the problems with the aqueous solution for the guaifenesin reference product, Sovereign stated that they believed the problem was with the aqueous mono-comparator and not with their formulation. Sovereign stated that they believed they were following the precedent set by the OTC monograph that allows for combinations of drugs that do not have DDIs and that may be combined without impacting safety, efficacy, and PK. Sovereign indicated that under the monograph there were no major excipient concerns when there were no DDIs, and that sponsors have latitude with using the excipients that are known and acceptable. Therefore, it was not clear why the BE requirement was an issue if there were no DDI issues.***

FDA responded with general development comments on combination products containing hydrocodone and the rationale for our feedback, as the initial feedback at the Pre-IND meeting was not correct with respect to the bioavailability of guaifenesin. The context for the updated BE information provided in the 2009 correspondence was that FDA started a concerted effort to look at the development of hydrocodone containing products, with the end goal of getting unapproved products off the market. FDA stated that Sovereign's proposed product combines a monograph ingredient (guaifenesin) with a non-monograph ingredient (hydrocodone). FDA indicated that this combination is not one of the permitted combinations under the OTC Cough, Cold, Allergy, and Bronchodilator (CCABA) monograph. In order to create a fixed-dose combination of a monographed product and a non-monograph product, Sovereign would need to provide clinical data to satisfy the combination rule, 21 CFR 300.50, using factorial design studies that demonstrate the contribution of each ingredient to the efficacy of the combination. However, FDA pointed out that there is past precedence for use of a BE approach for certain combinations. The precedent was established with Tussionex, which is a combination of hydrocodone and chlorpheniramine, where BE was allowed to be established without additional clinical data. Based on this precedent, it is possible to avoid the regular clinical development

Reference ID: 3052369
Reference ID: 3052397

program and go through the BE pathway. However, Sovereign has not established BE for the proposed combination.

FDA also noted that the scientific validity of the cough cold monograph was under close review and examination within the Agency. If a sponsor plans to rely on the Agency's findings of safety and efficacy, the shortest route is through the BE pathway. FDA further clarified in response to the sponsor's comments that "OTC ingredients can be combined with anything" that in fact OTC combinations of ingredients have to comply with requirements under 21 CFR Subpart A-General Provisions 330.1 (e) which states that products should contain only suitable inactive ingredients which are safe in the amounts administered and do not interfere with the effectiveness of the formulation. The Agency stated that we believe the (b) (4) of inactive ingredients are responsible for the results in Sovereign's studies. Inactive ingredients, such as sorbitol and propylene glycol, can impact product disposition, for example by inducing changes in osmolarity within the GI tract and permeability of the GI membrane, resulting in changes in bioavailability.

Sovereign stated that these excipients are present in many guaifenesin products that are available in the market. Their interpretation was that the Agency seems to have no issues about the bioavailability or use of these excipients when the guaifenesin product is manufactured as monotherapy. Given this, they wanted to know if (b) (4) guaifenesin exposure from their product is really a safety issue or an efficacy issue?

FDA responded that if the product delivers (b) (4) the active ingredient, then the issue is not only safety but also efficacy. For a fixed dose combination, if there is a (b) (4) one active ingredient than the other, it is possible that both ingredients may not be necessary. For example, if enough guaifenesin is given, then it by itself it may have the desired effect on cough and hydrocodone may not be necessary. Without clinical data, the shortest route to show that both ingredients are needed is the BE route.

Sovereign reiterated that, given the problems with the aqueous solution for the reference guaifenesin product, they believed the problem was with the aqueous mono-comparator and not with their formulation. Sovereign asked whether using a different monographed RLD for guaifenesin might yield different results, and, therefore, they are seeking help with deciding on the RLD to use for the guaifenesin component. Sovereign indicated that they thought they had used the right reference product but wondered if FDA might identify a different reference.

FDA stated that Sovereign has the right reference product, but the issue is that Sovereign did not show that their product was BE to the reference product. FDA advised Sovereign to also consider the possible issues with the formulation for their product, for example the (b) (4) propylene glycol and sorbitol. FDA stated that for approval, Sovereign will need to show BE between the combination and the mono-components in the fasted state.

Sovereign proposed variations in the formulation for the reference guaifenesin product and asked for FDA's input on those variations. FDA responded that we could not answer

Reference ID: 3662307
Reference ID: 3055769

formulation questions on the spot at this meeting. FDA indicated that the sponsor could submit a request for advice on formulation alternatives, and FDA would provide a response. Generally, depending on resources, the Agency tries to respond to such requests within 60 days after receipt of the submission.

General guidance for the 505(b)(2) pathway: *A 505(b)(2) regulatory pathway may be a reasonable approach for your proposed product. Assuming that you develop your product under the 505(b)(2) regulatory pathway, FDA recommends that sponsors considering submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54 and FDA's Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf. In addition, the FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408, available at http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf.*

If you intend to submit a 505(b)(2) application that relies on approval of FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a bridge (e.g., via a relative bioavailability study) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference, but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies. The use of labeling statements taken from the labeling of other drug products may cause those products to also be listed drugs. It is important to identify all listed drugs at the time of the initial 505(b)(2) NDA submission.

Circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

Discussion: The sponsor accepted DPARP's general guidance for the 505(b)(2) pathway and there was no discussion.

Question #2: Does the Agency agree that based upon the results presented for Guaifenesin relative bioavailability requirement set forth in the Pre-IND meeting (April 14, 2008) for the proposed drug

Reference ID 3866897

product Guaifenesin and Hydrocodone Bitartrate Oral Solution, 200 mg /2.5 mg per 5 mL, that it ɔears that no further Guaifenesin studies would be required for the Agency to accept the NDA filing ɔ5(b)(2) of the Act]?

Response: *No, we do not agree. Please see response to question #1.*

Discussion: ***See the discussion under Question 1.***

2.2. Chemistry, Manufacturing, and Controls

Question #3: Does the Agency agree that a minimum of 6 months accelerated and 12 months room temperature stability data on three (3) batches is sufficient for the Agency to accept the NDA filing [505(b)(2) of the Act]?

Response: *Yes, we agree.*

Discussion: ***The sponsor accepted FDA's response, no discussion occurred.***

Question #4: Does the Agency agree that an additional single lot manufactured with a new flavor excipient, submitted with 3 months of accelerated and room temperature stability data in addition to the required three (3) batches is sufficient for the Agency to accept the NDA filing [505(b)(2) of the Act] and to consider the flavor change?

ɔponse: *This will be acceptable if:*

1. *You provide a stability protocol and submit updated stability data during the course of the review.*

2. *Commit to placing three lots on stability, collecting stability data and reporting the data post-approval in a CBE-0 supplement.*

Discussion: ***The sponsor accepted FDA's response, no discussion occurred.***

2.3. Nonclinical

Additional Comments: *Provide information pertaining to the approved use of the new flavoring agent (referred to in Question #4) in drugs or food in the U.S. and/or safety information for the flavoring agent as a whole or all individual ingredients.*

Any impurities or degradants exceeding thresholds described in the ICH Q3A(R2) and Q3B(R2) Guidance should be qualified in appropriate toxicity studies as described by the Guidances. Any impurities or degradants that are identified as possessing ***structural alerts*** *should be at or below acceptable qualification thresholds for genotoxic and carcinogenic impurities as described in the draft FDA Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: ɔmmended Approaches (December 2008) for assessment of impurities to support an NDA.*

Reference ID: 3055769
Reference ID: 3662307

Discussion: ***The sponsor accepted FDA's response, no discussion occurred.***

Meeting Summary:

- ***FDA indicated that Sovereign had the right comparator, but that Sovereign had failed to establish bioequivalence.***

- ***FDA will work with Sovereign on the formulation issues that it experienced in the course of its development program, as well as alternative reference products that they may propose. To obtain FDA's input, Sovereign would need to submit specific questions to the IND, and FDA would respond within 60 days.***

Post-meeting Comment:

- ***With respect to the reference for the guaifenesin component, Sovereign can use any legally marketed OTC guaifenesin product as a comparator.***

3.0 ADDITIONAL INFORMATION

3.1 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

3.2 ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

eference ID: 3055769
Reference ID: 3662307

ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

5.0 ACTION ITEMS

There are no action items pending from this meeting.

6.0 HANDOUTS

There were no handouts at the meeting.

Reference ID: 3662307

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/s/

WAYNE S AMCHIN
12/08/2011