

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206323Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 206323

SUPPL #

HFD #

Trade Name: None

Generic Name: Codeine phosphate and chlorpheniramine maleate

Applicant Name: Spriaso LLC

Approval Date, If Known June 22, 2015

### 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.

Spriaso has submitted this application through 505(b) (2) pathway and is relying on FDA's safety and efficacy findings from:

- i. Previously approved product, Codeprex Pennkinetic, NDA 21-369
- ii. Over-The-Counter (OTC) monographs for codeine as an antitussive (21 CFR 341.14) and chlorpheniramine maleate as an antihistamine (21 CFR 341.12)

The clinical development program in this application comprised of two pilot and two pivotal relative bioavailability/bioequivalence (BA/BE) studies which included comparison of systemic exposure of

the 2 components in test vs. reference and evaluation of effect of food on the PK of the 2 components from the test product. No clinical safety/efficacy studies were conducted. As no immediate (IR) or extended release (ER) codeine and chlorpheniramine combination products are currently marketed, the relative BA assessments were conducted using a codeine and chlorpheniramine combination IR tablet manufactured by the sponsor as the reference product, which is deemed acceptable.

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

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# 021369 (Codeprex)

NDA# 19111 (Tussionex)

NDA# 18928 (Penntuss)

NDA# 207768 (Tuzistra XR)

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 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:

(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:

(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:

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Name of person completing form: Laura Musse  
Title: Regulatory Health Project Manager  
Date: June 22, 2015

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;

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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.**  
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/s/  
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LAURA MUSSE  
06/22/2015

LYDIA I GILBERT MCCLAIN  
06/22/2015

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 206323 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Established/Proper Name: Codeine phosphate and chlorpheniramine maleate Dosage Form: Tablet, ER		Applicant: Spriaso, LLC Agent for Applicant (if applicable): Nexgen Pharma
RPM: Laura Musse		Division: DPARP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b></li> </ul> <p><input checked="" type="checkbox"/> No changes June 22, 2015  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check:</p> <p><i>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.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is June 22, 2015</li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input checked="" type="checkbox"/> 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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> 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.

<sup>2</sup> 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).

<sup>3</sup> 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 4  
 (*confirm chemical classification at time of approval*)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- 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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- 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 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> 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	<input checked="" type="checkbox"/> No <input type="checkbox"/> 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.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) June 22, 2015
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> <li>Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> June 22, 2015
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> August 22, 2014
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letters</li> <li>Reviews</li> </ul>	Denial Letter -February 17, 2015 Denial Review- February 18, 2015
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> November 11, 2014 DMEPA: <input checked="" type="checkbox"/> May 4, 2015 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> June 4, 2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	November 12, 2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> June 22, 2015
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director) Draft</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP               <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo <i>(indicate date)</i></li> <li>If yes, OC clearance for approval <i>(indicate date of clearance communication)</i></li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC</li> <li>If PeRC review not necessary, explain: _____</li> </ul>	May 27, 2015 and June 25, 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.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	June 16, 10, 3, and 3, May 19, and 1, April 30, 22, 13, and 10, March 26, and 24, February 23, and January 20, 2015, November 4, October 20 and 30, September 12 and August 27, 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)	November 3, and 4, 2014
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> October 10, 2013
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> October 4, 2010
<ul style="list-style-type: none"> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	None
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/>
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> May 29, 2015
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> Two
<b>Clinical</b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	May 18, 2015, and March 3, 2015
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	May 18, 2015
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/>
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> March 5, 2015, October 21, 2014
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input type="checkbox"/> May 18, 2015, December 4, and November 3, 2014
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> May 18, 2015, October 3, 2014, and June 18, 2015
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
❖ <b>Product Quality Discipline Reviews</b>	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> May 18, 2015, September 8, 2014, December 19, 2014,
❖ <b>Microbiology Reviews</b> <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> April 22, 2015, October 24, 2014
❖ <b>Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer</b> <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> May 23, 2015
❖ <b>Environmental Assessment (check one) (original and supplemental applications)</b>	
<input checked="" type="checkbox"/> <b>Categorical Exclusion</b> <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	May 18, 2015
<input type="checkbox"/> <b>Review &amp; FONSI</b> <i>(indicate date of review)</i>	
<input type="checkbox"/> <b>Review &amp; Environmental Impact Statement</b> <i>(indicate date of each review)</i>	
❖ <b>Facilities Review/Inspection</b>	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years of action date</b> ) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>	Date completed: June 12, 2015 December 19, 2014 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days of action date</b> ) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input checked="" type="checkbox"/> Completed-November 3, 2014 <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>5</sup> 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)	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
• Finalize 505(b)(2) assessment	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> None
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> N/A
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/  
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LAURA MUSSE  
06/22/2015



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: June 16, 2015**

<b>To:</b> Lara Noah Director, Regulatory Affairs	<b>From:</b> Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
<b>Company:</b> Spriaso LLC c/o Nexgen Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 719- 576-3087	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> 719-579-9650	<b>Phone number:</b> (240) 402-3720
<b>Subject</b> NDA 206323- codeine phosphate and chlorpheniramine maleate- Label information Request, #20	

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**Total no. of pages including cover:**

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**Comments:**

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

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Your submission dated August 22, 2014, to NDA 206323, for codeine phosphate and chlorpheniramine maleate is currently under review. The enclosed label contains the Division's edits to your propose package insert (PI) and carton and container labels. The Division's proposed insertions are underlined; deletions are in strike-outs. These comments are not all-inclusive and we may have additional comments as we continue our review. We also have the following comments:

1. While you can also use lower case letters, for clarity and consistency we recommend changing the current naming of the product in the labeling to UPPER CASE "CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS" in both the prescribing information and Patient Information Sheet.
2. In the Highlights and Patient Information Sheet: Per 21 CFR 201.57(11)(ii) you must include contact information (name and phone number), and in (iv) website (if available) where indicated.
3. Section 8.1: The numerical change (from (b) (4) to 9) was made to reflect animal: human ratios using chlorpheniramine base, as was done for codeine.
4. Section 8.3: Nursing language changed to be consistent with that for the other recently approved codeine and chlorpheniramine product, Tuzistra XR.
5. Section 13.1: The numerical changes made (from (b) (4) to 25 and 20) was to reflect animal: human ratios using chlorpheniramine base, as was done for codeine.

Please provide a response to the requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by 12 noon on Thursday June 18, 2015. 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.

Initiated by: Clinical 6/16/15  
Cleared by: SBarnes 6/16/15  
Finalized: LMusse 6/16/15  
File Name: Label IR #3 6/16/15

18 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)  
immediately following this page.

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/s/  
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LAURA MUSSE  
06/16/2015

**PeRC Meeting Minutes**  
**May 27, 2015**

**PeRC Members Attending:**

Lynne Yao

Wiley Chambers

George Greeley

Ruthanna Davi [Redacted] Non Responsive

Belinda Hayes

Kristiana Brugger

Tom Smith

Daiva Shetty

Andrew Mulberg [Redacted] Non Responsive

Adrienne Hornatko-Munoz [Redacted] Non Responsive

Barbara Buch [Redacted] Non Responsive

Peter Starke [Redacted] Non Responsive

Hari Cheryl Sachs

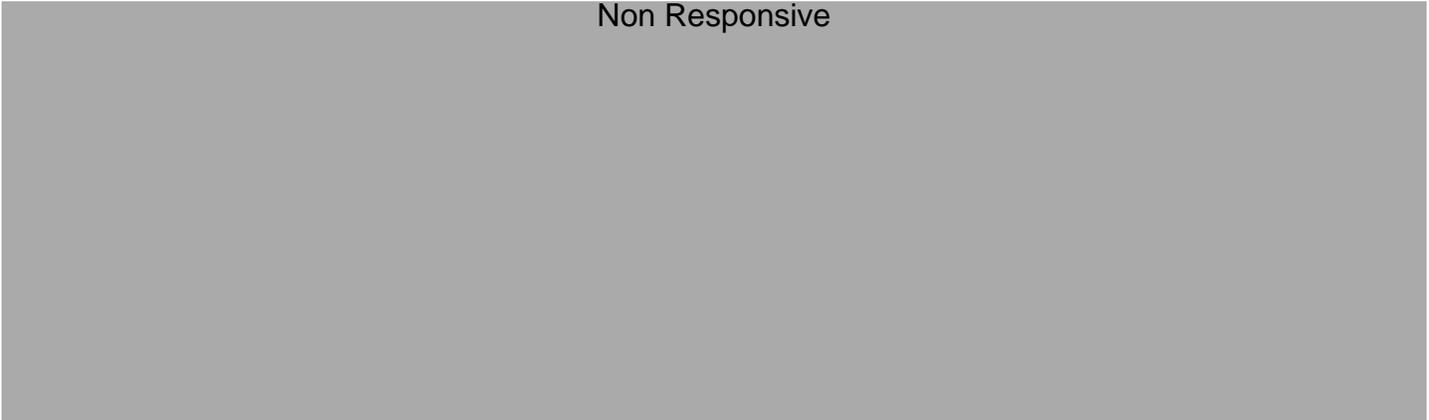
Lily Mulugeta

Dianne Murphy

Maura O'Leary [Redacted] Non Responsive

**Agenda**

Non Responsive



11:10	NDA	206323	Codeine Phosphate/Chlorpheniramine Maleate (Partial Waiver/Deferral) w/Agreed iPSP	Relief of cough and symptoms associated with upper respiratory allergies or a common cold
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Non Responsive



4 Pages have been Withheld in Full as Non Responsive immediately following this page.

Non Responsive

**Codeine Phosphate/Chlorpheniramine Maleate (Partial Waiver/Deferral/Plan)**

- Proposed Indication: Relief of cough and symptoms associated with upper respiratory allergies or a common cold
- The Division noted that the plan is the same as the one agreed upon in the Agreed iPSP for this product.
- The division clarified that the policy related to cough and cold products is evolving because of the recent EMA decision to contraindicate all codeine products in children less than 12 years of age because of the safety concern related to codeine and ultrametabolizers (CYP 2D6). However, the current plan included in the agreed iPSP is to obtain PK and safety data in patients 6 years of age and older.
- Because of the evolving policies related to codeine-containing products in pediatric patients, the PeRC agreed that the pediatric plan as agreed upon in the iPSP is acceptable. However, the PeRC continues to be interested in identifying a path forward for cough and cold products in pediatric patients (i.e., establishment of efficacy and safety in a segment of the pediatric population so that extrapolation can be relied upon separate from efficacy related to a monograph ruling).
- PeRC Recommendations:
  - The PeRC agreed to the plan for deferred studies in patients 6 to (b) (4) years and a waiver in patients 0 to less than 6 years as stated in the Agreed iPSP.

Non Responsive

Non Responsive

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/s/  
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GEORGE E GREELEY  
06/16/2015



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: June 12, 2015**

<b>To:</b> Lara Noah Director, Regulatory Affairs	<b>From:</b> Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
<b>Company:</b> Spriaso LLC c/o Nexgen Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 719- 576-3087	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> 719-579-9650	<b>Phone number:</b> (240) 402-3720
<b>Subject</b> NDA 206323- codeine phosphate and chlorpheniramine maleate- Label information Request, #2	

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**Total no. of pages including cover: 3**

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**Comments:**

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

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Your submission dated August 22, 2014, to NDA 206323, for codeine phosphate and chlorpheniramine maleate extended release tablets, is currently under review. We have the following request for information. We may have additional comments as we continue our review.

1. Carton and Container Label

- a. Revise the carton and container labels such that the drug product strength is consistent with the established name, i.e., Codeine Phosphate and Chlorpheniramine Maleate Extended-Release Tablets, 54.3/8 mg.
- b. Include a statement in smaller text indicating that 54.3 mg of codeine phosphate is equivalent to 40 mg of codeine.
- c. Remove reference, in all parts of the labeling where there is a description of the dosage form, as a (b) (4) since this terminology is used only (b) (4)

Please provide a response to the requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by 12 noon on Friday June 12, 2015. 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.

Initiated by:	CMC	6/12/15
Cleared by:	SBarnes	6/12/15
Finalized:	LMusse	6/12/15

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/s/  
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LAURA MUSSE  
06/10/2015

NDA 206323



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: June 3, 2015**

<b>To:</b> Lara Noah Director, Regulatory Affairs	<b>From:</b> Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
<b>Company:</b> Spriaso LLC c/o Nexgen Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 719- 576-3087	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> 719-579-9650	<b>Phone number:</b> (240) 402-3720
<b>Subject:</b> NDA 206323 - (codeine phosphate and chlorpheniramine maleate)- Information Request for PMR/PMC Commitment	

**Total no. of pages including cover: 3**

**Comments:**

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

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Your NDA submission dated, August 22, 2014, for codeine phosphate and chlorpheniramine maleate, is currently under review. We request written confirmation of your agreement to conduct the following post marketing studies and to the schedule milestones.

1. Pharmacokinetic Study: Conduct a single-dose pharmacokinetic study whose primary objective is to identify the dose(s) of Codeine Phosphate and Chlorpheniramine Maleate ER tablet that results in exposures of codeine and chlorpheniramine in approximately 25-35 children and adolescents 6 to 17 years of age that are similar to the exposures seen in adults at the recommended dose. The population eligible for enrollment should be otherwise healthy children and adolescents with cough/cold symptoms for whom a combination product that includes an opioid antitussive would be an appropriate symptomatic treatment.

Final Protocol Submission:	July	2015
Study Completion:	January	2017
Final Report Submission:	October	2017

2. Safety Study: Conduct an open-label, multi-dose safety and tolerability study in children and adolescents 12 to 17 years of age. The population eligible for the study would be children and adolescents with cough/cold symptoms for whom a combination product that includes an opioid antitussive would be an appropriate symptomatic treatment. The study will enroll a total of approximately 400 children aged 6 to 17 inclusive in two cohorts (6-11 years, 12 to 17 years). The dose used in this study will be based upon the results of the pharmacokinetic study in children and adolescents ages 6 to 17 years.

3.

Final Protocol Submission:	June	2018
Study Completion:	December	2020
Final Report Submission:	July	2021

Respond to these Information Requests by email ([Laura.Musse@fda.hhs.gov](mailto:Laura.Musse@fda.hhs.gov)) or facsimile (301-796-9728), by Wednesday June 12, 2015. 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.

Drafted by:	LMusse	Date:	6/2/15
Revised by:	SBarnes	Date:	6/2/15
Clearance:	SBarnes	Date:	6/2/15
	ADurmowicz/XWang	Date:	6/3/15
Finalized:	LMusse	Date:	6/3/15
File Name:	PMC/PMR Commitment	Date:	6/3/15

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/s/  
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LAURA MUSSE  
06/03/2015



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: June 2, 2015**

<b>To:</b> Lara Noah Director, Regulatory Affairs	<b>From:</b> Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
<b>Company:</b> Spriaso LLC c/o Nexgen Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 719- 576-3087	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> 719-579-9650	<b>Phone number:</b> (240) 402-3720
<b>Subject</b> NDA 206323- codeine phosphate and chlorpheniramine maleate- Label information request	

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**Total no. of pages including cover: 39**

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**Comments:**

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Your submission dated August 22, 2014, to NDA 206323, for codeine phosphate and chlorpheniramine maleate extended release tablets is currently under review. The enclosed label contains the Division's edits to your propose package insert (PI) and carton and container labels. Edits are primarily based on the labeling of recently approved codeine-containing cough and cold extended release product(s). The Division's proposed insertions are underlined; deletions are in strike-outs. These comments are not all-inclusive and we may have additional comments as we continue our review. We also have the following comments:

1. Prescribing Information

Section 11: Description: The description of the chemical name for codeine and the figure of the structure of codeine should reflect the hemihydrate (b) (4)

2. Carton and Container Label

- a. Revise the presentation of the name from (b) (4) to the same color to improve readability of the name.
- b. Ensure the prominence of both active ingredients (codeine phosphate and chlorpheniramine maleate) are equal. As currently presented, chlorpheniramine maleate appears to have greater prominence than codeine phosphate.

3. Request for inclusion of a Patient Information Sheet

As you are aware, your proposed extended release codeine phosphate and chlorpheniramine maleate product label includes a Boxed Warning related to the codeine component. We feel that in order to help ensure patients are aware of the safety issues related to codeine that a Patient Information Sheet should be included with the labeling as has been done for a similar extended release codeine and chlorpheniramine containing cough and cold product and request that you submit one for review. We anticipate that it would be highly similar to the Patient Information Sheet for the similar recently approved extended release codeine and chlorpheniramine containing product.

Please provide a response to the requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by 12 noon on Monday June 8, 2015. 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.

Initiated by:	Clinical	6/2/15
Cleared by:	SBarnes	6/2/15
	ADurmowicz	6/3/15
Finalized:	LMusse	6/3/15
File Name:	Label IR R1	6/3/15

37 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)  
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LAURA MUSSE  
06/03/2015



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 Center for Drug Evaluation and Research  
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

**DATE:** May 19, 2015

<b>To:</b> Lara Noah Director, Regulatory Affairs	<b>From:</b> Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
<b>Company:</b> Spriaso LLC c/o Nexgen Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 719- 576-3087	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> 719-579-9650	<b>Phone number:</b> (240) 402-3720
<b>Subject</b> NDA 206323- (codeine phosphate and chlorpheniramine maleate) Information Request	

**Total no. of pages including cover:** 3

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

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NDA 206323  
Spriaso LLC

Your submission dated August 22, 2014, to NDA 206323, is currently under review. We have the following request for information:

The drug product specification must reflect the entire product name and the correct dosage, therefore revise the drug product specification as follows:

Change the assay for codeine phosphate from [REDACTED] (b) (4) [REDACTED] to "Codeine phosphate: [REDACTED] (b) (4) % of 54.3 mgs.

Please provide a response to the requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by 12 noon on Thursday, May 21, 2015. 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.

Initiated by:	YHu	5/18/15
Cleared by:	CJackson for SBarnes	5/19/15
Finalized:	LMusse	5/19/15
File Name:	FDA CMC IR	5/19/15

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LAURA MUSSE  
05/19/2015



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Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** May 1, 2015

<b>To:</b> Lara Noah Director, Regulatory Affairs	<b>From:</b> Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
<b>Company:</b> Spriaso LLC c/o Nexgen Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 719- 576-3087	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> 719-579-9650	<b>Phone number:</b> (240) 402-3720
<b>Subject</b> NDA 206323- codeine phosphate and chlorpheniramine maleate Information Request	

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Your submission dated August 22, 2014, to NDA 206323, is currently under review. We have the following requests for information:

1. You responded on March 24, 2015 that you revised the product acceptance criterion deleting NLT from the specification criterion, however the correction you stated in file 32p51-spec.pdf has not been made. Revise the specification criterion as requested.

The correct specification criterion should read as follows:

Codeine Phosphate:

1 hour – (b) (4) 0%  
4 hours – (b) (4) 0%  
6 hours – (b) (4) 0%  
12 hours –NLT (b) (4) 0%

Chlorpheniramine Maleate:

1 hour – (b) (4) 0%  
4 hours – (b) (4) 0%  
6 hours – (b) (4) 0%  
12 hours-NLT (b) (4) 0%

2. You responded on April 24, 2015, that you deleted different contents in various serial submissions to ascertain that only the current documents were showing in the “Current view” tab, however there continues to be two 3.2.P.5 sections under 3.2.P reflecting two different specifications (different dissolution specification). Update the file to make it consistent with our April 22, 2015 request.

Please provide a response to the request by email ([Laura.Musse@fda.hhs.gov](mailto:Laura.Musse@fda.hhs.gov)) or facsimile (301-796-9728), by 12 noon on Tuesday, May 3, 2015. Your response must also be submitted formally to your NDA application shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

Initiated by:	PDuan/KKitchens	4/30/15
Cleared by:	SBarnes	5/1/15
Finalized:	LMusse	5/1/15
File Name:	Biopharm IR	5/1/15

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/s/  
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LAURA MUSSE  
05/01/2015



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** April 30, 2015

<b>To:</b> Lara Noah Director, Regulatory Affairs	<b>From:</b> Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
<b>Company:</b> Spriaso LLC c/o Nexgen Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 719- 576-3087	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> 719-579-9650	<b>Phone number:</b> (240) 402-3720
<b>Subject</b> NDA 206323- (codeine phosphate and chlorpheniramine maleate) Information Request	

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**Total no. of pages including cover:** 3

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Your submission dated August 22, 2014, to NDA 206323, is currently under review. We have the following requests for information:

You have not provided adequate information to justify a specification of NMT (b) (4) % for (b) (4) in the drug product.

In order to justify the higher specification, you must provide additional data (e.g. circulating human plasma levels of (b) (4) following chlorpheniramine administration to allow comparison between human plasma levels of (b) (4) versus levels in your product at the proposed level of NMT (b) (4) %).

In the absence of additional supportive information, lower the specification of (b) (4) to NMT (b) (4) %.

Please provide a response to the requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by 12 noon on Wednesday, May 6, 2015. 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.

Initiated by:	MWood	4/30/15
Cleared by:	SBarnes	4/30/15
Finalized:	LMusse	4/30/15
File Name:	FDA Nonclinical IR	4/30/15

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/s/  
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LAURA MUSSE  
04/30/2015



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Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** April 22, 2015

<b>To:</b> Lara Noah Director, Regulatory Affairs	<b>From:</b> Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
<b>Company:</b> Spriaso LLC c/o Nexgen Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 719- 576-3087	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> 719-579-9650	<b>Phone number:</b> (240) 402-3720
<b>Subject</b> NDA 206323- (codeine phosphate and chlorpheniramine maleate) Information Request	

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**Total no. of pages including cover:** 3

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**Comments:**

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

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Your submission dated August 22, 2014, to NDA 206323, is currently under review. We have the following requests for information:

You must maintain your application submissions in such a way that only the current documents/modules are showing in the “current” view tab.

1. Your application has two 3.2.P. Modules, which appear to have different contents. Please identify which one of these is the current version.
2. One of the 3.2.P.5.1 sections contains four different versions of the drug product specification. Please identify which one of these is the current version.

Please provide a response to the requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by 12 noon on Friday, April 24, 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.

**Clearance**

Initiated by:	HYong/JPinto	4/20/15
Cleared by:	SBarnes	4/22/15
Finalized:	LMusse	4/22/15
File Name:	FDA CMC IR	4/22/15

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/s/  
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LAURA MUSSE  
04/22/2015



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** April 13, 2015

<b>To:</b> Lara Noah Director, Regulatory Affairs	<b>From:</b> Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
<b>Company:</b> Spriaso LLC c/o Nexgen Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 719- 576-3087	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> 719-579-9650	<b>Phone number:</b> (240) 402-3720
<b>Subject</b> NDA 206323- (codeine phosphate and chlorpheniramine maleate) Information Request	

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**Total no. of pages including cover:** 3

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Your submission dated August 22, 2014, to NDA 206323, is currently under review. We have the following requests for information:

The codeine phosphate impurity (b) (4) possesses a (b) (4)

(b) (4) submitted under DMF

(b) (4) Based on currently available data, we cannot agree that the weight-of-evidence indicates that (b) (4) is not genotoxic; therefore, the current (b) (4) drug product specification of NMT (b) (4)% is not acceptable. Lower the specification limit for this impurity in the final drug product to NMT (b) (4)%.

Please provide a response to the requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by 12 noon on Friday, April 17, 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.

Initiated by:	MWood	4/10/15
Cleared by:	SBarnes	4/13/15
Finalized:	LMusse	4/13/15
File Name:	FDA Nonclinical IR	4/13/15

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/s/  
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LAURA MUSSE  
04/13/2015



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE: April 10, 2015**

<b>To:</b> Lara Noah Director, Regulatory Affairs	<b>From:</b> Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
<b>Company:</b> Spriaso LLC c/o Nexgen Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 719- 576-3087	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> 719-579-9650	<b>Phone number:</b> (240) 402-3720
<b>Subject</b> NDA 206323- (codeine phosphate and chlorpheniramine maleate) Pediatric Study Plan Information Request	

**Total no. of pages including cover: 3**

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NDA 206323  
codeine phosphate and chlorpheniramine maleate  
Spriaso LLC c/o Nexgen Pharma

Your submission dated August 22, 2014, is currently under review. We have the following requests for information:

We acknowledge your response under IND 106992 submission dated August 15, 2014, to our comments dated July 5, 2014, regarding the Pediatric Study Plan (PSP) for your proposed codeine and chlorpheniramine product. We do not agree with your rationale that (b) (4)

Therefore, submit a revised PSP to NDA 206323 in accordance with the accompanying cough and cold combination product guidelines. The PSP should include the set of safety studies that we had originally conveyed to you on July 5, 2014. In addition to the required studies, note the timelines that are considered acceptable for their completion. Note that failure to agree on pediatric post-marketing required studies would be an approvability issue.

Please provide a response to the request by email ([Laura.Musse@fda.hhs.gov](mailto:Laura.Musse@fda.hhs.gov)) or facsimile (301-796-9728), by 12 noon on Friday, April 17, 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.

## **General Cough and Cold Combination Product PREA Requirements**

Below are our current general requirements for pediatric PMR studies for opioid-containing combination cough and cold products. The requirements could change in the future based on changes in regulatory policy or the acquisition.

### Waivers and Deferrals

- Waiver for pediatric patients less than 6 years of age based on evidence the product would be unsafe or ineffective
- Deferral for pediatric patients 6-17 years of age until drug product is approved for the adult population.

### Pediatric Studies

- A single-dose pharmacokinetic study whose primary objective is to identify the dose(s) of INSERT PRODUCT that result in exposures of INSERT DRUG COMPONENTS in children (aged 6 to 11) and adolescents (aged 12 to 17 years) that are similar to the exposures seen in adults at the recommended dose. The population eligible for enrollment should be otherwise healthy children and adolescents with cough/cold symptoms for whom a combination product that includes an opioid antitussive would be an appropriate symptomatic treatment. The results of this study will be used to determine the appropriate dose of your proposed product to evaluate in a safety study in children 6-17 years of age.
- An open-label multi-dose safety and tolerability study at the dose(s) that result in drug exposures in children (aged 6 to 11) and adolescents (aged 12 to 17 years) that are similar to the exposures seen in adults at the recommended dose. The population eligible for the study would be children and adolescents with cough/cold symptoms for whom a combination product that includes an opioid antitussive would be an appropriate symptomatic treatment. The study will enroll a total of approximately 400 children aged 6 to 17 inclusive in two cohorts (6-11 years, 12 to 17 years).

### Timelines

In general, the submission of the single-dose PK study report should take no longer than 2-3 years from the start. The submission of the safety study report should take no longer than about 3-4 years from the start.

NDA 206323- Clinical IR Clearance page.

Initiated by:	XWang/ADurmowicz	4/09/15
Clearance:	ADurmowicz	4/10/15
	CJackson	4/10/15
Finalized:	LMusse	4/10/15
File Name:	FDA Clinical/PSP IR	4/10/15

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/s/  
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LAURA MUSSE  
04/10/2015



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: March 26, 2015**

<b>To:</b> Lara Noah Director, Regulatory Affairs	<b>From:</b> Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
<b>Company:</b> Spriaso LLC c/o Nexgen Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 719- 576-3087	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> 719-579-9650	<b>Phone number:</b> (240) 402-3720
<b>Subject</b> NDA 206323- codeine phosphate and chlorpheniramine maleate -Information Request	

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**Total no. of pages including cover: 3**

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Your submission dated August 22, 2014, to NDA 206323, is currently under review. We have the following requests for information:

1. Your specification for the chlorpheniramine maleate API does not meet the requirements in the current chlorpheniramine maleate monograph in USP 37. Include the following tests in your specification as per USP 37:
  - a. A second identification test, which is based on the retention times of the (b) (4) and chlorpheniramine peaks, as obtained in the Assay test.
  - b. A test for Organic Impurities using the method defined in the current USP monograph or its equivalent. The acceptance criteria for the individual impurities and total impurities should meet the USP monograph requirements.
  - c. Optical Rotation.
2. The particle size distribution of the chlorpheniramine maleate API should be controlled to ensure the content uniformity of the final product, in which the chlorpheniramine maleate API accounts for only (b) (4)% w/w.
  - a. Include particle size distribution in the chlorpheniramine maleate API specification.
  - b. Provide batch data to justify the acceptance criteria.
3. Revise the Assay test method for Chlorpheniramine Maleate API from (b) (4) to the HPLC method defined in the current USP monograph or its equivalent.
4. As you stated, the drugs are (b) (4), therefore you must provide a rationale for including (b) (4) (polysorbate 80) in the formulation.
5. Provide the batch analysis data for the immediate-release tablets used as the reference product. If the data has been included in the NDA, provide the location of the data.
6. The Master Batch Record (MBR) for the preparation of (b) (4) lactose monohydrate and polysorbate 80 (b) (4) did not specify the (b) (4)  
(b) (4)  
(b) (4)
7. (b) (4)

- (b) (4)
8. (b) (4)
9. Justify the acceptance criterion of NMT (b) (4) % for the RSD values for the tests on (b) (4) or tighten it to NMT (b) (4) %.
10. (b) (4)
11. (b) (4)
12. The acceptance criterion of NMT (b) (4) % for the degradant (b) (4) in the drug product specification exceeds the ICH Q3B qualification threshold (0.5%). Revise the acceptance criterion to NMT (b) (4) % or provide safety information to justify a higher limit for this degradant.
13. The acceptance criterion (NMT (b) (4) %) in the drug product specification for Total Degradants of each drug is not justified by the stability data. Tightened the acceptance criterion to NMT (b) (4) % for both drugs.

14. Include microbial limits in the drug product specification or provide the rationale and data to justify the omission of microbial limits in the specification.
15. In conforming to the requirements in the applicable sections of the Code of Federal Regulations (CFR), Title 21, Indirect Food Additives:
  - a. Clarify whether all the materials of the container closure system, including the ingredients added to the polymers and those used in the fabrication of the containers, conform to the requirements.
  - b. Provide the CFR reference(s) that each of the materials conforms to or other information to support the safety of the materials.
16. Explain the timepoint-to-timepoint variability in some of the degradant levels observed during your drug product stability studies. For example, the level of (b) (4) in the Lot 100097 varied from (b) (4) % at the initial timepoint to (b) (4) % at six months to (b) (4) % at 18 months.
17. Provide the statistical analysis for the drug product degradant stability data to justify your proposed 24-months expiration dating period. Note the limit for the degradant (b) (4) in the drug product should be NMT (b) (4) % in accordance with the ICH Q3B qualification threshold.
18. Provide photostability data for the drug product. Refer to the ICH Q1B.
19. Your NDA does not include drug product stability data on production batches. In accordance with the ICH Q1A:
  - a. Provide a commitment to place the first three production batches on long term stability studies through the proposed shelf life and on accelerated studies for 6 months.
  - b. Include the accelerated stability studies in your post-approval stability protocol for the first three production scale batches in addition to the long-term stability studies.

Please provide a response to the request by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by 12 noon on Friday, April 10, 2015. Your response must also be submitted formally to your NDA application shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

Initiated by:	YHu/CBertha	3/25/15
Cleared by:	SBarnes	3/26/15
Finalized:	LMusse	3/26/15
File Name:	CMC IR	3/26/15

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/s/  
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LAURA MUSSE  
03/26/2015



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: March 24, 2015**

<b>To:</b> Lara Noah Director, Regulatory Affairs	<b>From:</b> Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
<b>Company:</b> Spriaso LLC c/o Nexgen Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 719- 576-3087	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> 719-579-9650	<b>Phone number:</b> (240) 402-3720
<b>Subject</b> NDA 206323- codeine phosphate and chlorpheniramine maleate Information Request	

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Your submission dated August 22, 2014, to NDA 206323, is currently under review. We have the following requests for information:

The dissolution specification you stated in file 32p51-spec.pdf as follows is not correct:

Codeine Phosphate

1 hr: (b) (4) %  
4 hrs: (b) (4) %  
6 hrs: (b) (4) %  
12 hrs: NLT (b) (4) %

Chlorpheniramine Maleate

1 hr: (b) (4) %  
4 hrs: (b) (4) %  
6 hrs: (b) (4) %  
12 hrs: NLT (b) (4) %

The correct specification should be as we requested in the information request dated February 23, 2015.

Delete "NLT" from the specs in 1hr , 4hr, and 6 hrs for each drug component):

Codeine Phosphate:

1 hour - (b) (4) %  
4 hours - (b) (4) %  
6 hours - (b) (4) %  
12 ours -NLT (b) (4) %

Chlorpheniramine Maleate:

1 hour - (b) (4) %  
4 hours - (b) (4) %  
6 hours - (b) (4) %  
12 ours -NLT (b) (4) %

Please provide a response to the request by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by 12 noon on Friday, March 27, 2015. Your response must also be submitted formally to your NDA application shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

Initiated by:	PDuan/KKitchens	3/23/15
Cleared by:	SBarnes	3/23/15
Finalized:	LMusse	3/23/15
File Name:	Biopharm IR	3/23/15

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/s/  
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LAURA MUSSE  
03/24/2015



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

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**DATE:** February 19, 2014

<b>To:</b> Lara Noah Director, Regulatory Affairs	<b>From:</b> Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
<b>Company:</b> Spriaso LLC c/o Nexgen Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 719- 576-3087	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> 719-579-9650	<b>Phone number:</b> (240) 402-3720
<b>Subject</b> NDA 206323- codeine phosphate and chlorpheniramine maleate Information Request	

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Your submission dated August 22, 2014, to NDA 206323, is currently under review. We have the following requests for information:

Based on the data you submitted for all the batches tested in response to our information request dated January 20, 2015, we recommend the following acceptance criteria for your drug product:

a. Codeine Phosphate:

1 hour – (b) (4) 0%  
4 hours – (b) (4) 0%  
6 hours – (b) (4) 0%  
12 ours –NLT (b) (4) %

b. Chlorpheniramine Maleate:

1 hour – (b) (4) 0%  
4 hours – (b) (4) 0%  
6 hours – (b) (4) 0%  
12 ours –NLT (b) (4) %

Implement the recommended dissolution acceptance criteria and provide the revised specifications table with the updated acceptance criteria for the dissolution test.

Please provide a response to the requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by 12 noon on Wednesday, March 4, 2015. 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.

Initiated by:	Biopharm (Duan, Peng)	2/19/15
Cleared by:	SBarnes	2/23/15
Finalized:	LMusse	2/23/15
File Name:	Biopharm IR	2/23/15

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LAURA MUSSE  
02/23/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 206323

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

Spriaso, LLC  
46 Corporate Park, Suite 100  
Irvine, CA 92606

ATTENTION: Lara Noah  
Director, Regulatory Affairs

Dear Ms. Noah:

Please refer to your New Drug Application (NDA) dated and received August 22, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Codeine Phosphate and Chlorpheniramine Maleate Extended Release Tablets, 40 mg/8 mg.

We also refer to your correspondence, dated and received November 25, 2014, requesting review of your proposed proprietary name, Rinotuss12.

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





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.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

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}*

Todd Bridges, RPh  
Deputy Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES  
02/18/2015



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** January 20, 2015

<b>To:</b> Lara Noah Director, Regulatory Affairs	<b>From:</b> Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
<b>Company:</b> Spriaso LLC c/o Nexgen Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 719- 576-3087	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> 719-579-9650	<b>Phone number:</b> (240) 402-3720
<b>Subject</b> NDA 206323- (codeine phosphate and chlorpheniramine maleate) Information Request	

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Your submission dated August 22, 2014, to NDA 206323, is currently under review. We have the following requests for information:

In the dissolution results of your stability data (Section 3.2.P.8.3), you only submitted the mean value. In order to evaluate your proposed acceptance criteria for dissolution, you will need to submit the raw dissolution data for your stability reports including the complete data (i.e., individual value, mean, and standard deviation).

Please provide a response to the requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by 12 noon on Friday, January 30, 2015. Your response must also be submitted formally to the IND shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

**Clearance History**

Initiated by:	Biopharm	1/20/15
Cleared by:	LJafari	1/20/15

Finalized: LMusse 1/20/15  
File Name: FDA IR 1/20/15

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LAURA MUSSE  
01/20/2015



NDA 206323

FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED

Spiraso LLC.  
C/O Nexgen Pharma Inc.  
46 Corporate Park, Suite 100  
Irvine, CA 92606

Attention: Lara Noah,  
Director, Regulatory Affairs

Please refer to your New Drug Application (NDA) dated August 20, 2014, received August 22, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for codeine phosphate and chlorpheniramine maleate, extended release, 40 mg/8 mg tablet.

We also refer to your amendment dated October 23, 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 commitment requests by November 24, 2014.

During our filing review of your application, we identified the following potential review issues:

### **Clinical Pharmacology**

1. Your food effect study (1084-12-002) indicates that the presence of a high-fat, high-calorie meal leads to 28% increase in C<sub>max</sub> of the codeine component in your ER product. Considering the safety risks associated with codeine, this observed food effect is a potential review issue. The totality of evidence will be considered in evaluating the risk-

benefit profile of your product for the proposed indication and for the proposed population.

2. Your multiple-dose study (1084-13-001) indicates that the systemic concentrations of codeine and chlorpheniramine from your extended release product are lower than those observed with the respective immediate release formulations in the last few hours of the 12 hour dosing interval. The implication of the lower systemic concentrations is a potential review issue.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

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).
2. Conduct a search for post-marketing adverse events reported for the active ingredients of your proposed drug for the period of last 5 years, including published literatures, FDA AERS database, and the company's database, if any. Submit the search result as tabular and descriptive summaries.
3. We note that microbial limits testing is not included in either the drug product specification or the post approval stability protocol. If you propose to waive microbial limits release and stability testing for your drug product, this proposal may be acceptable provided adequate upstream controls are established and documented. More information on your process is needed. Address the following points:
  - a. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.
    - i. Define the maximum processing time [REDACTED] (b) (4).
    - ii. Define the maximum holding time [REDACTED] (b) (4).
  - b. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
  - c. Describe activities taken when microbiological acceptance criteria are not met at control points.

4. If you elect to perform microbial limits testing for drug product release and stability, please submit a revised drug product specification and stability protocol indicating microbial limits testing and corresponding acceptance criteria, as well as methods suitability verification data for the microbiological methods used to demonstrate the microbiological quality of the drug product.

### **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.
2. Remove the yellow highlights throughout the label.
3. Insert control substance symbol at the end of the product title.
4. Insert route of administration in product title.
5. Add Important Limitations of Use section after Indications and Usage section.
6. Under the Contraindication section add the Pregnancy Category C and reference in the contraindications section of the FPI section.

### **Highlights (HL)**

7. Reconfigure the margins to ½ inch on all sides and in-between the columns.
8. Edit the length of HL to the ½ page or less requirement.

9. Edit the product name to appear in UPPERCASE.
10. Insert the year in the Initial US Approval section.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by November 24, 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 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.

We note that you have submitted pediatric studies with this application for pediatric patients (b) (4). Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

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

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/s/  
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LYDIA I GILBERT MCCLAIN  
11/04/2014



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: October 30, 2014**

<b>To:</b> Lara Noah Director, Regulatory Affairs	<b>From:</b> Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
<b>Company:</b> Spriaso LLC c/o Nexgen Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 719- 576-3087	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> 719-579-9650	<b>Phone number:</b> (240) 402-3720
<b>Subject</b> NDA 206323-(codeine phosphate and chlorpheniramine maleate) Information Request	

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**Total no. of pages including cover: 3**

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**Comments:**

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Your submission dated August 22, 2014, to NDA 206323, is currently under review. We have the following requests for information:

In addition to comparing the codeine plasma profile from your ER product to that of 10 and 60 mg codeine IR products separately, as requested in the information request sent on October 20, 2014, also provide a single chart that includes the following four steady state plasma profiles for a 24-hour dosing period:

1. Codeine 10 mg IR administered every 6 hours using simulated PK data from your own reference IR product (lowest approved OTC).
2. Codeine 20 mg IR administered every 4 hours using simulated PK data from your own reference IR product (highest approved OTC).
3. Codeine with your 40 mg ER product under fed conditions.
4. Codeine with your 40 mg ER product under fasted conditions.

Please provide a response to the requests by email ([Laura.Musse@fda.hhs.gov](mailto:Laura.Musse@fda.hhs.gov)) or facsimile (301-796-9728), by 12 noon on Friday, November 7, 2014. Your response must also be submitted formally to the IND shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

Initiated by: Sheetal/Brar **October 29, 2014**  
Cleared by: SBarnes **October 30, 2014**  
Finalized: LMusse **October 30, 2014**  
File Name: Third CP IR **October 30, 2014**

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/s/  
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LAURA MUSSE  
10/30/2014



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Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: October 20, 2014**

<b>To:</b> Lara Noah Director, Regulatory Affairs	<b>From:</b> Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
<b>Company:</b> Spriaso LLC c/o Nexgen Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 719- 576-3087	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> 719-579-9650	<b>Phone number:</b> (240) 402-3720
<b>Subject</b> NDA 206323-(codeine phosphate and chlorpheniramine maleate) Information Request	

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**Total no. of pages including cover: 3**

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Your submission dated August 22, 2014, to NDA 206323, is currently under review. We have the following requests for information:

1. We have reviewed your response to our information request dated 9/12/2014. Provide a table comparing predicted or observed steady state PK parameters for codeine at 10 and 60 mg with the approved codeine IR tablets, as well as using your own codeine IR product that was employed in the relative BA studies. If similar, this will provide support for the submitted PK simulations. If significantly different, conduct the same simulations using simulated PK data from your own codeine IR product. Submit PK datasets for all the simulations.
2. In your relative BA single and multiple dose studies, it is not clear which C<sub>max</sub> (C<sub>max</sub> after the first dose [C<sub>max1</sub>] or C<sub>max</sub> after the second dose [C<sub>max2</sub>]) of the reference IR, was used in the BE analyses to compare against the C<sub>max</sub> of the ER. Please clarify. Provide BE analyses using both C<sub>max1</sub> and C<sub>max2</sub> separately, for both your single dose and multiple dose studies. Similarly, provide BE analyses for ER fed vs IR fasted, using both C<sub>max1</sub> and C<sub>max2</sub> of the IR formulation. In addition to providing the BE analyses, also provide a table listing the C<sub>max1</sub> and C<sub>max2</sub> PK parameters employed in the analyses.
3. Acknowledging that you employed Codeprex (NDA 21369 approved in 2004) labeling to construct the label for your ER product, we recommend that you conduct a literature search to be able to update your label with the most recent information for both the drugs, for e.g., PK in special populations such as renal and hepatic impairment.

Please provide a response to the requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by 12 noon on Friday, November 7, 2014. Your response must also be submitted formally to the IND shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

Initiated by: Sheetal/Brar **October 20, 2014**  
Cleared by: MJordanGarner (for) SBarnes **October 20, 2014**  
Finalized: LMusse **October 20, 2014**  
File Name: Second PT IR **October 20, 2014**

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/s/  
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LAURA MUSSE  
10/20/2014



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: September 12, 2014**

<b>To:</b> Lara Noah Director, Regulatory Affairs	<b>From:</b> Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
<b>Company:</b> Spriaso LLC c/o Nexgen Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 719- 576-3087	<b>Fax number:</b> (301) 796-9728
<b>Phone number:</b> 719-579-9650	<b>Phone number:</b> (240) 402-3720
<b>Subject</b> NDA 206323- (codeine phosphate and chlorpheniramine maleate) Information Request	

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**Total no. of pages including cover: 3**

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**Comments:**

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Your submission dated August 22, 2014, to NDA 206323, is currently under review. We have the following requests for information:

1. Your multiple dose relative BA/BE study (1084-13-001) indicates that between 6-12 hours, codeine systemic concentrations with your ER product are lower than with the IR product (Figure 14.2.1-1 on page 77/119 of your study report). Provide PK simulations comparing the systemic concentrations of codeine with your ER product through the dosing interval (0-12 hours at steady state) with codeine IR PK data at 10 mg (lowest approved codeine OTC dose for the indication you are seeking) to evaluate how codeine systemic concentrations with your product compare with the IR reference product at 10 mg. You may use [Drugs@FDA](mailto:Drugs@FDA) as a resource to obtain PK data for IR codeine products.
2. Your food effect study (1084-12-002) indicates that presence of food leads to 28% increase in Cmax of codeine (Table 14.2.1-2 on page 66/884 of your study report). Provide PK simulations comparing the systemic concentrations of codeine with your ER product through the dosing interval (0-12 hours) with codeine IR PK data at 60 mg (highest approved codeine OTC dose for the indication you are seeking) to evaluate how codeine systemic concentrations with your product in the presence of food, compare with the maximum expected codeine systemic concentrations with the IR reference product at 60 mg. You may use [Drugs@FDA](mailto:Drugs@FDA) as a resource to obtain PK data for IR codeine products.
3. Provide contents of the high-fat breakfast used in your food effect study 1084-12-002.

Please provide a response to the requests by email ([Laura.Musse@fda.hhs.gov](mailto:Laura.Musse@fda.hhs.gov)) or facsimile (301-796-9728), by 12 noon on Friday, September 26, 2014. Your response must also be submitted formally to the IND shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

Initiated by:	Sheetal/Brar	9/12/14
Cleared by:	SBarnes	9/12/14
Finalized:	LMusse	9/12/14

File Name: FDA IR

9/12/14

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/s/  
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LAURA MUSSE  
09/12/2014



NDA 206323

**NDA ACKNOWLEDGMENT**

Spiraso LLC.  
C/O Nexgen Pharma Inc.  
46 Corporate Park, Suite 100  
Irvine, CA 92606

Attention: Lara Noah,  
Director, Regulatory Affairs

Dear Ms. Noah:

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: codeine phosphate and chlorpheniramine maleate, ER Tablet, 40 mg; 8 mgs

Date of Application: August 20, 2014

Date of Receipt: August 22, 2014

Our Reference Number: NDA 206323

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 October 21, 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](mailto: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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LAURA MUSSE  
08/27/2014



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** October 10, 2013, at 12 P.M.  
**Meeting Location:** White Oak, Building 22, Conference Room 1309

**Application Number:** 106992  
**Product Name:** codeine/chlorpheniramine melete

**Indication:** upper respiratory allergies (b) (4)  
**Sponsor/Applicant Name:** Spriaso, LLC

**Meeting Chair:** Lydia Gilbert McClain, M.D.  
**Meeting Recorder:** Laura Musse, R.N., M.S., C.R.N.P.

**FDA ATTENDEES**

Lydia Gilbert McClain, M.D., Deputy Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)  
Anthony Durmowicz, M.D., Clinical Team Leader, DPARP  
Kimberly Witzmann, M.D., Clinical Reviewer, DPARP  
Marcie Wood, Ph.D., Non-Clinical Supervisor, DPARP  
Grace S. Lee, Ph.D., Non-Clinical Reviewer, DPARP  
Prasad Peri, Ph.D., Branch Chief, Branch VIII, Division of New Drug Quality Assessment III (DNDQA III)  
Craig M. Bertha, Ph.D., Acting CMC Lead, DNDQA III  
Yong Hu, Ph.D., Chemistry Reviewer, Division of Pre-Marketing Assessment III, Branch VIII  
Satjit Brar, Ph.D., Clinical Pharmacology, Team Leader, DCPII  
Arun Agrawal, Ph.D., Clinical Pharmacology Reviewer, DCPII  
Kareen Riviere, Ph.D., Biopharmaceutics Reviewer, OPS/ONDQA  
Laura Musse, R.N., M.S. C.R.N.P., Regulatory Project Manager, DPARP

**SPONSOR ATTENDEES**

Firoozeh A. Patel, R.Ph, M.B.A, Chief Executive Officer, Spriaso LLC.  
(b) (4)



(b) (4)

## 1.0 BACKGROUND

This IND was previously owned by Lipocine Inc., and transferred to Spriaso, LLC on July 31, 2013. Lipocine, Inc. had an End of Phase II meeting on June 24, 2010, to seek guidance on the development program for codeine and chlorpheniramine extended-release tablet in support of a 505(b)(2). Spriaso submitted a meeting request to discuss their plan to submit a 505(b)(2) NDA application for codeine 40 mg (as codeine phosphate)/chlorpheniramine maleate 8 mg combination extended release tablet, dosed twice-a-day indicated for upper respiratory allergies (b) (4). In response to the August 9, 2013 request, formally submitted on August 12, 2013 the FDA granted a meeting to be held on October 10, 2013. On October 8, 2013, the FDA provided preliminary comments for the questions posed by Spriaso's briefing document dated September 19, 2013. The sponsor requested further clarification of questions 4, 8 and 10.

## 2. DISCUSSION

### Regulatory

**Question 1.** Does the division agree that inclusion from the above cited (a to e) information would suffice to support the safety and efficacy aspect of 505(b)(2) NDA application? If not, please comment.

#### FDA Response to Question 1:

*In general, the information you state will be included in your NDA submission may suffice to support safety and efficacy of your product, but the determination of such will be a review issue. See also the response to Question 3 below.*

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

### Pharmacology/Toxicology

**Question 2.** Does the Division still agree that no additional non-clinical studies will be needed for our proposed COD/CPM ER tablet?

#### FDA Response to Question 2:

*Yes, we agree. In addition, refer to the Additional Pharmacology/Toxicology Comments below.*

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

**Clinical**

- Question 3.** Does the Division agree that the clinical studies conducted are sufficient to support an NDA application for this product and that no additional clinical studies are required?

**FDA Response to Question 3:**

*While your approach appears adequate to establish bioequivalence, whether no additional studies will be required will be a review issue.*

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

- Question 4.** Does the Division agree that LPCN 1084 can be administered without regard to meals? Please comment.

**FDA Response to Question 4:**

*We do not necessarily agree at this time. The increased C<sub>max</sub> seen with food will be a review issue.*

**Discussion:** *The sponsor stated that increased C<sub>max</sub> seen with food is not clinically relevant. The Division asked the sponsor to justify the clinical relevance of increased C<sub>max</sub> seen with food in the NDA. The totality of the data will be considered by the Division upon NDA submission*

- Question 5.** Does the division agree that the in vitro dissolution data in the presence of alcohol is sufficient and that no additional clinical studies are required to evaluate "alcohol dose dumping" effects?

**FDA Response to Question 5:**

*Based on your current submission, there is insufficient information/data to determine whether your proposed dissolution method is the optimal method for your proposed product; therefore we cannot assess whether the provided in vitro dissolution data in the presence of alcohol is sufficient. We recommend that you submit an amendment to your IND containing a dissolution method development report for your proposed dissolution method justifying that your method is the optimal method (refer to the additional Biopharmaceutics comments). The in vitro alcohol dissolution data can be included in this amendment. If your proposed dissolution method is not optimal, you may have to conduct the in vitro alcohol interaction study in pH 4.5 and 6.8 as well.*

*The following points should be considered during the evaluation of the in vitro alcohol-induced dose dumping of your product:*

1. *Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.*
2. *The following alcohol concentrations for the in vitro dissolution studies are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.*
3. *In general, if the optimal dissolution medium is 0.1N HCl; dissolution profiles in this 0.1 N HCl (pH 1.2) containing the above range of alcohol concentrations would be sufficient.*
  - a. *If the optimal dissolution medium is NOT 0.1N HCl; dissolution profiles using the above range of alcohol concentrations in 0.1N HCl and in the optimal dissolution medium are recommended.*
  - b. *If the optimal dissolution medium has not been identified; dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.*
  - c. *If the dissolution of the ER product is pH independent; then dissolution data in 0.1N HCl with the above range of alcohol concentrations is sufficient.*
4. *The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours.*
5. *The f<sub>2</sub> values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).*
6. *The report with the complete data (i.e., individual, mean, SD, comparison plots, f<sub>2</sub> values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided to FDA for review and comment*

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

**Question 5.** Does the division agree that the product does not need REMS review?

**FDA Response to Question 6:**

*In general, monograph products would not require a REMS, but the determination of need for a REMS specific for your product will be a review issue.*

**Question 7.** Spriaso believes that the literature data will be sufficient and that no additional drug interaction studies or special population studies are warranted. Does the FDA still concur with this evaluation?

**FDA Response to Question 7:**

*While no additional clinical drug interaction studies or special population studies are warranted, we recommend that you review published information and update the clinical pharmacology section of the drug's label for your NDA submission.*

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

**Question 8.** Does the FDA agree that the CMC plan and information for ER and IR product is adequate to support a 505(b) (2) NDA filing for the ER product?

**FDA Response to Question 8:**

*The CMC plan appears reasonable to support a 505b(2) filing, however, the adequacy of the information will be a review issue.*

- a) *Provide the information about the IR tablets in the Pharmaceutical Development section including: manufacturer, batch formula, description of manufacturing process and in-process controls, executed batch record(s), analytical methods and validation, batch analyses data, container and closure system, and stability data.*
- b) *The proposed limit of (b) (4) % for the degradant (b) (4) in your drug product specification exceeds the ICH qualification threshold. Reduce the limit as appropriate or provide adequate qualification information for this degradant.*

**Discussion:** *The sponsor requested clarification regarding the type of data that could be considered qualification information for exceeding the ICH qualification threshold. The Division would consider data from a literature search of the safety level of the impurity. Data from comparison to other approved products on the market, or from a side-by-side comparison of levels of (b) (4) in your product and an approved product(s) on the market may also be acceptable*

*Post meeting note: For a side-by-side comparison of the levels of the (b) (4) in your product and an approved product(s) on the market, the analytical method used for the approved product(s) should be validated as well the method for your product. Provide the analytical method details and validation information in your NDA.*

- c) Justify the omission of microbial limits testing in your ER tablet specification.*
- d) In addition, refer to the Additional Biopharmaceutics Comments below.*

**Question 9.** Does the Division have any comments on the Target Product Profile?

**FDA Response to Question 9:**

*The Division does not have any comments at this time. Labeling will be addressed during the review period.*

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

**Request for Pediatric Study Waiver**

**Question 10.** Does the division agree that (b) (4)

**FDA Response to Question 10:**

*Since the time of your EOP2 meeting in 2010, the requirements regarding pediatric studies and the pediatric waiver process have changed. As you may be aware, 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) to FDA. 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 (also see Section 3.0 below).*

*Note that the FDA definition of pediatrics is any patient up to 18 years of age. Therefore, your PSP should include your plan for 12-17 year olds, and, if you believe you have justification for it, a waiver request (including your justification) for those less than 12 years of age.*

**Discussion:** *The sponsor inquired when they should submit a PSP waiver or deferral. The Division clarified that a pediatric study plan (PSP) should be submitted at or before the time of NDA submission, and that it would need to describe the plans for the full range of ages covered by pediatrics, up to age 18. Specifically, reliance on monograph language alone (for 12-18 years) may not meet the requirements covered under the Pediatric Research Equity Act (PREA). The PSP should provide plans for study or justification for waiver requests for all pediatric age groups.*

### **Brand Name Review**

**Question 11.** Does the division agree that name review submission can be done while the NDA is under review?

#### **FDA Response to Question 11:**

*Yes, the request for name review should be submitted during the NDA review period.*

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

### **Small Business Fee Waiver**

**Question 12.** Does the division agree that the company qualifies for small business application fee waiver and that submission of such request with the NDA is reasonable / acceptable?

#### **FDA Response to Question 12:**

*The division does not decide whether a product qualifies for a small business waiver of the application fee. If an applicant submits a request for a small business waiver and they meet the criteria, we would expect that a waiver would be granted. For further information on the criteria for a waiver please see section 736(d) of the Federal Food, Drug, and Cosmetic Act, as well as FDA's guidance for industry on User Fee Waivers, Reductions, and Refunds for Drug and Biologic Products (the guidance is available on the internet). In addition, please refer to the guidance on how an applicant should submit their waiver request. For further questions regarding waivers you may contact Michael Jones, Office of Management, at 301-796-7900.*

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

**Procedural**

**Question 13.** Does the division have any comments for the detailed listing of the sections of eCTD submission?

**FDA Response to Question 13:**

*We have received your proposed detailed listing of sections for the eCTD submission, and it is correct that you should not be submitting placeholder documents for sections where you have no regulatory content to submit. Please contact [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov) directly if you have any questions about the placement of specific documents or any other questions related to preparing your electronic submission. For additional information, please refer to the following FDA webpages and Guidance provided:*

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM085361>

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm>

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

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

**Pharmacology/Toxicology Comments**

1. *Provide structures of any impurities and degradants of the drug substance and drug product in your NDA submission. Monitor impurities and degradation products of all active ingredients and refer to ICH Guidance [ICH Q3A(R2) and ICH Q3B(R2)] for possible qualification requirements. Impurities or degradants of active ingredients that are identified as structural alerts should be at or below acceptable qualification thresholds to support an NDA as described in the ICH M7 Draft Consensus Guideline, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (Step 2 Version dated February 6, 2013)."*

**Biopharmaceutics Comments**

*Additional comments regarding your ER Product and the development of the dissolution method, establishing dissolution acceptance criteria, and establishing the extended release claim for the ER product are as follows:*

2. **Dissolution Method:** *Provide the dissolution method report including the complete dissolution profile data collected during the development and validation of the proposed dissolution method. The dissolution report should include the following information:*
  - a. *A detailed description of the optimal in vitro dissolution methodology and the developmental parameters (i.e., solubility data for the drug substance across the pH range, selection of the equipment/apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.) that were used to identify this method as most appropriate should be included in the report. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The dissolution profile should be complete and cover at least 80% of drug dissolved or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend using at least twelve samples per testing variable. The dissolution data (individual, mean, SD, profiles) should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim). The testing conditions used for each test should be clearly specified.*
  - b. *The testing conducted to demonstrate the discriminating capability of the selected test as well as the validation data for the test method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.). The chosen dissolution method should be discriminating and sensitive enough to reject lots that would have less than acceptable clinical performance.*
  
3. **Dissolution Acceptance Criteria:** *Provide the dissolution profile data from the clinical and stability batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values). For setting of the drug dissolution acceptance criteria, the following points should be considered:*
  - a. *The in vitro dissolution specifications should encompass the timeframe over which at least 80% of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.*
  - b. *Data from lots used in the clinical trials and primary stability studies must be used.*

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- c. *For extended release products the establishment of at least three specification time-points covering the initial, middle, and terminal phases of the complete dissolution profile data must be set. The acceptance criteria ranges must be based on the overall dissolution data generated at these times.*
  - d. *In general, the selection of the dissolution acceptance criteria ranges is based on mean target value  $\pm 10\%$  and NLT 80% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved In Vitro-In Vivo Correlation (IVIVC) model.*
  - e. *The dissolution acceptance criteria should be set in a way to ensure consistent performance from lot to lot and these criteria should not allow the release of any lots with dissolution profiles outside those that were tested clinically.*
4. ***Extended Release Claim:*** *Based on the Code of Federal Regulations, [21 CFR 320.25 (f)], if any part of your drug product includes an extended-release component, you should provide the data supporting the approval of the controlled-release claim made for your drug.*

## 3.0

**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) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. 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-

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796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to:  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

### **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at:  
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

### **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>.

### **MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided

in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CRN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

**505(b)(2) REGULATORY PATHWAY**

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, 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 comparative bioavailability data) 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 or on the other studies is scientifically appropriate. You should include a copy of

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such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

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) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the 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 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. 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.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>

2. Example: NDA XXXXXX "TRADENAME"	Previous finding of effectiveness for indication X
3. Example: NDA YYYYYY "TRADENAME"	Previous finding of safety for Carcinogenicity, labeling section XXX
4.	

Please be advised that 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 a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to 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 Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

**4.0 ISSUES REQUIRING FURTHER DISCUSSION**

No issues requiring further discussion were identified during the meeting.

**5.0 ACTION ITEMS**

No action items were identified during the meeting.

**6.0 ATTACHMENTS AND HANDOUTS**

No attachments or handouts were used during the meeting.

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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.**

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/s/

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LAURA MUSSE  
10/18/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 106992

MEETING MINUTES

Lipocine, Inc.  
675 Arapeen Drive, Suite 202  
Salt Lake City, Utah 84108

Attention: Srinivasan Venkateshwaran, Ph.D.  
Chief Technology Officer and Vice President, R&D

Dear Dr. Venkateshwaran:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for codeine and chlorpheniramine extended-release tablet.

We also refer to the meeting between representatives of your firm and the FDA on October 4, 2010. The purpose of the meeting was to discuss your drug development program in support of a 505(b)(2) NDA.

A copy of the official minutes of the meeting is attached 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) 796-2466.

Sincerely,

*{See appended electronic signature page}*

Philantha M. Bowen, M.P.H., RN  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

Reference ID: 2858174

Reference ID: 3785917

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** End of Phase II

**Meeting Date and Time:** October 4, 2010; 4:00 – 5:00 PM EST  
**Meeting Location:** Building 22, Conference Room 1421

**Application Number:** IND 106992  
**Product Name:** Codeine and Chlorpheniramine

**Indication:** Temporary relief of cough (b) (4) common cold (b) (4)  
inhaled (b) (4)  
itching of (b) (4)  
other upper respiratory allergies (b) (4)

**Sponsor/Applicant Name:** Lipocine, Inc.

**Meeting Chair:** Sally Seymour M.D., Deputy Director for Safety

**Meeting Recorder:** Philantha M. Bowen, MPH, R.N.  
Sr. Regulatory Management Officer

**FDA ATTENDEES**

Office of Drug Evaluation II

Phlantha Bowen, M.P.H., RN, Sr. Regulatory Management Officer, Division of Pulmonary, Allergy, and Rheumatology Products

Anthony Durmowicz, M.D., Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

Kimberly Witzmann, M.D., Clinical Reviewer, Division of Pulmonary, Allergy, and Rheumatology Products

Sally Seymour, M.D., Deputy Director of Safety, Division of Pulmonary, Allergy, and Rheumatology Products

Molly Topper, Ph.D., Pharmacology/Toxicology Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

Grace S. Lee, Ph.D., Pharmacology/Toxicology Reviewer, Division of Pulmonary, Allergy, and Rheumatology Products

Office of New Drug Quality Assessment

Prasad Peri, Ph.D., Acting Branch Chief, Division of Pre-Marketing Assessment III, Branch VIII

Yong Hu, Ph.D., Chemistry Reviewer, Division of Pre-Marketing Assessment III, Branch VIII

Chen Tien Mien, Ph.D., Biopharmaceutics Reviewer

Office of Clinical Pharmacology

Yun Xu, Ph.D., Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II

Ping, Ji, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II

**SPONSOR ATTENDEES**

Mahesh V. Patel, Ph.D., President & Chief Executive Officer

Srinivasan Venkateshwaran, Ph.D., Chief Technology Officer and VP R&D

Consultants

(b) (4)

## 1.0 BACKGROUND

Lipocine, Inc. submitted an End of Phase II meeting request dated June 24, 2010, to seek guidance on the development program for codeine and chlorpheniramine extended-release tablet in support of a 505(b)(2) NDA. The Division reviewed the briefing package dated August 31, 2010. In a facsimile dated October 1, 2010, the Division responded to the questions contained in Lipocine's meeting package.

Any discussion that took place at the meeting is captured directly under the original response including any changes in our original position. Lipocine's questions are in **bold italics**; FDA's response is in *italics*; and the discussion is in normal font.

## 2. DISCUSSION

### Question 2.1:

***Does the Division agree that the 505(b)(2) submission route is appropriate with the cited Reference NDA Drug and appropriate OTC Monographs? If not, please comment.***

### Division Response:

*Based on the data provided, the 505(b)(2) pathway appears to be one of the acceptable approaches for filing your proposed NDA.*

*We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway, consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry: Applications Covered by Section 505(b)(2) available at:*

*<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, 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/oct03/102303/02p0447-pdn0001vol1.pdf>).*

*If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, 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 comparative bioavailability data) 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 the literature studies refer to a proprietary product, then that drug product must be a listed drug.*

*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 you rely. 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:

Lipocine pointed out that OTC monographs for codeine and chlorpheniramine will be the basis for safety and efficacy, such that Codeprex will not be cited as a RLD in the NDA application. The Codeprex NDA will be used as a model for the design of Lipocine's PK studies.

Lipocine requested clarification on the statement, "the use of labeling statements taken from the labeling of other drug products may cause those products to also be listed drugs," in the Division's response. Lipocine proposes to use information from the literature to compose their product label and questioned the applicability of this statement to their NDA, if no RLDs will be cited, only the monographs. Lipocine proposes to request a pre-NDA meeting in 2011.

The Division responded that Lipocine should decide what RLDs are relied upon for their development program. Regarding the monographs, a justification for any differences from the OTC monographs, in the context of a 505(b)(2) framework, should be provided in the NDA. Additionally, the Division commented that Lipocine should review their development program and determine the necessary information to include in the product label and determine if information is referenced from another approved product. A pre-NDA meeting will allow for further discussion and clarification of this matter.

Post-Meeting FDA Comment:

Be aware that, while data from literature studies may be relied upon to support labeling statements, if the literature identifies a listed drug as having been used in the published study, then that listed drug is considered to be relied upon for possible approval of the (b)(2) application and appropriate patent certification must be done against it.

**Question 2.2A**

***Does the Division agree that the proposed pharmacokinetic studies will be adequate to demonstrate the safety and efficacy of Lipocine's codeine phosphate/chlorpheniramine maleate ER tablet? If not, please comment.***

Division Response:

*Given the information provided, it appears that the proposed PK studies will be adequate to assess the bioequivalence of your ER tablet with the reference IR tablet as well as food effect. However, whether it demonstrates the safety and efficacy of the ER tablet will be a review issue based on your data.*

Discussion:

Lipocine commented that they plan to request a pre-NDA meeting next year to discuss the data from the bioequivalence (BE) studies, food effect, and proposed labeling.

**Question 2.2b:**

***Does the Division agree that no additional clinical efficacy/safety studies would be required in support of the NDA?***

Division Response:

*While your approach appears adequate to establish bioequivalence, we cannot agree that no additional studies will be necessary until you are able to demonstrate that your product meets bioequivalence. Also, in addition to assessing for food effect, you should evaluate the effect of alcohol dose dumping as additional information to support the safety of your proposed combination ER product. Initially, a reasonable approach would be to conduct an in vitro dissolution study to evaluate the effect of alcohol on the drug release. If a dose dumping effect is observed in vitro, you should evaluate the effect of alcohol on dose dumping in a clinical trial. Include the results of the assessment of alcohol dose dumping in your NDA submission.*

Discussion:

Lipocine stated that their *in vitro* testing, using increased alcohol percentages, revealed a slowing down of the alcohol on drug release; thus it is believed that no *in vivo* pharmacokinetic study on alcohol dose dumping is necessary. The Division recommended that Lipocine submit the *in vitro* test results to the IND and include a request for comments regarding the results.

Question 2.3:

*Does the Division agree that no additional drug interaction studies or special population studies are warranted? If not, please comment.*

Division Response:

*While no additional clinical drug interaction studies or special population studies may be required, we recommend that you review published information and update the clinical pharmacology section of the drug's label for your NDA submission.*

Discussion:

There was no discussion on 2.3

Question 2.4:

*Does the Division agree that a fixed-dose, combination IR reference product prepared in-house containing 20 mg codeine (27.15 mg codeine phosphate) and 4 mg chlorpheniramine maleate that complies with the OTC monograph and meets the USP assay and dissolution specifications (as outlined in Section 6) will be acceptable for use as the reference product in the proposed PK studies? If not, please comment.*

Division Response:

*Yes, we agree that in-house preparation of a codeine/chlorpheniramine IR product that complies with the OTC monograph is acceptable for use as the reference product. Submit complete CMC information pertaining to the drug substances and the drug product for the comparator drug product manufactured in house in your NDA submission. Include (along with other information) data on impurities and degradation products.*

Discussion:

Lipocine requested that the Division clarify whether the submission of the complete CMC information, as mentioned in the response, should be provided in the IND versus the NDA. The Division responded that INDs may contain detailed summaries, but not complete stability

information. For the NDA submission, the Division stated that CMC information should be provided in Module 3. The Division agreed to provide further guidance on the appropriate Module location and stated that this matter could be further addressed at the pre-NDA meeting. Lipocine agreed to seek clarification on the appropriate NDA module at that time.

For the immediate-release product, Lipocine states that the extent of the stability in the NDA will be over the duration of the studies. The Division stated that stability over the duration of the studies would be acceptable.

**Question 2.5:**

***Does the Division agree that this product qualifies [REDACTED] (b) (4) pediatric study requirement? If not, please comment.***

**Division Response:**

*If you believe that this drug qualifies for a waiver of the pediatric study requirement, submit a request for a waiver when submitting your NDA application. Include supporting information and documentation in accordance with the provisions of 21 CFR 314.55. You may find more information on CDER's Pediatric Drug Development Page (<http://www.fda.gov/www.fda.gov/cder/pediatric/>) and in the Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act (<http://www.fda.gov/cder/guidance/6215dft.pdf>).*

*Additionally, discussions at the Joint meeting of the Nonprescription Drugs Advisory committee and Pediatric Advisory committee on "Safety and Efficacy of Over-the-counter Cough and Cold Products Marketed for Pediatric Use" ([www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4323t1](http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4323t1)) has led to re-evaluation of our approach to combination products. We are updating our policy regarding the way we should approach these products for allergic rhinitis, and cold indications in the pediatric population. Internal Agency deliberations are still ongoing on this issue. Be advised that the Agency's final determination on the requirements for approval of combination cough/cold products in the pediatric population may impact your development program, such that separate studies may be necessary to support approval of your combination product in the pediatric population.*

**Discussion:**

Lipocine proposes to [REDACTED] (b) (4) Referring to paragraph 2, Lipocine requested that the Division further explain the rationale for the comment. The Division responded that the purpose of the comment is to provide awareness that the Agency is involved in ongoing discussions pertaining to the use of cough and cold products in children. The discussions focus on the entire pediatric range and affect all products. Lipocine pointed out that

(b) (4) The  
Division recommended that Lipocine submit their justification in the NDA.

**Question 3:**

***Does the Division agree that no additional non-clinical pharmacology and toxicology studies will be required for approval? If not, please comment.***

**Division Response:**

*We generally agree that no additional nonclinical studies will be needed for your proposed fixed dose combination, codeine/chlorpheniramine extended-release tablet product.*

**Discussion:**

There was no discussion question 3.

**Question 5.1:**

***Does the Division agree that the proposed pharmacokinetic studies will be adequate to demonstrate the safety and efficacy of Lipocine's codeine phosphate/chlorpheniramine maleate ER tablet? If not, please comment.***

**Division Response:**

*Refer to our response to question 2.2a.*

**Discussion:**

There was no discussion question 5.1.

**Question 5.2:**

***Does the Division agree that no additional drug interaction studies or special population studies are warranted? If not, please comment.***

**Division Response:**

*Refer to our response to questions 2.2b and 2.3.*

Discussion:

There was no discussion question 5.2.

**Question 5.3:**

***Does the Division agree that for purposes of NDA approval, it will not be necessary for Lipocine to establish bioequivalence between its proposed product when given in the fasted state as compared to the fed state, and that the results of the food effect bioavailability study can be handled as an element of labeling?***

Division Response:

*No, we do not necessarily agree. Whether or not the results of the food effect bioavailability study may be handled as an element of labeling will be a review issue.*

Discussion:

Lipocine deferred discussion of this question to the pre-NDA meeting.

**Question 6.1:**

***Does the Division agree that a fixed dose combination IR reference product prepared in-house containing 20 mg codeine (as 27.15 mg codeine phosphate) and 4 mg chlorpheniramine maleate that complies with the OTC monograph and meets the USP assay and dissolution specifications be acceptable for use as the reference product in the proposed PK studies? If not, please comment.***

Division Response:

*Refer to our response to question 2.4.*

Discussion:

There was no discussion question 6.1.

**Question 7.1:**

***Does the Division agree that this drug product qualifies (b) (4) pediatric study requirement? If not, please comment.***

**Division Response:**

*Refer to our response to question 2.5.*

**Discussion:**

There was no discussion question 7.1.

**Question 7.2:**

***If Lipocine's product is not (b) (4) the Division agree that pediatric studies (b) (4)?***

**Division Response:**

*Refer to our response to question 2.5.*

**Discussion:**

There was no discussion question 7.2.

**Question 8.1:**

***Does the Division concur (b) (4)***  
***(b) (4)***

**Division Response:**

*Refer to the response below to question 8.2.*

**Discussion:**

There was no discussion question 8.1.

**Question 8.2:**

***Does the Division concur***

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

**Division Response:**

*We cannot agree at this time. Submit the proposed supporting data (e.g., release and stability) for drug products manufactured by both the primary and secondary suppliers of codeine phosphate and chlorpheniramine maleate in your NDA for our review. In your pivotal clinical studies, we strongly recommend that you use the drug substances manufactured at the intended commercial site with the intended commercial process. We recommend that you submit all information on any proposed future changes in manufacturing site, manufacturing process, or suppliers (if applicable) in the proposed NDA for review as a comparability protocol.*

*In addition, our understanding is that you propose to*

(b) (4)

*We remind you that we may request stability data for more drug product batches containing the drug substances from each source in the event that data variability is observed in the data submitted in the NDA.*

**Discussion:**

Lipocine commented they (b) (4) will make the registration batch with the primary source (b) (4)

**Question 8.3:**

***Will the Division require that Lipocine develop any additional dissolution profile data (e.g., using different media, apparatus, and/or rotational speeds) for NDA submission? If so, what conditions are recommended?***

**Division Response:**

*In the NDA submission, provide the following:*

- *Final dissolution development report (investigating different media, apparatus, rotational speeds, and/or surfactants, etc.) with your justification and conclusion on the selection of the proposed dissolution methodology and specifications.*

- *Individual and mean dissolution data and mean dissolution profile (12 tablets/batch) using the final to-be-marketed tablet formulation/product.*

*No additional dissolution profile data are needed regarding a secondary or alternative source of API as long as you comply with CMC requirements/specifications for the API.*

Discussion:

There was no discussion question 8.3.

**Question 8.4:**

***Does the Division agree that***

(b) (4)

Division Response:

*We do not agree. Submission of twelve-month long-term stability data is recommended in the NDA submission in accordance with ICH Q1A, in order to set a meaningful and commercially viable shelf life. Shelf life of the product will depend on the review of the data in the NDA.*

Discussion:

Lipocine questioned if the Division

(b) (4)

The Division stated that Lipocine's question was too premature to address at this time. The Division recommended that Lipocine submit adequate data for a viable shelf life. Additionally, the Division pointed out that due to the availability of resources, it could not commit to the review of amendments; thus, it is recommended that 12 months of stability data be provided at the time of the NDA submission.

**Question 8.5:**

***Will the Division accept and consider the data for the 9 and 12 month long term stability test stations while the NDA is under review?***

Division Response:

*We strongly recommend submitting all long term data at the time of NDA submission. Any significant stability update amendments submitted later may not be reviewed depending on availability of resources.*

Discussion:

There was no discussion question 8.5.

**Question 9.1:**

***Does the Division agree that the search of the worldwide published literature can be limited to the period commencing July, 2004 (the first full month following approval of the NDA for the Listed Drug, Codeprex™ Extended Release Suspension) through the month immediately prior to the NDA filing date?***

Division Response:

*Based on the information provided, the proposed scope of the literature review appears reasonable.*

Discussion:

There was no discussion question 9.1.

**Question 9.2:**

***Does the Division agree that the above searches can be limited to orally administered Codeine and Chlorpheniramine?***

Division Response:

*Based on the information provided, limiting the proposed literature searches to orally-administered drugs appears reasonable.*

Discussion:

There was no discussion question 9.2.

**Question 9.3:**

***Does the Division agree that the results from the searches identified above should form a sufficient basis for the ISS and that no additional safety information will be required for the NDA submission?***

Division Response:

*If your product's bioequivalence criteria are met, it is reasonable that the literature review described above, as well as AERS safety database search for codeine, chlorpheniramine, and combined codeine/chlorpheniramine, should be sufficient for the Integrated Summary of Safety and NDA submission; but ultimately, the safety of your product and whether additional safety information is necessary will be a review issue.*

Discussion:

There was no discussion question 9.3.

FDA ADDITIONAL COMMENTS

1. *Monitor impurities and degradation products of all active ingredients, particularly of (b) (4) in the drug substance of codeine and (b) (4) in the drug substance of chlorpheniramine (b) (4). Impurities or degradants that are identified as 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: Recommended Approaches (December 2008) for assessment of impurities to support clinical studies for an IND and NDA. In addition, refer to the ICH Guidance for qualification of drug impurities in drug substances [ICH Q3A(R)] and degradants in drug products [ICH Q3B(R)]. If applicable, conduct the appropriate toxicity studies to qualify impurities and degradants. Particularly, the level of impurity (b) (4) which was observed at the level of (b) (4)% in the drug substance of codeine from (b) (4) should be reduced the specifications to (b) (4)% NMT or provide adequate safety qualification as per ICH Q3A(R).*

Discussion:

Lipocine acknowledged the Division's comment on structural alerts and plans to discuss the issue with their suppliers. Lipocine will seek further discussion with the Division at the pre-NDA meeting. In addition, Lipocine acknowledged that genotoxicity studies had been conducted for (b) (4) but would investigate whether similar studies have been conducted for (b) (4) in the drug substance of chlorpheniramine.

The Division reminded Lipocine to obtain letters of authorization to use the DMFs for their drug product.

2. *We remind you that use of any novel excipient or excipient exceeding levels in currently approved oral products will need to be qualified for safety prior to initiating clinical studies.*

Discussion:

There was no discussion on additional comment 2.

**3.0 ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion.

**4.0 ACTION ITEMS**

There were no outstanding action items for this meeting.

**5.0 ATTACHMENTS AND HANDOUTS**

There were no attachments or handouts for the meeting minutes.

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PHILANTHA M BOWEN  
11/01/2010

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