

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206323Orig1s000**

**CHEMISTRY REVIEW(S)**



NDA 206323-Orig1-New/NDA(1) » Manufacturing Facility Inspection

### Overall Manufacturing Inspection Recommendation

Edit Task | Task Actions

Task Summary Task Details Issues Updates **Inspection Management Form**

#### Inspection Management Form

As of 2:00 PM

Inspection Management Form

NDA 206323-Orig1-New/NDA(1)

(b) (4)  
| Approve Facility (b) (4)

(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility (b) (4)

(b) (4) Approve Facility -  
(D) (4)

NEXGEN PHARMA INC | 1717927 | TTR TABLETS, EXTENDED RELEASE | Approve Facility - 2017-02-27

#### Overall Manufacturing Inspection Recommendation

- Approve
- Withhold

Overall Application Re-evaluation Date

9/6/15

Cancel

Assigned To

**Linda Ng**

Edit Assignment

This was done on  
**Jun 12, 2015**  
(5 days ago)

**Status**  
**Complete**

This task is waiting on  
2 Tasks

Last Update Submitted On  
Jun 12, 2015 Sep 25, 2014

Reference Number  
2058233

**NDA 206323**

**Codeine Phosphate and Chlorpheniramine Maleate  
Extended-release Tablets**

**Spriaso, LLC**

**Yong Hu, Ph.D.**

**Office of Pharmaceutical Quality**

**For**

**Division of Pulmonary, Allergy and Rheumatology Products**

# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>3</b>
<b>The Executive Summary .....</b>	<b>8</b>
I. Recommendations .....	8
A. Recommendation and Conclusion on Approvability .....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments .....	8
A. Description of the Drug Product(s) and Drug Substance(s) .....	8
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	10
<b>Chemistry Assessment .....</b>	<b>12</b>
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data .....	12
S DRUG SUBSTANCE [Chlorpheniramine Maleate USP, (b) (4)] .....	12
S DRUG SUBSTANCE [Codeine Phosphate USP, (b) (4)] .....	23
P DRUG PRODUCT [Codeine Phosphate and Chlorpheniramine Maleate Extended-release Tablets ] .....	30
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....	74
A. Labeling & Package Insert .....	74
B. Environmental Assessment Or Claim Of Categorical Exclusion .....	75
III. Comments to be communicated to the applicant .....	76

# Chemistry Review Data Sheet

1. NDA: 206323
2. REVIEW #: 1
3. REVIEW DATE: 5-18-2015
4. REVIEWER: Yong Hu, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Response to information request	5/4/2015
Response to information request	4/24/2015
Response to information request	4/17/2015
Response to information request	4/10/2015
Response to information request	3/24/2015
Response to information request	3/4/2015
Response to information request	2/5/2015
Original submission	8/22/2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Spriaso, LLC
Address:	The Parc at Gateway, #911, 5 South 500 West, Salt Lake City, UT84101
Representative:	Lara Noah- Director of Regulatory Affairs, Nexgen Pharma, Inc.
Telephone:	719-579-9650

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Rinotuss 12
- b) Non-Proprietary Name (USAN): Codeine Phosphate and Chlorpheniramine Maleate
- c) Code Name/# (ONDC only): LPCN 1084
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 4
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION:

505 (b)(2). The reference product is the codeine (20 mg) and chlorpheniramine maleate (4 mg) immediate-release tablet that was manufactured by the applicant and met the individual USP monographs for codeine phosphate tablet and chlorpheniramine maleate tablet, respectively.

## 10. PHARMACOL. CATEGORY:

An antitussive and an antihistamine

## 11. DOSAGE FORM:

Extended-release tablet.

## 12. STRENGTH/POTENCY:

Each tablet contains 54.3 mg codeine phosphate (equivalent to 40 mg codeine) and 8 mg chlorpheniramine maleate (equivalent to 5.6 mg chlorpheniramine).

## 13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED:  Rx  OTC

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

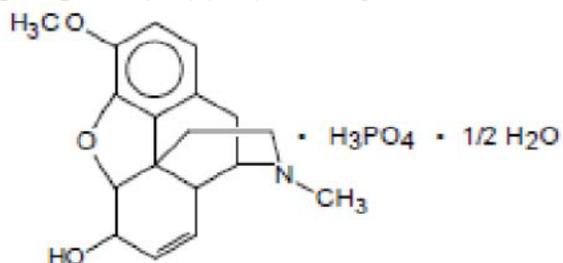
SPOTS product – Form Completed

Not a SPOTS product

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

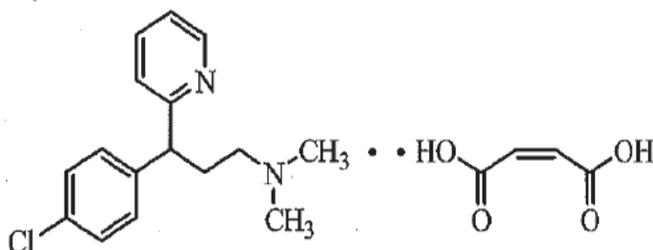
## Chemistry Review Data Sheet

Codeine phosphate:

 Chemical name: Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-, (5 $\alpha$ ,6 $\alpha$ )-, phosphate (1:1)(salt), hemihydrate

 Molecular Formula: C<sub>18</sub>H<sub>21</sub>NO<sub>3</sub>•H<sub>3</sub>PO<sub>4</sub>• ½H<sub>2</sub>O

Molecular Weight: 406.37

Chlorpheniramine Maleate:

 Chemical name: 2-Pyridinepropanamine,  $\gamma$ -(4-chlorophenyl) – N,N-dimethyl,(Z)-2-butenedioate (1:1)

 Molecular Formula: C<sub>16</sub>H<sub>19</sub>ClN<sub>2</sub>•C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>

Molecular Weight: 390.86

**17. RELATED/SUPPORTING DOCUMENTS:**
**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	7/9/2012	
	II			1	Adequate	12/12/2014	
	III			4	NA		
	III			4	NA		
	III			4	NA		

Chemistry Review Data Sheet

(b) (4)	(b) (4)				
III		4	NA		
III		4	NA		
III		4	NA		
III		4	NA		
III		4	NA		
III		4	NA		
III		4	NA		
III		4	NA		

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	106992	The IND supporting this NDA

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not requested.		
EES	Pending		
Pharm/Tox	The drug product degradant should be controlled to NMT (b) (4) % and the degradant (b) (4) is not qualified for the limit of (b) (4) %.	Emails	Dr. Marcie Wood

## Chemistry Review Data Sheet

Biopharm	The revised dissolution specification is acceptable.	Emails	Dr. Peng (Vincent) Duan
LNC	The product should be named using the codeine phosphate salt to be consistent with the USP monographs where all products contain codeine have the codeine salts included as part of the name.	Emails	Dr. Richard Lostritto; Dr. Yana Mille
Methods Validation	Standard methods. Consult not requested.		
OPDRA	Not requested.		
EA	NA. Categorical exclusion requested.		
Microbiology	Approval.	4/22/2015	Denise Miller

# The Chemistry Review for NDA 202450

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The NDA is recommended for approval pending the facilities assessment from the Office of Process and Facilities.

In addition, we have a minor comment that should be sent to the applicant. See Chemistry Assessment Section III - Comments to be communicated to the applicant.

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

None.

### II. Summary of Chemistry Assessments

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

The drug substances are codeine phosphate and chlorpheniramine maleate, both of which conform to their respective USP monographs. The codeine phosphate is manufactured by (b) (4) under DMF (b) (4) and the chlorpheniramine maleate by (b) (4) under DMF (b) (4). Both drug substances are highly water soluble.

The drug product is codeine phosphate and chlorpheniramine maleate extended-release tablet. Each tablet contains 54.3 mg codeine phosphate (equivalent to 40 mg codeine) and 8 mg chlorpheniramine maleate (equivalent to 5.6 mg chlorpheniramine). (b) (4) hypromellose (b) (4). The other excipients include lactose monohydrate, polysorbate 80, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate. (b) (4)

As concurred by the Biopharmaceutics reviewer, the in-vitro dissolution data showed that ethanol in concentrations as high as 40% are not likely to cause dose dumping .

The product is manufactured by Nexgen Pharma, Inc. in Colorado. The manufacturing process (b) (4)

Executive Summary Section

(b) (4)  
 The registration/clinical PK batches were manufactured at 1/10 of the proposed production scale. No production scale batches have been manufactured so far. However, the scale-up risk is relatively low as, when compared to the registration scale, (b) (4)

Due to low percentage (b) (4) % w/w) of chlorpheniramine maleate in the product, one of the failure modes is not achieving content uniformity for this drug. To mitigate the risk, besides batch release testing for chlorpheniramine content uniformity, the applicant proposes to (b) (4)

The tablets are packaged in a 100-count, 75 cc HDPE heavy wall round bottle, with a white (b) (4) 33 mm Child Resistant Cap fitted with an aluminum heat-sensitive foil liner (b) (4) and a desiccant pack. The product is stored at 20 to 25 °C (68 to 77 °F). [See USP Controlled Room Temperature.] The proposed 24-month expiration dating period is acceptable based on the 24-month long-term and 6-month accelerated stability data provided for the three registration batches.

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

<b>Proprietary Name of the Drug Product</b>	Rinotuss 12
<b>Non Proprietary Name of the Drug Product</b>	The applicant-proposed name is (b) (4). This CMC team recommends the name Codeine Phosphate and Chlorpheniramine Maleate ER Tablet (see II.A. in body of the review)
<b>Non Proprietary Name of the Drug Substance</b>	Codeine phosphate and chlorpheniramine maleate
<b>Proposed Indication(s) including Intended Patient Population</b>	<ul style="list-style-type: none"> <li>• Relief of cough (b) (4) associated with common cold.</li> <li>• Relief of symptoms (b) (4) associated with upper respiratory allergies.</li> <li>• Adults (b) (4)</li> </ul>
<b>Duration of Treatment</b>	Not defined.
<b>Maximum Daily Dose</b>	1 tablet every 12 hours, not to exceed 2 tablets in 24 hours.
<b>Alternative Methods of Administration</b>	The tablets must not be chewed, broken or



Executive Summary Section

<p align="center">Content uniformity</p>	<p>Lack of blend uniformity (segregation) prior to (b) (4)</p>	<p align="center">18</p>	<p>(b) (4)</p>	<p align="center">Acceptable.</p>
<p align="center">Microbial limits</p>	<ol style="list-style-type: none"> <li>1. Microbial load of input materials for formulation</li> <li>2. Microbial contamination during processing</li> <li>3. Microbial growth during shelf life</li> </ol>	<p align="center">15</p>	<p>Lactose, Mg stearate, microcrystalline cellulose, and polysorbate are tested for microbial contamination as per their respective specifications. The manufacturing process is (b) (4). The applicant analyzed three batches of the drug product as per USP &lt;61&gt; and found no detected CFUs for total aerobes or for yeast and mold. The Microbiology reviewer recommends approval of this NDA.</p>	<p align="center">Acceptable.</p>
<p align="center">Alcohol Dose Dumping</p>	<p>Extended release properties compromised in the presence of ethanol</p>	<p align="center">24</p>	<p>In vitro dissolution data indicate that increasing levels of ethanol lead to slightly decreasing release for both chlorpheniramine and codeine (see P.2). The (b) (4) hypromellose is not soluble in ethanol.</p>	<p align="center">Acceptable.</p>
<p align="center">Drug Release or Dissolution</p>	<ol style="list-style-type: none"> <li>1. Polymorph conversion</li> <li>2. Changes in input excipients and APIs</li> <li>3. API particle size change</li> <li>4. Tablet moisture content</li> <li>5. Tablet hardness</li> </ol>	<p align="center">18</p>	<p>Standard (and stable) (b) (4) forms of both APIs are used in the formulation; Excipients are also of compendial grade and in common use; The grade of the (b) (4) hypromellose is defined (b) (4); API particle size growth not expected based on manufacturing process (b) (4). No testing of final tablet moisture content proposed for specification, however, the manufacturing process is a (b) (4) is controlled by its (b) (4) specification.</p>	<p align="center">Acceptable.</p>

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

## Chemistry Assessment Section

Reviewer evaluation: The 24-month real time data support the proposed 24-month expiration dating period. Note that the specification has been revised to reduce the limit of (b) (4) to NMT (b) (4)% and the limit of (b) (4) to (b) (4)% (see Module 3.2.P.5.1).

**FDA Comment:** *Provide photostability data for the drug product. Refer to the ICH Q1B.*

**Response:** We provided the Assay Method Validation package in Module 32P5-drug product controls. That validation report at section 15 describes the photo degradation studies of the drug product directly under a both UV light at (b) (4) and fluorescent light at (b) (4). (b) (4) Samples were stored in direct exposure to both for 3 days. There was no degradation of either API and the peaks were all spectrally pure. This is consistent with the progression outlined in Appendix A of ICH Q1B *Photostability Testing* where the drug product is directly exposed and to move on to (b) (4) in the marketing container as necessary. With no photo degradation observed, no additional studies were undertaken.

Reviewer Evaluation: The response is acceptable.

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

### A. Labeling & Package Insert

The proposed carton and container label is as follows.



Per Drs. Richard Lostritto and Yana Mille in the Office of Pharmaceutical Quality, all USP monographs for the drug products containing codeine use the codeine salts in the names of the products. They recommend following the USP convention for naming this NDA product so as to avoid confusion when the prescribers compare the codeine strength in this product with other marketed codeine products. Therefore, it is recommended that this product is named as “Codeine phosphate and chlorpheniramine maleate extended-release tablet, 54.3 mg and 8 mg.”

However, the recently approved NDA 207768, Tuzistra XR (Codeine Polistirex and Chlorpheniramine Polistirex) Extended Release Oral Suspension, which is the first codeine and

## Chemistry Assessment Section

chlorpheniramine combination drug product, defines the strengths as the amount of the free bases (14.7 mg of codeine and 2.8 mg chlorpheniramine per 5 mL). It is advised by the clinical team that patients may need to switch to the suspension if they cannot swallow the tablets, subject of this NDA. Therefore, having information on the label about the strengths of the tablet expressed as the free bases would help the prescriber make the informed decision when comparing the products.

In reference to the draft Guidance for Industry – Naming of Drug Products Containing Salt Drug Substances, the following name and content are recommended to be on the label:

*Codeine phosphate and Chlorpheniramine Maleate Extended-Release Tablets, 54.3 and 8 mg*

*Each tablet contains:*

*Codeine phosphate.....54.3 mg*

*(equivalent to 40 mg codeine)*

*Chlorpheniramine maleate.....8 mg*

*(equivalent to 5.6 mg chlorpheniramine)*

**The following labeling comment is recommended to send to the applicant:**

**Revise the product name and strength on the carton/container label to “Codeine phosphate and Chlorpheniramine Maleate Extended-Release Tablets, 54.3 mg and 8 mg.”**

**In addition, include the following content on the label:**

**Each tablet contains:**

**Codeine phosphate.....54.3 mg**

**(equivalent to 40 mg codeine)**

**Chlorpheniramine maleate.....8 mg**

**(equivalent to 5.6 mg chlorpheniramine)**

## **B. Environmental Assessment Or Claim Of Categorical Exclusion**

### **Adequate.**

The applicant/petitioner requires a Categorical Exclusion [21 CFR 314.50(d)(1)(iii)] in that this drug product will not be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect. To the applicant’s knowledge, no extraordinary circumstances exist.

In addition, the applicant certifies that the production of this product meets the requirements of all Federal, State and Local Environmental Laws.

## Chemistry Assessment Section

**III. Comments to be communicated to the applicant**

The following minor comment should be sent to the applicant:

**Revise your drug product specification as follows:**

1. Change the assay for codeine phosphate from [REDACTED] (b) (4) to “Codeine phosphate: [REDACTED] (b) (4) % of 54.3 mg”.

## Chemistry Assessment Section

**Signatures**Reviewed by: **Yong Hu, Ph.D., Chemist**

Yong Hu -S

Digitally signed by Yong Hu -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Yong Hu -S,  
0.9.2342.19200300.100.1.1=2000336960  
Date: 2015.05.18 14:19:08 -04'00'

Concurred by: **Julia Pinto, Ph.D., Branch Chief**

Julia C. Pinto -A

Digitally signed by Julia C. Pinto -A  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,  
cn=Julia C. Pinto -A, 0.9.2342.19200300.100.1.1=1300366849  
Date: 2015.05.18 14:27:40 -04'00'

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

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

## I. Review Cover Sheet

1. OMPQ Reviewer: Linda Ng, Ph.D.
2. NDA Number: NDA 206323  
Submission Date: August 22, 2014  
21<sup>st</sup> C. Review Goal Date: April 22, 2015  
PDUFA Goal Date: June 22, 2015

### 3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	None proposed
Established or Non-Proprietary Name (USAN) and strength:	Codeine Phosphate and Chlorpheniramine Maleate Extended Release Tablets, 40 mg / 8 mg
Dosage Form:	Extended Release Tablets

### 4. SUBMISSION PROPERTIES:

Review Priority :	STANDARD
Applicant Name:	Spriaso LLC (Nextgen Pharma filed on their behalf)
Responsible Organization (OND Division):	DPARP

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

## II. Application Detail

1. INDICATION: Temporary relief of cough (b) (4)  
 common cold (b) (4)  
 upper respiratory allergies (b) (4)

2. ROUTE OF ADMINISTRATION: Oral delivery

STRENGTH/POTENCY:  
 Temporary relief of cough (b) (4) common  
 cold (b) (4)  
 upper respiratory allergies (b) (4)

3. Rx/OTC DISPENSED: x  Rx       OTC

4. ELECTRONIC SUBMISSION (yes/no)? Yes

5. PRIORITY CONSIDERATIONS:

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

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

### III. FILING CHECKLIST

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

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		APIs are provided in DMFs. Chorpheniramine maleate USP is supplied by (b) (4) DMF # (b) (4). Codeine phosphate USP supplied by (b) (4) . DMF (b) (4)
12.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
15.	Additional notes (non-filing issue)	X		
	1. Are all sites registered or have FEI #?		X	
	2. Do comments in EES indicate a request to participate on inspection(s)?		X	
	3. Is this first application by the applicant?		X	

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

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

<b>B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
16.	Have any Comparability Protocols been requested?		X	Stated none for APIs in Section 3.2.R

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

## IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			None
Nanotechnology	RTRT Proposal	PAT	Drug/Device Combo
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
PET	Design Space	Continuous Mfg	Naturally derived API
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other (explain):			

### Manufacturing Highlights

#### 1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	Both APIs are USP products

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

#### 2. Drug Product

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

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

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

(b) (4)



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

**3. Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues. None that is obvious**

**4. Drug Product Facility Inspectional History that could impact the manufacturing of this product. The drug product facility has never been inspected for TTR.**

**Additional information not covered above**

None

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

**Manufacturing Facilities Chart** (generated from 602A DARRTS report and OMPQ macro):

<b>NDA:</b>	<b>206323 Codeine Phosphate and Chlorpheniramine Maleate Extended Release Tablets, 40 mg / 8 mg</b>								
<b>Sponsor:</b>	<b>SPRIASO LLC</b>								
<b>Indication:</b>	Temporary relief of (b) (4)								
<b>PDUFA:</b>	6/22/2015 under STANDARD Review								
<b>Responsible Organization:</b>	CDER/ODEII/DPARP								
<b>EERS Submitted By:</b>									
<b>Chart Generated On:</b>	9/26/2014								
					<b>Overall OC Recommendation:</b>	entered into EES on			
					<b>Reevaluation date:</b>				
<b>Establishment Name</b>	<b>EER Creation Date</b>	<b>FEI Num</b>	<b>District Short</b>	<b>Country Code</b>	<b>Responsibilities</b>	<b>Profile Code</b>	<b>Firm Profiles - Current Status</b>	<b>Inspection History, Dates, Classifications</b>	<b>Comment</b>
(b) (4)									
NEXGEN PHARMA, INC.	9/17/2014	1717927	DEN	USA	Drug Product Manufacturing, Packaging, Analytical Testing-Release and Stability	TTR	<a href="http://intranetapps.fda.gov/scripts/mpqa/profile.cfm?FEI=1717927">http://intranetapps.fda.gov/scripts/mpqa/profile.cfm?FEI=1717927</a>	Never been inspected for TTR	

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

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

## V. Overall Conclusions and Recommendations

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

## REVIEW AND APPROVAL (DARRTS)

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

/s/  
-----

LINDA L NG  
12/19/2014

MAHESH R RAMANADHAM  
12/19/2014

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

## APPLICATION INFORMATION

### 1. NEW DRUG APPLICATION NUMBER: N206323

<b>Submission Date</b>	8/22/2014
<b>Product name, generic name of the active</b>	Codeine Phosphate and Chlorpheniramine Maleate Extended Release Tablets
<b>Dosage form and strength</b>	ER Tablets; 40 mg /5.6 mg <sup>1</sup>
<b>Applicant</b>	Spriaso, LLC
<b>Clinical Division</b>	DPARP
<b>Indication</b>	Temporary relief of cough (b) (4) common cold (b) (4) upper respiratory allergies (b) (4) (b) (4)
<b>Type of Submission</b>	505(b)(2) NDA
<b>CMC Reviewer</b>	Yong Hu, PhD
<b>Acting CMC Lead</b>	Craig M. Bertha, PhD
<b>Acting Branch Chief</b>	Julia Pinto, PhD
<b>Biopharmaceutics Reviewer</b>	Kareen Riviere, PhD
<b>Biopharmaceutics Team Leader</b>	Tapash Ghosh, PhD
<b>Biopharmaceutics Supervisor (acting)</b>	Paul Seo, PhD

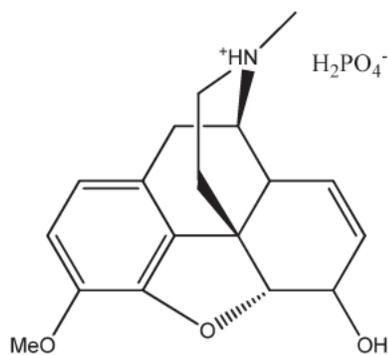
Codeine (40 mg) and chlorpheniramine (5.6 mg) extended-release tablets<sup>1</sup> from Spriaso are for BID dosing (every 12 hours) for the indication as listed above. The drugs used in the formulation are codeine phosphate and chlorpheniramine maleate, from (b) (4) (DMF (b) (4)) and (b) (4) (DMF (b) (4)), respectively. The codeine phosphate from (b) (4) under DMF (b) (4), was recently found to be acceptable to be used in an oral solution drug product (see review dated 31-JUL-2012). The chlorpheniramine maleate from (b) (4) under DMF (b) (4) was recently found to be acceptable to be used in an oral solution drug product (see review dated 21-MAR-2014). Both codeine phosphate and chlorpheniramine maleate (CPM) are BCS class I (high solubility, high permeability).

<sup>1</sup> Note that the drug product contains 40 mg of codeine from 54.3 mg of codeine phosphate and 5.6 mg of chlorpheniramine from 8.0 mg of chlorpheniramine maleate. The labeling and nomenclature committee will need to be consulted regarding the established name to be used for this drug product, as there is currently no related USP monograph, nor any reference listed drug. Currently the applicant proposes an established name of (b) (4)

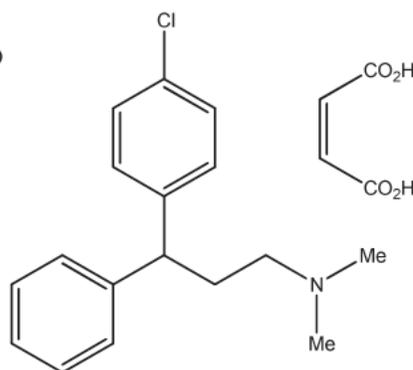
**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

NDA #: 206323

Received Date: 22-AUG-2014



codeine phosphate



Chlorpheniramine Maleate

The drug product for this NDA is an extended-release tablet containing 40 mg of codeine (as 54.3 mg of codeine phosphate) and 5.6 mg of chlorpheniramine (as 8.0 mg of chlorpheniramine maleate). These two drugs are stated to comply with their associated USP monographs. In addition, the excipients also comply with the USP/NF monograph requirements. All of the excipients have been used in approved oral drug products.

2. Drug Name: Codeine/Chlorpheniramine Extended-Release Tablets

Although there is no formal policy, the chemistry classification codes for the drug product (see draft of MaPP 7500.3) would appear to be types 4 and 5 (**New Combination; New Formulation or New Manufacturer, Same or New Indication**). There are no codeine/chlorpheniramine combination drug products listed in the Orange Book. Previously there were two different codeine polistirex/chlorpheniramine polystirex extended release oral suspensions approved but both have been discontinued from the market (Penntuss® NDA 18928 and Codeprex® NDA 21369).

3. RECEIVED DATE: 22-AUG-2014 (Applicant: Spriaso, LLC)

4. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	2	(b) (4)	(b) (4)	05-DEC-2013	Last review 21-MAR-2014; no subsequent amendments/ARs
	2			19-NOV-2013	Last review 31-JUL-2012; no subsequent amendments/ARs
	3			19-NOV-2013	Last review 05-NOV-2004
	3			21-NOV-2013	

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

NDA #: 206323

Received Date: 22-AUG-2014

(b) (4)	3		19-NOV-2013	
	3		12-MAR-2014	Last review 21-MAR-2012
	3		22-NOV-2013	Last review 27-JAN-2014
	3		12-MAR-2014	Last review 07-JUN-2005
	3		11-AUG-2014	
	3		25-NOV-2013	Last review 07-DEC-2004
	3		13-MAR-2014	Last review 15-JUN-2007
	3		13-MAR-2014	Last review 14-AUG-2014
	3		17-MAR-2014	Last review 17-MAR-2001

**b. Recommended Consults**

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Request evaluation of stability data if trends in parameters appear to limit expiry. Applicant does not provide any analyses of stability data.
Clin Pharm	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
EES	<input checked="" type="checkbox"/>	<input type="checkbox"/>	ONDQA PM was informed of submission on 26-AUG-2014. EER pending submission in EES to the Office of Compliance.
Pharm/Tox	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>The specification for the drug product includes a limit for the codeine related degradant (b) (4) of NMT (b) (4)%. (b) (4)</p> <p>The pharmacologist should also be made aware that the drug product specification still includes a limit of NMT (b) (4)% for the (b) (4) impurity (at the Pre-NDA meeting the applicant was informed that qualification data would be needed as this limit was above the ICH Q3B threshold for qualification).</p>
Methods Validation	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Left to reviewer's discretion if any drug product methods are questionable, but codeine and chlorpheniramine are not NMEs so it is not mandatory that any methods be assessed by the Agency laboratory.
EA	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Applicant claims a categorical exclusion under 21 CFR 314.50(d)(1)(iii), and states that action on the application will not increase the use of the active moiety.
New Drug Micro	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The drug product is not sterile. The drug product

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

NDA #: 206323

Received Date: 22-AUG-2014

			specification does not include any parameters related to microbial testing. The microbiology team has been notified (26-AUG-2014) of the application and will determine if any microbiology review is needed.
CDRH	<input type="checkbox"/>	X	N/A
Other	<input type="checkbox"/>	X	N/A

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

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND	Submitted 14-OCT-2009, currently active	106992	LPCN 1084 (codeine phosphate 40 mg/chlorpheniramine maleate 8 mg combination extended release tablet)

**ONDQA Initial Quality Assessment (IQA) and Filing Review**

**For Pre-Marking Applications**

NDA #: 206323

Received Date: 22-AUG-2014

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

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
Meeting Minutes (EoP2)	04-OCT-2010	IND 106992	Minor CMC comments related to IR reference product supporting information
Meeting Minutes (Pre-NDA)	10-OCT-2013	IND 106992	Applicant was asked to include justification in the NDA for lack of microbial testing for the drug product; Applicant was asked to provide appropriate qualification data for the <span style="background-color: gray; color: gray;">(b) (4)</span> impurity as the level allowed in the drug product is > the 0.5% qualification threshold of ICH Q3B

## OVERALL PRODUCT QUALITY CONCLUSIONS AND RECOMMENDATIONS

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

Yes	No	CMC Filing Issues
X	<input type="checkbox"/>	N/A

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

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

**Does the submission contain any of the following elements?**

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

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

NDA #: 206323

Received Date: 22-AUG-2014

QbD Elements	<input type="checkbox"/>	X	
SPOTS	<input type="checkbox"/>	X	

<b>Is a team review recommended?</b>		
Yes	No	Suggested expertise for team
<input type="checkbox"/>	X	

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

NDA #: 206323

Received Date: 22-AUG-2014

**Drug Product Risk Assessment**

DP attribute/ CQA	Factors that can impact the CQA	O <sup>2</sup>	S <sup>2,3</sup>	D <sup>2</sup>	FMECA RPN #	Comment & considerations
Identification	<ul style="list-style-type: none"> <li>incorrect drugs formulated</li> <li>no drug formulated</li> </ul>	1	3	1	3	<ul style="list-style-type: none"> <li>Probability of occurrence should be low and detectability high if applicant adheres to GMPs: specifications for both drug substances include specific identification testing (IR spectra relative to USP reference standards)</li> <li>Severity of failure would depend on situation (incorrect or no drug present)<sup>3</sup></li> <li>Final drug product specification includes two non-specific tests for each drug for identity confirmation</li> </ul>
Assay, Stability	<ul style="list-style-type: none"> <li>input purity of APIs</li> <li>input purity of excipients</li> <li>incorrect amounts of API formulated</li> <li>impurity formation due to interaction of drugs with excipients or catalyzed by excipients</li> <li>degradation of drug substances due to moisture and oxidation (protection from environment)</li> <li>presence of organic solvents</li> <li>CU problems (<i>vide infra</i>)</li> </ul>	3	3	2	18	<ul style="list-style-type: none"> <li>Total impurities allowed in input APIs limited by respective specifications</li> <li>Excipients are of compendial quality, i.e., suitable for solid oral dosage forms</li> <li>GMP adherence should prevent incorrect API amounts formulated</li> <li>Applicant does not address API and excipient compatibility, but this can be gauged indirectly based on stability data provided</li> <li>(b) (4)</li> <li>(b) (4)</li> </ul>
Physical stability (solid)	<ul style="list-style-type: none"> <li>polymorphic conversion of one or</li> </ul>	1	3	5	15	<ul style="list-style-type: none"> <li>Codeine phosphate is stable as a (b) (4) hemi-hydrates<sup>4</sup>; both forms are stable at room temperature and</li> </ul>

<sup>2</sup> O = Probability of Occurrence; S = Severity of Effect; D = Detectability

<sup>3</sup> Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs.

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

NDA #: 206323

Received Date: 22-AUG-2014

**Drug Product Risk Assessment**

state of API, dosage form)	both drug substances					<p>are freely soluble in water (note that the RS from USP is said to be the hemi-hydrate) but melting point of 154-158°C is consistent with the hemi-hydrate form</p> <ul style="list-style-type: none"> <li>• CPM does not appear to exist in different polymorphic forms</li> <li>• (b) (4)</li> </ul>
Content uniformity	<ul style="list-style-type: none"> <li>• lack of blend uniformity (segregation) prior to (b) (4)</li> </ul>	2	3	3	18	<ul style="list-style-type: none"> <li>• (b) (4)</li> <li>• (b) (4)</li> <li>• (b) (4)</li> <li>• (b) (4)</li> </ul>
Microbial limits <sup>5</sup>	<ul style="list-style-type: none"> <li>• microbial load of input materials for formulation</li> <li>• microbial contamination during processing</li> <li>• microbial growth during shelf life</li> </ul>	1	3	5	15	<ul style="list-style-type: none"> <li>• The applicant analyzed three batches of the drug product as per USP &lt;61&gt;, “showed no detected CFUs for total aerobes or for yeast and mold”</li> <li>• Applicant concludes that it is not necessary to routinely test the drug product for microbial properties</li> <li>• Lactose, Mg stearate, microcrystalline cellulose, and polysorbate are tested for microbial contamination as per their respective specifications</li> </ul>
Alcohol Dose Dumping	<ul style="list-style-type: none"> <li>• extended release properties compromised in the presence of ethanol</li> </ul>	2	3	4	24	<ul style="list-style-type: none"> <li>• <i>In vitro</i> dissolution data indicate that increasing levels of ethanol lead to slightly decreasing release for both chlorpheniramine and codeine (see P.2)</li> </ul>

<sup>4</sup> See T. Runcevski et al., On the Hydrates of Codeine Phosphate: The Remarkable Influence of Hydrogen Bonding on the Crystal Size, *Chem. Commun.*, 2014, 50, p. 6970.

<sup>5</sup> Evaluation to be done by the microbiology team (as per microbiology pilot).

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

NDA #: 206323

Received Date: 22-AUG-2014

**Drug Product Risk Assessment**

Drug Release or Dissolution	<ul style="list-style-type: none"> <li>polymorph conversion</li> <li>changes in input excipients and APIs</li> <li>API particle size change</li> <li>tablet moisture content</li> <li>tablet hardness</li> </ul>	3	3	2	18	<ul style="list-style-type: none"> <li>Standard (and stable) crystalline forms of both APIs are used in the formulation</li> <li>Excipients are also of compendial grade and in common use</li> <li>API particle size growth not expected based on manufacturing process (b) (4)</li> <li>Some potential for API particle size attrition during (b) (4)</li> <li>No testing of final tablet moisture content proposed for specification</li> <li>Tablet breaking force tested in-process (see P.5.1)</li> </ul>
-----------------------------	--	---	---	---	----	---

ONDQA Initial Quality Assessment (IQA) and Filing Review

For Pre-Marking Applications

NDA #: 206323

Received Date: 22-AUG-2014

## CMC Summary: Critical Issues and Complexities

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

- Currently the established name of the drug product and strength is consistent, however, the name includes the (b) (4) [redacted]. The chair of the Labeling and Nomenclature Committee has been asked to comment on what is the most appropriate established name (and corresponding strength) for this drug product. A response is currently pending prior to various internal discussions necessary.

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

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

The chlorpheniramine maleate is manufactured internationally by (b) (4) [redacted]. The codeine phosphate is manufactured by (b) (4) [redacted]. Information for the manufacturer of the drug substances is provided in DMFs referenced in the application. The oral extended release tablet drug product is manufactured by Nexgen Pharma at their Colorado Springs, CO facility. This latter site has not been inspected for the TTR (tablets, extended release) profile class according to the FACTS database.

## Biopharmaceutics Filing Review: Summary, Critical Issues and Complexities

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS				
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?	x		

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

NDA #: 206323

Received Date: 22-AUG-2014

3.	Does the application contain the dissolution method development report?	x		
4.	Is there a validation package for the analytical method and dissolution methodology?	x		
5.	Does the application contain data from in vitro alcohol interaction studies?	x		
6.	Does the application include a biowaiver request?		x	Not Applicable
7.	Is there information provided to support the biowaiver request?		x	Not Applicable
8.	Does the application include a IVIVC model?		x	Not Applicable
9.	Is information such as BCS classification mentioned, and supportive data provided?	x		The Applicant reports that chlorpheniramine maleate is a BCS Class 1 compound and that codeine phosphate is a BCS Class 3 compound.
10.	Is information on mixing the product with foods or liquids included?		x	Not Applicable
11.	Is there any in vivo BA or BE information in the submission?	x		The Applicant conducted 2 studies to show bioequivalence of the ER tablet to IR tablet. A single-dose study (LPCN 1084-12-002) was conducted to compare 1 dose of the ER tablet with 2 doses of the IR tablet dosed 6 hours apart. Another study was a multiple-dose study (LPCN 1084-13-001) conducted over 6.5 days of dosing. These studies will be reviewed by the Office of Clinical Pharmacology.

<b>B. FILING CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	<b>IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>	x		
13.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.	-	-	

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

NDA #: 206323

Received Date: 22-AUG-2014

14.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		x	
-----	--	--	---	--

**INITIAL BIOPHARMACEUTICS ASSESSMENT**

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of 1) the proposed dissolution methodology and acceptance criteria, 2) the data from the in vitro alcohol dose dumping study, and 3) the data supporting the ER claim.

The proposed dissolution method is:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	50 rpm	900 ml	37 °C	SGF w/o enzyme (pH 1.2) buffer

The proposed dissolution acceptance criterion is:

Acceptance Criteria	
1 hr: NLT	(b) (4)0.
4 hrs: NLT	(b) (4)0.
6 hrs: NLT	(b) (4)0.
12 hrs: NLT	(b) (4)0.

**RECOMMENDATION:**

The ONDQA Biopharmaceutics team has reviewed NDA 206323 for filing purposes. We found this NDA **fileable** from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission.

## CMC FILING REVIEW CHECKLIST

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

A. GENERAL					
	Parameter	Yes	No	N/A	Comment
15.	Is the CMC section organized adequately?	X	<input type="checkbox"/>	<input type="checkbox"/>	
16.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X	<input type="checkbox"/>	<input type="checkbox"/>	

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

NDA #: 206323

Received Date: 22-AUG-2014

17.	Are all the pages in the CMC section legible?	<input type="checkbox"/>	<input type="checkbox"/>		All pages examined for production of this IQA/filing review were legible.
18.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X	<input type="checkbox"/>	<input type="checkbox"/>	The qualification issue for the (b) (4) impurity will need to be examined by the pharmacologist.

**B. FACILITIES\***

	Parameter	Yes	No	N/A	Comment
1	Is a single, comprehensive list of all involved facilities available in one location in the application?	X	<input type="checkbox"/>	<input type="checkbox"/>	See form 356h
2	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>	<input type="checkbox"/>	<input type="checkbox"/>	X	Note, however, that it is likely that precursor compounds in the synthesis of codeine are derived from natural sources (e.g., from poppys).
2	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> <li>Name of facility,</li> <li>Full address of facility including street, city, state, country</li> <li>FEI number for facility (if previously registered with FDA)</li> <li>Full name and title, telephone, fax number and email for on-site contact person.</li> <li>Is the manufacturing responsibility and function identified for each facility?, and</li> <li>DMF number (if applicable)</li> </ul>	<input type="checkbox"/>	X	<input type="checkbox"/>	The 356h incorrectly lists (b) (4) DMF (b) (4) (for (b) (4) ) instead of their DMF (b) (4) for (b) (4)

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

NDA #: 206323

Received Date: 22-AUG-2014

2	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X	<input type="checkbox"/>	<input type="checkbox"/>	
2	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X	<input type="checkbox"/>	<input type="checkbox"/>	<p>(b) (4) is an analytical testing firm used by the applicant for raw material and packaging component testing.</p>

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

NDA #: 206323

Received Date: 22-AUG-2014

2	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X	<input type="checkbox"/>	<input type="checkbox"/>	
---	---	---	--------------------------	--------------------------	--

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT					
	Parameter	Yes	No	N/A	Comment
25.	Has an environmental assessment report or categorical exclusion been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	Exclusion requested as per 21 CFR 314.50(d)(1)(iii); Applicant also claims that they know of no extraordinary circumstances regarding the EA.

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

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

NDA #: 206323

Received Date: 22-AUG-2014

<b>E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>					
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
27.	Does the section contain a description of the DS manufacturing process?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Reference is made to DMFs (b) (4) and (b) (4) See table above for current review status.
28.	Does the section contain identification and controls of critical steps and intermediates of the DS (in process parameters)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
29.	Does the section contain information on impurities?	X	<input type="checkbox"/>	<input type="checkbox"/>	Also, see comment 13 above.
30.	Does the section contain information regarding the characterization of the DS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
31.	Does the section contain controls for the DS?	X	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above; the NDA also contains the specifications and analytical methods for testing of the drug substances by Nexgen, the drug product manufacturer.
32.	Has stability data and analysis been provided for the drug substance?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
33.	Does the application contain Quality by Design (QbD) information regarding the DS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
34.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
35.	Does the section contain container and closure information?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.

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

NDA #: 206323

Received Date: 22-AUG-2014

<b>F. DRUG PRODUCT (DP)</b>					
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
36.	Does the section contain quality controls of excipients?	X	<input type="checkbox"/>	<input type="checkbox"/>	
37.	Does the section contain information on composition?	X	<input type="checkbox"/>	<input type="checkbox"/>	
38.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X	<input type="checkbox"/>	<input type="checkbox"/>	
39.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X	<input type="checkbox"/>	<input type="checkbox"/>	
40.	Is there a batch production record and a proposed master batch record?	X	<input type="checkbox"/>	<input type="checkbox"/>	See R and P.3.3
41.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X	<input type="checkbox"/>	<input type="checkbox"/>	See P.2
42.	Have any biowaivers been requested?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The biopharmaceutics team has addressed any biowaiver requests ( <i>vide infra</i> ).
43.	Does the section contain description of to-be-marketed container/closure system and presentations?	X	<input type="checkbox"/>	<input type="checkbox"/>	There is a 75 cc HDPE bottle with child-resistant closure and desiccant.
44.	Does the section contain controls of the final drug product?	X	<input type="checkbox"/>	<input type="checkbox"/>	
45.	Has stability data and analysis been provided to support the requested expiration date?	X	<input type="checkbox"/>	<input type="checkbox"/>	Stability data are provided, but there has been no analyses information included.

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

NDA #: 206323

Received Date: 22-AUG-2014

46.	Does the application contain Quality by Design (QbD) information regarding the DP?	<input type="checkbox"/>	X	<input type="checkbox"/>	The applicant does not appear to be requesting any regulatory relief based on any QbD-related studies.
47.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	<input type="checkbox"/>	X	<input type="checkbox"/>	

**G. METHODS VALIDATION (MV)**

	Parameter	Yes	No	N/A	Comment
48.	Is there a methods validation package?	X	<input type="checkbox"/>	<input type="checkbox"/>	Although neither drug substance is an NME, if the reviewer decides that the Agency should evaluate any of the methods, the applicant can be asked to provide sample and reference materials to the Agency laboratory.

**H. MICROBIOLOGY**

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

**I. LABELING**

	Parameter	Yes	No	N/A	Comment
50.	Has the draft package insert been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	
51.	Have the immediate container and carton labels been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	
52.	Does section contain tradename and established name?	<input type="checkbox"/>	X	<input type="checkbox"/>	No trademark is proposed yet for the drug product, but the tradename of the drug product manufacturer is included on the label.

**A. FILING CONCLUSION**

	Parameter	Yes	No	N/A	Comment
53.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	X	<input type="checkbox"/>	<input type="checkbox"/>	

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

NDA #: 206323

Received Date: 22-AUG-2014

54.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.	<input type="checkbox"/>	<input type="checkbox"/>	X	
55.	Are there any potential review issues identified?	<input type="checkbox"/>	X	<input type="checkbox"/>	
56.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?	<input type="checkbox"/>	X	<input type="checkbox"/>	
57.	Are there any internal comments to other disciplines:	<input type="checkbox"/>	<input type="checkbox"/>	X	

## REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

Craig M. Bertha, PhD, Acting CMC Lead  
Kareen Riviere, PhD, Biopharmaceutics Reviewer  
Tapash Ghosh, PhD., Biopharmaceutics Team Leader  
Julia Pinto, PhD, Acting Branch Chief

*{See appended electronic signature page}*

---

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

/s/  
-----

CRAIG M BERTHA  
09/04/2014

KAREEN RIVIERE  
09/04/2014

TAPASH K GHOSH  
09/04/2014

JULIA C PINTO  
09/08/2014