

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202245Orig1s000**

**CHEMISTRY REVIEW(S)**

# Codeine Sulfate Oral Solution

## NDA 202245

### Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

- Applicant:** Roxane Labs, Inc.  
1809 Wilson Rd.,  
Columbus, OH 43228.
- Indication:** For management of moderate to severe pain where the use of an opioid analgesic is appropriate.
- Presentations:** The oral solution formulated as 30 mg/5mL and packaged in 500 mL PET amber colored bottles, packed in a carton with five oral syringes (5 mL) and one measuring cup (5 mL).
- EER Status:** Acceptable as of Jan 24, 2011.
- Consults:** **EA** – Granted  
**Methods Validation** – Revalidation by Agency will not be requested since the methods listed are standard.  
**Pharmacology/Toxicology** – Acceptable.  
**Biopharmaceutics** – Acceptable, with PMC  
**Quality Microbiology** – Acceptable

**Original Submission:** 27-Sep-20010

#### Post-Approval CMC Commitments:

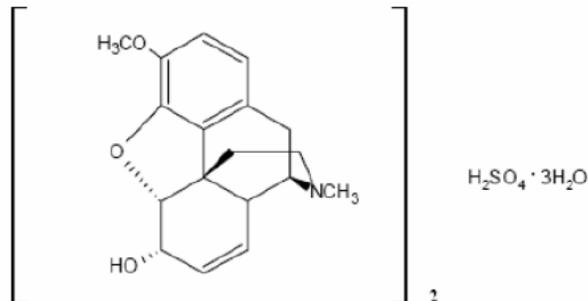
The applicant has committed

- To develop a validated method for quantitative monitoring of the drug product color and update the drug product specifications with data-based acceptance criteria by July 8, 2011.
- To collect adequate systematic release and stability data for the drug product, according to the updated specifications, and submit in a prior-approval supplement by September 30, 2012. The submission will include analysis of release and stability data for color, pH, content of ascorbic acid, and the content of codeine sulfate. Additionally, the applicant committed to providing a statistical evaluation of the observed changes for each of these attributes and proposes data-reflecting acceptance criteria for drug product color, pH and the content of ascorbic acid. They will also revise, as needed, drug product specifications and stability protocol with detailed references to the validated analytical methods

**Drug Substance:** The drug substance codeine sulfate trihydrate is a derivative of codeine alkaloid, which belongs to the Morphinan-6 $\alpha$ -ol group of opioids occurring naturally in the opium poppy plant. It is manufactured by (b) (4)  
The manufacturing and controls are supported by two

DMFs: (b) (4) and (b) (4) Both DMFs have currently adequate status to support the application, and the manufacturing site has an Acceptable cGMP recommendation as of Jan 24, 2011.

Codeine sulfate trihydrate is a fine crystalline powder with specific rotation of  $-112.5^{\circ}$  to  $-115.0^{\circ}$ , and pH 5.0. It is soluble in water and insoluble in chloroform and ether.



Molecular Formula:  $(\text{C}_{18}\text{H}_{21}\text{NO}_3)_2 \cdot \text{H}_2\text{SO}_4 \cdot 3\text{H}_2\text{O}$  Molecular Weight: 750.85 g/mol  
Morphinan-6 $\alpha$ -ol,7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-,(5 $\alpha$ ,6 $\alpha$ )-, sulfate (2:1) (salt), trihydrate

The drug substance specifications has acceptable controls for description, identification (ID), specific rotation, acidity, water content, readily carbonizable substances, residue on ignition, limits on morphine, heavy metals, microbial limits, residual solvents, related compounds, and assay. Note that (b) (4) is controlled at NMT (b) (4) which was found to be acceptable by the Pharm Tox team.

The container closure system details are provided in the DMFs. A retest period of (b) (4) months is established by the DMF holder.

**Conclusion:** The drug substance is satisfactory.

**Drug Product:**

The drug product is a (b) (4) oral solution of codeine sulfate in a concentration of 30 mg/5 mL. The formulation contains about (b) (4) sorbitol, (b) (4) glycerine, (b) (4) ascorbic acid (b) (4) citric acid (b) (4) sucralose (b) (4), sodium benzoate and EDTA (b) (4) artificial coloring (FD&C Yellow #6 and Red #40), and orange flavoring mixture XBF-709818. The formulation has a low pH 3.3.

(b) (4)

The drug product is manufactured by Boehringer Ingelheim's Roxane Inc., in Columbus, OH. Acceptable EER is available for the manufacturing facilities as of Jan 24, 2011. Pilot scale batches were (b) (4) and the commercial batch is intended to be (b) (4)

**30mg/5mL Oral Solution Component and Composition Table**

<u>Ingredients</u>	<u>Purpose</u>	<u>Quality Standard</u>	<u>Dosage (Amount per 5 mL)</u>	<u>Quantity (mg/mL)</u>	<u>Quantity (%w/w)</u>	<u>Quantity (Amount)</u> (b) (4)
Codeine Sulfate, USP	Active Ingredient	USP; BIRI Spec. No. 6081700R-01-06	30 mg			(b) (4)
Sorbitol Solution, USP (b) (4)	(b) (4)	USP	(b) (4)			(b) (4)
Glycerin, USP	(b) (4)	USP				(b) (4)
Ascorbic Acid, USP	(b) (4)	USP				(b) (4)
Citric Acid Anhydrous, USP (b) (4)	(b) (4)	USP				(b) (4)
Disodium Edetate, USP	(b) (4)	USP				(b) (4)
Sucralose, NF (b) (4)	(b) (4)	NF				(b) (4)
Sodium Benzoate, NF (b) (4)	(b) (4)	NF				(b) (4)
FD&C Yellow No. 6 (b) (4)	(b) (4)	BIRI Spec. No. 610800R-01-01				(b) (4)
FD&C Red No. 40	(b) (4)	BIRI Spec. No. 610500R-01-01				(b) (4)
Orange Flavor, XBF-709818	(b) (4)	BIRI Spec. No. 619400R-01-01				(b) (4)
Water, (b) (4) USP	(b) (4)	USP				(b) (4)

The manufacturing process is relatively simple being that this is a solution. The applicant has identified the following steps as critical steps of the manufacturing process: (b) (4)

The drug product is packaged in 500 mL PET amber bottles with a child resistant closure. Five oral calibrated syringes (5 mL) and 5 mL measuring cup are co-packaged in the same carton.

The release and stability controls for the drug product were revised significantly during the review process. The release specifications for bulk solution include description and density. The final solution is controlled for description, ID, pH, microbial content, Assays for codeine sulfate, sodium benzoate, and ascorbic acid, degradation products, (b) (4) and residual solvents. Additional changes to the controls for drug product color, pH, and content of ascorbic acid may be implemented upon submission of additional data in a prior approval supplement targeted for September 30, 2012.

The drug product is packaged in 500 mL amber bottles made of PET and capped with child resistant closures. In use studies demonstrate that the contents of the bottles should be used in 40 days, once opened.

An expiration dating period of 18 months is established based on the provided stability data.

**Conclusion:** The drug product is acceptable.

**Additional Items:**

Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Method validation will not be requested since all methods are standard.

**Overall Conclusion:**

From a CMC perspective, the application is recommended for **approval**.



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PRASAD PERI

06/17/2011

Recommend approval from CMC

**NDA 202-245**

**Codeine Sulfate Oral Solution, 30 mg / 5 mL  
(formulated with codeine sulfate trihydrate, USP)**

**Roxane Laboratories, Inc.**

**Eugenia M. Nashed, Ph.D.  
Office of New Drug Quality Assessment, Division III**

**Division of Anesthesia, Analgesia and Addiction Drug Products**

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# Chemistry Review Data Sheet

1. NDA 202-245
2. REVIEW #: 1
3. REVIEW DATE: 06-June-2011
4. REVIEWER: Eugenia M. Nashed
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	<u>Stamp Date</u>	<u>Assigned Date</u>
Original NDA	27-Sep-2010	27-Sep-2010	29-Nov-2010
Amendment BC	14-Jan-2011	14-Jan-2011	14-Jan-2011
Amendment BC	04-Feb-2011	04-Feb-2011	04-Feb-2011
Amendment BC	23-Feb-2011	23-Feb-2011	23-Feb-2011
Amendment BC	10-Mar-2011	10-Mar-2011	10-Mar-2011
Amendment BC	18-Mar-2011	18-Mar-2011	18-Mar-2011
Amendment BC	06-Apr-2011	06-Apr-2011	06-Apr-2011
Amendment BC	12-Apr-2011	12-Apr-2011	12-Apr-2011
Amendment BC	27-Apr-2011	27-Apr-2011	27-Apr-2011
Amendment BC	05-May-2011	05-May-2011	05-May-2011
Amendment BC	12-May-2011	12-May-2011	12-May-2011
Amendment BC	26-May-2011	26-May-2011	26-May-2011
Amendment BC	27-May-2011	27-May-2011	27-May-2011
Amendment BC	06-Jun-2011	06-Jun-2011	06-Jun-2011

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Roxane Laboratories, Inc.

Address: 1809 Wilson Rd., Columbus, OH 43228.

Representative: Elizabeth Ernst, Director, Drug Regulatory Affairs and Medical Affairs

Telephone: (614) 272-4785

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

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Codeine sulfate solution
- c) Code Name/# (ONDC only): None
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 4
  - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Analgesic

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 30 mg of codeine sulfate per 5 mL of solution

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

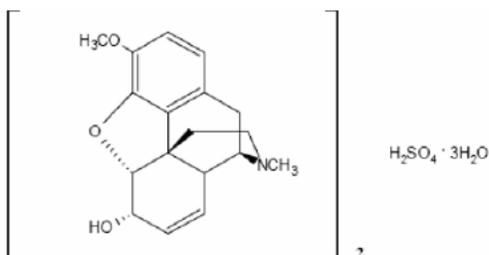
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

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

### Codeine Sulfate Trihydrate



Molecular Formula:  $(C_{18}H_{21}NO_3)_2 \cdot H_2SO_4 \cdot 3H_2O$

Molecular Weight: 750.85 g/mol

Morphinan-6 $\alpha$ -ol,7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-,(5 $\alpha$ ,6 $\alpha$ )-, sulfate (2:1) (SALT), trihydrate

CAS Number: 6854-40-6

## 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)	2	(b) (4)	Codeine sulfate, USP (b) (4)	1	Adequate	July 2009	Deficiency Letter Jan 28, 2009. Response acceptable from the CMC perspective. Also, acceptable from the PharmTox perspective -See review of PharmTox data by Delatte/Melon.
	2		Orange Flavor XBF-709818	1	Adequate	May 2, 2011	The list of ingredients was discussed with the PharmTox review team and was found acceptable from the safety perspective
	3		(b) (4)	4	Adequate		Meets the requirements in 21 CFR
	3			4	Adequate		Meets the requirements in 21 CFR 177.1520
	3			4	Adequate		Meets the requirements in 21 CFR
	3			4	Adequate		Meets the requirements in 21 CFR
	3			4	Adequate		Meets the requirements in 21 CFR
	3			4	Adequate		Meets the requirements in 21 CFR
	3			4	Adequate		Meets the requirements in 21 CFR; Approved N 22-292
	3			4	Adequate		Meets the requirements in 21 CFR; Approved N 22-292
	3			4	Adequate		Meets the requirements in 21 CFR; Approved N 22-195

<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 Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

#### C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT

### 18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORW'D	STATUS/ REVIEWER	COMMENTS
Biometrics	None			
EER	GMP Inspections of the manufacturing and testing facilities	Oct 6, 2010	AC 24-Jan-2011	Status for all manufacturing and testing facilities was assigned by DO based on the file review.
Pharm/Tox	Safety of the proposed acceptance criteria for impurities and composition of artificial orange flavor.	Jan, 2011	AC	The content of (b) (4) impurities, above-ICH-levels impurities, and flavor components were found adequately justified based on submitted data by the Delatte/Mellon review team.
Methods Validation				Analytical methods are standard and no need for validation is anticipated
DMEPA	Labeling review		Pending	
EA			AC	Categorical exclusion accepted based on the information provided in module 1.12.14.
Microbiology	Microbial specifications	Feb, 2011	AC	Additional microbial limits for B.cepacia are implemented to drug product controls – review by Jessica Cole (May 4, 2011)

# The Chemistry Review for NDA 202-245

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application is recommended for approval from the CMC perspective, based on provided data and commitment outlined in section I.B., of this review.

The overall EER status for this NDA is acceptable (AC) as of Jan 24, 2011. The supporting DMFs have adequate status as of May 2, 2011. The provided controls for impurities and microbial safety are adequate based on consult reviews by Pharmacology-Toxicology and Microbiology review teams.

The drug product expiry period granted is limited to 18 month for drug product stored at controlled room temperature, based on the 12 months of real time stability data submitted for three pilot-scale batches of the drug product and current drug product specifications. The re-evaluation of drug product specifications is a subject of the pending commitment from the Applicant (refer to section I.B., below).

The in-use stability period is limited to 40 days, based on the submitted in-use stability data, i.e., the drug product should be used within 40 days from the first opening of the bottle.

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

The original NDA application has lacked testing for the pH, color and microbial limits for *Burkholderia cepacia*. In response to our comments (IR letters dated Feb 28, Apr 7, 2011, and additional IR dated May 25, 2009), the Applicant has implemented testing for the pH and proposed interim acceptance criteria due to the limited data available. Also, a Phase 4 commitment was submitted (amendments dated May 27, and June 6, 2011) to provide a validated quantitative method for monitoring the color of drug product along with data-based acceptance criteria by July 8, 2011. In addition, the Applicant committed to present complete stability data and to revise the specifications for drug product, in a prior-approval supplement by September 30, 2012. Upon review of Applicant's responses dated May 27, and June 6, 2011, regarding the observed changes in drug product color and pH during stability testing, the CMC team drafted the revised Commitment, which needs to be forwarded to the Applicant in the action letter.

#### Phase 4 Commitment

You commit to develop a validated method for quantitative monitoring of the drug product color and update the drug product specifications with data-based acceptance criteria by July 8, 2011. You commit to collect adequate systematic release and stability data for the drug product,

according to the updated specifications, and submit in a prior-approval supplement by September 30, 2012. The submission will include analysis of release and stability data for color, pH, content of ascorbic acid, and the content of codeine sulfate. You will provide statistical evaluation of the observed changes for each of these attributes and propose data-reflecting acceptance criteria for drug product color, pH and the content of ascorbic acid. You will submit, revised as needed, drug product specifications and stability protocol with detailed references to the validated analytical methods.

## II. Summary of Chemistry Assessments

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

This NDA, dated Sep 27, 2010, for Codeine Sulfate Oral Solution, 30 mg/5 mL was filed as a 505(b)(2) application, standard review. The Reference Listed Drug (RLD) for this application is Codeine Sulfate Tablets, 15 mg, 30 mg and 60 mg (NDA 22-402) from the same sponsor, which was approved on July 16, 2009. One pivotal bioequivalence study was submitted to bridge the oral solution formulation and the codeine sulfate tablets.

The drug product contains codeine sulfate trihydrate, which is present in the RLD, marketed by the Applicant. The indication for codeine sulfate solution is the (b) (4) of mild to severe pain in adults. The API is a Schedule II controlled substance due to the potential for drug abuse.

#### Drug substance

The drug substance codeine sulfate trihydrate is a derivative of codeine alkaloid, which belongs to the Morphinan-6 $\alpha$ -ol group of opioids occurring naturally in the opium poppy plant. It is manufactured by (b) (4). The manufacturing and controls are supported by two DMFs: (b) (4) and (b) (4). Both DMFs have currently adequate status to support the application, and the manufacturing site has Acceptable EER recommendation from the OC, as of Jan 24, 2011.

Codeine sulfate trihydrate is a fine crystalline powder with specific rotation of  $-112.5^{\circ}$  to  $-115.0^{\circ}$ , and pH 5.0. It is soluble in water and insoluble in chloroform and ether.

#### Drug Product

The drug product is a (b) (4) oral solution of codeine sulfate in concentration 30 mg/5 mL. The formulation contains about (b) (4) of sorbitol, (b) (4) glycerine, (b) (4) (b) (4) ascorbic acid (b) (4), (b) (4) citric acid (b) (4) sucralose (b) (4) sodium benzoate and EDTA (b) (4) artificial coloring (FD&C Yellow #6 and Red #40), and orange flavoring mixture XBF-709818. The formulation has very low pH 3.3.

The drug product is packaged in 500 mL PET amber bottles with a child resistant closure. Five oral calibrated syringes (5 mL) and 5 mL measuring cup are co-packaged in the same carton.

The drug product is manufactured by Boehringer Ingelheim Roxane, Inc. in Columbus, OH. Acceptable EER is available for the manufacturing facilities as of Jan 24, 2011.

The release and stability controls for the drug product were revised significantly during the review process. Most likely additional changes to the controls for drug product color, pH, and content of ascorbic acid will be implemented upon submission additional data in PAS on September 30, 2012.

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

The drug product, Codeine sulfate oral solution, 30 mg/5mL, is intended for <sup>(b) (4)</sup> of mild to moderately severe pain in adults. It is administered with the use of calibrated oral syringe (5 mL) which is included in the package – refer to measuring instructions in the Patients Instructions. Codeine sulfate is an opioid agonist of the morphine-type and a Schedule II controlled substance.

The drug product storage conditions are specified as controlled room temperature, 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F). In addition, the drug product must be protected from light and moisture.

The shelf life expiry period for drug product is limited to 18 months, when stored at controlled room temperature, based on the 12 months of stability data submitted up to date, and considering the pending commitment (see section I.B. of this review).

The in-use stability period is 40-days, based on the submitted in-use stability data, i.e., the drug product should be used within 40 days from the first opening of the bottle.

### **C. Basis for the CMC Recommendation**

This NDA application is recommended for approval from the CMC perspective, based on provided data and commitment outlined in section I.B., of this review.

The safety of the drug substance and drug product impurities which possess structural alert for carcinogenicity/genotoxicity <sup>(b) (4)</sup> or occur above the ICH-recommended threshold <sup>(b) (4)</sup> is adequate and is addressed in the Pharmacology-Toxicology review by Marcus Delatte and Dan Mellon.

The preservative effectiveness and microbial safety is considered adequate and it is addressed in the Microbiology review dated May 4, 2011, by Jessica Cole.

The overall EER status for this NDA is acceptable (AC) as of Jan 24, 2011. The supporting DMFs have adequate status as of May 2, 2011.

See complete list of commitments compiled in section I.B. of the Executive Summary, and additional comments listed at the end of this review.

The original NDA application has lacked testing for the pH, color and had incomplete microbial safety controls. Also, only 6 months of incomplete stability data for three pilot-scale batches of drug product was submitted in the original submission and no in-use stability data were provided. Stability updates were submitted late in the review cycle, 12 months stability data for three pilot batches on Apr 27, 2011, and complete 40 days in-use stability testing results were submitted on May 25, 2011.

During the NDA review cycle multiple CMC comments were forwarded to the applicant as follow:

Nov 2010 – Request for in-use stability data, LOA to DMF for orange flavor, photostability data and extractables/leachables, in the 74 day filing letter.

Jan 2011 - IR letter requesting update to stability data, since only 6 months data were submitted, and evaluation of the in-use stability testing protocol, in response to the Applicant's request.

Feb 4, 2009 Request to include calibrated syringe for patients and measuring device for Pharmacy dispensing. Submit revised CMC section for container closure, including supporting DMFs. Provide empty sample packaging. Reminder that granted expiry and in-use stability label time will be based on real time data submitted to the NDA.

Feb 28, 2009 Microbiology IR: (b) (4) Yeast and Mold acceptance criteria to NMT (b) (4) (b) (4). Provide controls for *Burkholderia cepacia*.

As of Apr 7, 2011, the following items were listed as deficiencies (see copy of comments to IR letter Apr 7, 2011, listed at the end of this review):

1. Provide complete revised table for drug product composition.
2. Provide revised drug product specifications to include method and acceptance criteria for color, pH, microbial limits for *B. cepacia*, revised and complete impurity profile, updated acceptance criteria for (b) (4).
3. Provide updated stability data (12 months) and in-use stability data.

In subsequent amendments dated Apr 12, Apr 27, May 5, and May 12, 2011, all issues were resolved adequately except the method and acceptance criteria for color and changes in the drug product color and pH, occurring during storage. In addition, an apparent increase in API potency is observed for all drug product batches stored at 25°C/60%RH, contrary to the same batches stored at 40°C/75%RH, (b) (4). Another IR letter was forwarded to the Applicant on May 25, 2011, requesting clarification of the submitted stability data in regard to the change in color and pH and increasing values for API assay – refer to copy of IR letter dated May 25, 2011, listed at the end of the review.

The issue of quantitative method and acceptance criteria for drug product color was resolved by the Applicant's commitment to develop and submit a new quantitative method by Jul 8, 2011, as specified in amendment dated May 27, 2011.

The review of Applicant's response of May 27, 2011, regarding the pH and color change on stability, combined with the reported instability of the ascorbic acid necessitates the need for additional commitment due to the lack of adequate amount of supporting data.

The drug product formulation was compared to a similar marketed oral formulation of morphine sulfate solution (NDA 22-195, Roxane Labs) and was noted that changes in color and pH were not observed on stability for the morphine sulfate solution. One of the differences in composition is the presence of ascorbic acid in the codeine sulfate formulation. (b) (4)

(b) (4) Based on the above the CMC team recommended collection of systematic data for color, pH and content of ascorbic acid and re-evaluation of the drug product controls when additional year of production and stability data are available.

The issue of increasing API assay values during storage at 25° C/60% RH was addressed partially by (b) (4) the acceptance criteria for API assay at stability to (b) (4), from the originally proposed (b) (4) refer to amendment dated Apr 27, 2011. Although all current stability results for the assay are within the (b) (4) range, the increasing trend is apparent for the 25° C/60% RH storage conditions. Additional stability data for assay should be evaluated upon submission of the future annual reports and supplements.

Upon discussion of the above issues during the Wrap-up team meeting, the Applicant was contacted by the Project Manager regarding the lacking stability data and re-evaluation of drug product controls. The Applicant responded with amendment dated June 6, 2011, committing to collect systematic stability data, evaluate instability trends and to revise the drug product specifications in PA supplement by September 30, 2012. Refer to the Phase 4 Commitment listed in section I.B. of the Executive Summary, and at the end of this review.

Currently, 18 months expiry period is supported by the submitted data. The drug product storage conditions are specified as 25° C (77 °F) with excursions permitted to 15-30°C (59-86°F). In addition, the drug product must be protected from light and moisture.

The in-use stability period is 40-days, based on the submitted in-use stability data, i.e., the drug product should be used within 40 days from the first opening of the bottle.

### III. Administrative

#### A. Reviewer's Signature

#### B. Endorsement Block

Chemist Name/Date: Same date as draft review

Chemistry Team Leader Name/Date

Project Manager Name/Date

#### C. CC Block

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/s/  
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EUGENIA M NASHED  
06/09/2011

PRASAD PERI  
06/10/2011  
I concur

**NDA 202-245**

**Codeine Sulfate Oral Solution, 30 mg / 5 mL  
(formulated with codeine sulfate trihydrate, USP)**

**Roxane Laboratories, Inc.**

**Eugenia M. Nashed, Ph.D.  
Office of New Drug Quality Assessment, Division III**

**Division of Anesthesia, Analgesia and Addiction Drug Products**

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# Chemistry Review Data Sheet

1. NDA 202-245
2. REVIEW #: 1
3. REVIEW DATE: 27-May-2011
4. REVIEWER: Eugenia M. Nashed
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	<u>Stamp Date</u>	<u>Assigned Date</u>
Original NDA	27-Sep-2010	27-Sep-2010	29-Nov-2010
Amendment BC	14-Jan-2011	14-Jan-2011	14-Jan-2011
Amendment BC	04-Feb-2011	04-Feb-2011	04-Feb-2011
Amendment BC	23-Feb-2011	23-Feb-2011	23-Feb-2011
Amendment BC	10-Mar-2011	10-Mar-2011	10-Mar-2011
Amendment BC	18-Mar-2011	18-Mar-2011	18-Mar-2011
Amendment BC	06-Apr-2011	06-Apr-2011	06-Apr-2011
Amendment BC	12-Apr-2011	12-Apr-2011	12-Apr-2011
Amendment BC	27-Apr-2011	27-Apr-2011	27-Apr-2011
Amendment BC	05-May-2011	05-May-2011	05-May-2011
Amendment BC	12-May-2011	12-May-2011	12-May-2011
Amendment BC	26-May-2011	26-May-2011	26-May-2011
Amendment BC	27-May-2011	27-May-2011	27-May-2011

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Roxane Laboratories, Inc.

Address: 1809 Wilson Rd., Columbus, OH 43228.

Representative: Elizabeth Ernst, Director, Drug Regulatory Affairs and Medical Affairs

Telephone: (614) 272-4785

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

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Codeine sulfate solution
- c) Code Name/# (ONDC only): None
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 4
  - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Analgesic

11. DOSAGE FORM: Oral Solution

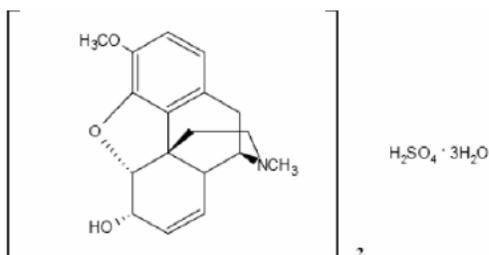
12. STRENGTH/POTENCY: 30 mg of codeine sulfate per 5 mL of solution

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#): SPOTS product – Form Completed Not a SPOTS product

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

### Codeine Sulfate Trihydrate



Molecular Formula:  $(C_{18}H_{21}NO_3)_2 \cdot H_2SO_4 \cdot 3H_2O$

Molecular Weight: 750.85 g/mol

Morphinan-6 $\alpha$ -ol,7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-, (5 $\alpha$ ,6 $\alpha$ )-, sulfate (2:1) (SALT), trihydrate

CAS Number: 6854-40-6

## 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)	2	(b) (4)	Codeine sulfate, USP (b) (4)	1	Adequate	July 2009	Deficiency Letter Jan 28, 2009. Response acceptable from the CMC perspective. Also, acceptable from the PharmTox perspective -See review of PharmTox data by Delatte/Melon.
	2		Orange Flavor XBF-709818	1	Adequate	May 2, 2011	The list of ingredients was discussed with the PharmTox review team and was found acceptable from the safety perspective
			(b) (4)	4	Adequate		Meets the requirements in 21 CFR
	3			4	Adequate		Meets the requirements in 21 CFR 177.1520
				4	Adequate		Meets the requirements in 21 CFR
				4	Adequate		Meets the requirements in 21 CFR
				4	Adequate		Meets the requirements in 21 CFR
				4	Adequate		Meets the requirements in 21 CFR
				4	Adequate		Meets the requirements in 21 CFR

<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 Supporting Documents:**

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

**C. Related Documents:**

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT

**18. CONSULTS/CMC-RELATED REVIEWS:**

CONSULTS	SUBJECT	DATE FORW'D	STATUS/ REVIEWER	COMMENTS
Biometrics	None			
EER	GMP Inspections of the manufacturing and testing facilities	Oct 6, 2010	AC 24-Jan-2011	Status for all manufacturing and testing facilities was assigned by DO based on the file review.
Pharm/Tox	Safety of the proposed acceptance criteria for impurities and composition of artificial orange flavor.	Jan, 2011	AC	
Methods Validation				Analytical methods are standard and no need for validation is anticipated
DMEPA	Labeling review		Pending	
EA			AC	Categorical exclusion accepted based on the information provided in module 1.12.14.
Microbiology	Microbial specifications	Feb, 2011	AC	Additional microbial limits for B.cepacia are implemented to drug product controls – review by Jessica Cole (May 4, 2011)

# The Chemistry Review for NDA 22-402

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application is recommended for approval from the CMC perspective, based on provided data and commitments outlined in section I.B., of this review.

Based on the 12 months of stability data submitted up to date, and considering pending commitments, the expiry period for drug product should be limited to 18 months, when stored at 25°C.

The overall EER status for this NDA is acceptable (AC) as of Jan 24, 2011. The supporting DMFs have adequate status as of May 2, 2011.

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

The original NDA application has lacked testing for the pH, color and microbial limits for *Burkholderia cepacia*. In response to our comments (IR letters dated Feb 28, Apr 7, 2011, and additional IR dated May 25, 2009), the Applicant has implemented testing for the pH and proposed interim acceptance criteria due to the limited data available. Also, a commitment was submitted in amendment dated May 27, 2011, to provide a validated quantitative method for monitoring the color of drug product along with data-based acceptance criteria by July 8, 2011. Upon review of Applicant's response dated May 27, 2011, regarding the observed changes in drug product color and pH during stability testing, the CMC team drafted Commitment #2, which needs to be forwarded to the Applicant.

### Commitments

1. You commit to provide a validated quantitative method for monitoring the color of drug product along with data-based acceptance criteria by July 8, 2011. Upon completion of the validation, you commit to provide this data in a prior-approval supplement on, or before July 8, 2011.
2. You commit to collect adequate amount of systematic release and stability data for drug product color, pH, and ascorbic acid content and propose a revised, data-based acceptance criteria for these attributes. You will provide supporting data and statistical evaluation of observed changes for each attribute. Also, you will address safety of the color impurities resulting from the decomposition of ascorbic acid. You will submit, revised as needed drug product specifications with data-reflecting acceptance criteria for drug product color, pH and for the content of ascorbic acid, in a prior-approval supplement by June 30, 2012.

## II. Summary of Chemistry Assessments

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

This NDA, dated Sep 27, 2010, for Codeine Sulfate Oral Solution 30 mg/5 mL was filed as a 505(b)(2) application, standard review. Reference Listed Drug is Codeine Sulfate Tablets (NDA 22-402) from the same sponsor, which was approved on July 16, 2009. One pivotal bioequivalence study was submitted to bridge the oral solution formulation and the codeine sulfate tablets.

The drug product contains codeine sulfate trihydrate, which is present in the approved product, Codeine sulfate tablets, NDA 22-402, marketed by the Applicant. The indication is for the (b) (4) of mild to severe pain in adults. The API is a Schedule II controlled substance due to the potential for drug abuse.

#### Drug substance

The drug substance codeine sulfate trihydrate is a derivative of codeine alkaloid, which belongs to the Morphinan-6 $\alpha$ -ol group of opioids occurring naturally in the opium poppy plant. It is manufactured by (b) (4), (b) (4). The manufacturing and controls are supported by two DMFs: (b) (4) and (b) (4). Both DMFs have currently adequate status to support the application, and the manufacturing site has Acceptable EER recommendation from the OC, as of Jan 24, 2011.

Codeine sulfate trihydrate is a fine crystalline powder with specific rotation of  $-112.5^{\circ}$  to  $-115.0^{\circ}$ , and pH 5.0. It is soluble in water and insoluble in chloroform and ether.

The safety of the drug substance and drug product impurities which either possess structural alert for carcinogenicity/genotoxicity (b) (4) or occur above the ICH-recommended level (b) (4) is addressed in the PharmTox review by Marcus Delatte and Dan Mellon.

#### Drug Product

The drug product is a (b) (4) oral solution of codeine sulfate in concentration 30 mg/5 mL. The formulation contains about (b) (4) of sorbitol, (b) (4) of glycerine, (b) (4) ascorbic acid, (b) (4) citric acid, (b) (4) sucralose, (b) (4) sodium benzoate and EDTA, (b) (4) artificial coloring and orange flavoring mixture XBF-709818. The formulation has very low pH 3.3.

The drug product is packaged in 500 mL PET amber bottles with a child resistant closure. A dispensing calibrated syringe (5 mL) and 5 mL measuring cup are co-packaged in the same carton.

The drug product is manufactured by Boehringer Ingelheim Roxane, Inc. in Columbus, OH. Acceptable EER is available for the manufacturing facilities as of Jan 24, 2011.

The release and stability controls for the drug product were revised significantly during the review process. Based on the 12 months of stability data submitted up to date, and considering pending commitments, the expiry period for drug product should be limited to 18 months, when stored at 25°C.

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

The drug product, Codeine sulfate oral solution, 30 mg/5mL, is intended for the (b) (4) of mild to moderately severe pain in adults. Codeine sulfate is an opioid agonist of the morphine-type and a Schedule II controlled substance.

The drug product storage conditions are specified as 25° C (77 °F) with excursions permitted to 15-30°C (59-86°F). In addition, the drug product must be protected from moisture and light. Currently, 18 months expiry period is supported by the submitted data.

### **C. Basis for the CMC Recommendation**

This NDA application is recommended for approval from the CMC perspective, based on provided data and commitments outlined in section I.B., of this review.

The safety of the drug substance and drug product ingredients and impurities is addressed in the PharmTox review (Delatte/Mellon) and the (b) (4) effectiveness and microbial safety is addressed in the Microbiology review dated May 4, 2011, by Jessica Cole.

The overall EER status for this NDA is acceptable (AC) as of Jan 24, 2011. The supporting DMFs have adequate status as of May 2, 2011.

See complete list of comments compiled in section I.B. of the Executive Summary, and at the end of this review.

The original NDA application has lacked testing for the pH, color and had incomplete microbial safety controls. Also, only 6 months of incomplete stability data for three registration batches was submitted in the original submission and no in-use stability data were provided. Stability updates were submitted late in the review cycle, 12 months stability data for three registration batches on Apr 27, 2011, and complete 40 days in-use stability testing results were submitted on May 25, 2011.

During the NDA review cycle multiple CMC comments were forwarded to the applicant as follow:

Nov 2010 – Request for in-use stability data, LOA to DMF for orange flavor, photostability data and extractables/leachables, in the 74 day filing letter.

- Jan 2011 - IR letter requesting update for stability data, since only 6 months data were submitted, and evaluation of the in-use stability testing protocol, in response to the Applicant's request.
- Feb 4, 2009 Request to include calibrated syringe for patients and measuring device for Pharmacy dispensing. Submit revised CMC section for container closure, including supporting DMFs. Provide sample packaging. Reminder that granted expiry and in-use stability label time will be based on real time data submitted to the NDA.
- Feb 28, 2009 Microbiology IR: (b) (4) Yeast and Mold acceptance criteria to NMT (b) (4) (b) (4) Provide controls for *Burkholderia cepacia*

As of Apr 7, 2011, the following items were listed as deficiencies (see copy of comments to IR letter Apr 7, 2011, listed at the end of this review):

1. Provide complete revised table for drug product composition
2. Provide revised drug product specifications to include method and acceptance criteria for color, pH, microbial limits for *B. cepacia*, revised and complete impurity profile, updated acceptance criteria for (b) (4).
3. Provide updated stability data and in-use stability data

In subsequent amendments dated Apr 12, Apr 27, May 5, May 12, and May 25, 2011, all issues were resolved adequately except the method and acceptance criteria for color and noted changes in the drug product color and pH, occurring during storage. Another IR letter was forwarded to the Applicant on May 25, 2011, requesting clarification of the submitted stability data in regard to the change in color and pH – refer to copy of IR letter dated May 25, 2011, listed at the end of the review. The issue of quantitative method and acceptance criteria for drug product color was resolved by the Applicant's commitment to develop the new method by Jul 8, 2011, as specified in amendment dated May 27, 2011.

The review of the Applicant's response of May 27, 2011, regarding the pH and color change on stability, combined with the reported instability of the ascorbic acid necessitates a need for additional commitment due to the lack of adequate amount of supporting data.

The drug product formulation was compared to another, similar oral formulation for morphine sulfate (NDA 22-195, Roxane Labs) and was noted that changes in color and pH were not observed on stability for the morphine sulfate solution. One of the differences in composition is the presence of ascorbic acid in the codeine sulfate formulation. (b) (4)

(b) (4). Based on the above the CMC team recommends collection of systematic data for color, pH and content of ascorbic acid and re-evaluation of the drug product controls when additional year of production and stability data are available.

Refer to the draft commitments listed in section I.B. of the Executive Summary, and at the end of this review.

Based on the 12 months of stability data submitted up to date, and considering pending commitments, the expiry period for drug product should be limited to 18 months, when stored at 25°C.

### **III. Administrative**

#### **A. Reviewer's Signature**

#### **B. Endorsement Block**

Chemist Name/Date: Same date as draft review  
Chemistry Team Leader Name/Date  
Project Manager Name/Date

#### **C. CC Block**

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/s/  
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EUGENIA M NASHED  
05/27/2011

PRASAD PERI  
05/28/2011  
Executive summary only. See full review #2 to follow shortly.

**Initial Quality Assessment  
Division III, Branch VIII  
Office of New Drug Quality Assessment  
Division of Anesthesia, Analgesia and Addiction Products**

OND Division:	Anesthesia, Analgesia and Addiction	
NDA:	202245	
Chemical Classification:	3S	
Applicant:	Roxane Laboratories, Inc.	
Stamp date:	September 27, 2010	
PDUFA Date:	July 27, 2011	
Trademark:	NA	
Established Name:	Codeine sulfate	
Dosage Form:	Oral solution, 30 mg/ml	
Route of Administration:	Oral	
Indication:	Treatment of mild to moderately severe pain	
Pharmaceutical Assessment Lead:	Danae D. Christodoulou, Ph.D.	
	YES	NO
ONDQA Fileability:	<u>√</u>	___
Comments for 74-Day Letter:	<u>√</u>	___

## Summary, Critical Issues and Comments

### A. Summary

The application is filed as a 505(b)(2), non-priority NDA with 10-month review clock. The referenced approved product is codeine sulfate tablets, 5 mg (NDA 22-402, Roxane). The applicant submitted a bridging relative bioavailability study to the approved product as per agreements with the Agency (Roxane's controlled correspondence of 9/20/2007, and FDA response of 10/6/2007).

Codeine sulfate solutions are used in hospice and palliative care when patients cannot ingest a large volume of solution without choking, and cannot receive IV analgesics.

The solution is packaged in amber 500 ml multi-dose bottles and dosed with a dosing (measuring) oral doser (syringe).

### B. Review, Comments and Recommendations

#### Drug Substance

#### Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight

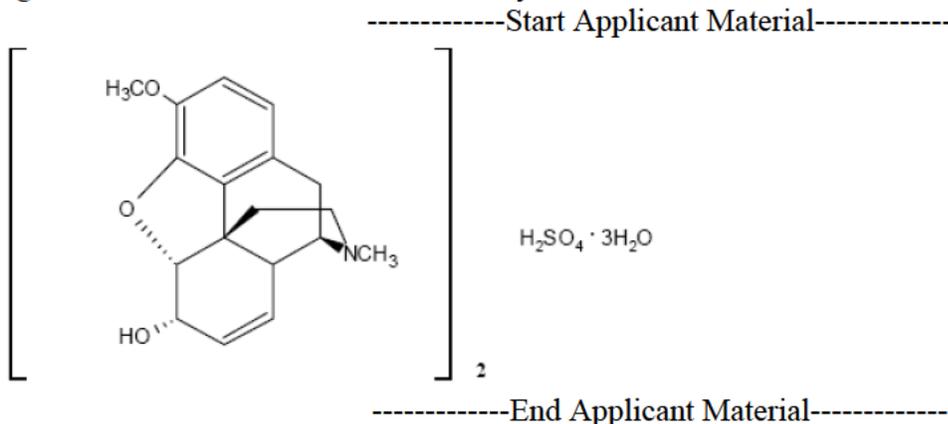
Chemical name:

• Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl, (5 $\alpha$ , 6 $\alpha$ )-, sulfate (2:1) (salt), trihydrate

CAS: 6854-40-6

MW: 750.85

Figure 1. Structure of codeine sulfate trihydrate



The drug substance, codeine sulfate trihydrate, is supplied by (b) (4)

Description of the manufacturing processes and controls are referenced to the Drug Master File (DMF) (b) (4) submitted in November 11, 2007 and reviewed for the referenced approved product, codeine sulfate tablets. Letter of Authorization (LoA) is included in the NDA. DMF (b) (4) has been reviewed previously for NDA 22-402 and deemed adequate.

#### Characterization:

Details of the drug substance manufacturing and characterization are referenced to DMF (b) (4). An amendment to the DMF, dated 2009, has been submitted to the NDA and includes purity profile, specifications, (b) (4) and stability information. A retest date of (u) (4) months is proposed. The applicant did not discuss (b) (4)

(b) (4) The physical properties of (b) (4), should be assessed by the primary reviewer, for impact on manufacturability, quality and performance (e.g., solubility, bioavailability, stability) of the drug product. Since this is an oral solution, (b) (4) properties of the API are not expected to impact drug product quality and performance.

**Potential Impurities and degradation products:**

(b) (4)



**Drug Substance Specifications:**

Drug substance specifications are shown below, in Table 1, as summarized from the (b) (4) document, submitted in the NDA. Methods Validation is provided for the non-compendial method for determination of assay, impurities/degradants. This method and its validation should be assessed as per ICH Q2B. The proposed limits for impurities/degradants should be assessed as per ICH Q3A(R2) in consultation with the Toxicology Division. (b) (4) be assessed for compliance with ICH Q3C; the applicant uses the USP<467> method, but stated that the limits are well below ICHQ3C guidelines, Option 1.

-----Start Applicant Material-----

Table 1. Drug Substance Specifications

**Batch analysis:**

Batch analysis results are included for batches 10036564 (b) (4) 15800909000683) and 10037089 (b) (4) 15800909000817). These two batches were used for manufacture of the NDA drug product batches, as follows:

Drug substance batch 10036564: drug product batches 4000060 and 4000093

Drug substance batch 10037089: drug product batch 4000092

**Reference standard:**

No Certificates of Analysis for the working reference standards have been included; SOP of Boeringer Ingelheim for handling reference standards has been included in this section. The applicant should be asked to identify reference standards used for their analytical methods in the NDA.

**Drug product**

The drug product formulation contains sorbitol, glycerin, (b) (4), colorants and a flavorant. No novel excipients are used in the formulation, but the colorants and flavorant are non-compendial. The drug product solution is packaged in 500 ml PET amber bottles with (b) (4) CR closures.

-----Start Applicant Material-----

Table 2. Quantitative composition of codeine sulfate oral solution.

<u>Ingredients</u>	<u>Purpose</u>	<u>Quality Standard</u>	<u>Dosage (Amount per 5 mL)</u>	<u>Quantity (Amount per (b) (4))</u>
Codeine Sulfate, USP	Active Ingredient	USP; BIRI Spec. No. 6081700R-01-05	30 mg	(b) (4)
Sorbitol Solution, USP (b) (4)	(b) (4)	USP		(b) (4)
Glycerin, USP		USP		(b) (4)
Ascorbic Acid, USP		USP		(b) (4)
Citric Acid (b) (4) USP (b) (4)		USP		(b) (4)
Disodium Edetate, USP		USP		(b) (4)
Sucralose, NF (b) (4)		NF		(b) (4)
Sodium Benzoate, NF (b) (4)		NF		(b) (4)
FD&C Yellow No. 6 (b) (4)	Coloring	BIRI Spec. No. 6108000R-01-01		(b) (4)
FD&C Red No. 40	Coloring	BIRI Spec. No. 6105600R-01-01		(b) (4)
Orange Flavor, XBF-709818	Flavor	BIRI Spec. No. 6194600R-01-01		(b) (4)
Water, (b) (4) USP	(b) (4)	USP		(b) (4)
<b>Theoretical Weight</b>	-	-		(b) (4)

-----End Applicant Material-----

The applicant estimated that the excipients are within the IIG limits for orally administered products. The orange flavor, XBF-709818 is not included in the IIG, however it is claimed as an (b) (4)

The applicant is asked to identify the supplier and provide LoA to the DMF for the orange flavor.

**Formulation and manufacturing process development:**

The applicant stated that the formulation comprises of (b) (4)

**Overages:** Not planned.

**Manufacturing Process:**

The manufacturing process consists of (b) (4) Batch records have been included in the NDA. The three NDA batches have been manufactured at the proposed commercial scale of (b) (4) Boeingerher Ingelheim, OH is the drug product manufacturer.

**Manufacturing Process Flow Chart:**

A schematic was provided, with minimal details with respect to manufacturing operations and process controls. These should be assessed from batch records. (b) (4) (b) (4)

(b) (4) The solution met specifications including assays for codeine sulfate, ascorbic acid and sodium benzoate, degradants and microbial limits. Antimicrobial preservative effectiveness is tested as per USP<51>.

#### **NDA Registration batches:**

The applicant submitted three NDA batches, 4000060, 4000092, 4000093, filled in 500 ml amber bottles with 6-month stability data under normal storage and 6-month under accelerated storage.

#### **Batch analysis data:**

All batches met specifications; Impurities/degradants are reported as (b) (4) at release. The analytical methods for the drug product do not present novel elements. For the HPLC assay and impurities method, validation should be assessed, to confirm the applicant's conclusion that the method resolves impurities of similar structure and chemical properties. Justification of specifications should be assessed as per the ICH Q3B(R) guidelines in consultation with the Toxicology Division.

-----Start Applicant Material-----

**Table 5. Drug Product Specifications:**

Test	Analytical Procedure	Release Acceptance Criteria	Stability Acceptance Criteria
Description	Visual	Clear, reddish-orange to (b) (4) orange solution.	See Release Acceptance Criteria
Identification A (HPLC)	1674-01	The retention time of the codeine sulfate peak in the <i>Sample Preparation</i> corresponds to that of the codeine sulfate peak in the <i>Standard Preparation</i> .	N/A
Identification B (TLC)	1674-02	The $R_f$ value of the principle spot obtained from the <i>Sample Preparation</i> corresponds to that of the <i>Standard Preparation</i> .	N/A
pH	USP <791>	2.8 – 3.8	N/A
Microbial	USP <61> and <62>	<i>E. Coli</i> - None Isolated Salmonella - None Isolated Yeast/Molds - NMT (b) (4) Total Aerobic Plate Count NMT (b) (4)	<i>E. Coli</i> - None Isolated Salmonella - None Isolated Yeast/Molds - NMT (b) (4) Total Aerobic Plate Count NMT (b) (4)
Assay Codeine Sulfate	1674-01	(b) (4) of the labeled amount.	(b) (4) of the labeled amount.
Assay Sodium Benzoate	1674-01	(b) (4) of the labeled amount of sodium benzoate.	(b) (4) of the labeled amount of sodium benzoate.
Assay Ascorbic Acid	1674-03	Record for information only.	Record for information only.

Test	Analytical Procedure	Release Acceptance Criteria	Stability Acceptance Criteria
Degradation Products	(b) (4)	Specified Degradants:	Specified Degradants:
	(b) (4)		
Preservative Effectiveness	USP <51>	N/A	Meets USP <51> requirements.
Residual Solvents	USP <467>	Meets USP <467> requirements.*	N/A

-----End Applicant Material-----

**Container Closure:**

The applicant provided the packaging components of the HDPE bottles, caps and references to their corresponding DMFs. Letters of Authorization to the packaging DMFs have been included in the NDA. The applicant stated that the proposed container/closure system complies with USP<661> and <671>. In addition, they stated that “the container/closure is same with that of the approved product”. However, the applicant did not submit any justification for leachables/extractables evaluation and compliance of the packaging components to appropriate CFR regulations for indirect food additives. The oral doser has not been submitted.

**Stability:**

Stability testing of the 30 mg/5ml solution in the 500 ml amber bottles is performed under standard ICH conditions at 25°C/60% RH, and 40°C/75% RH. The bottles were stored upright and on side. Stability protocols and post-approval stability commitment were provided in the NDA. The proposed expiration dating is (b) (4) months. Six months stability data under normal storage have been included in the NDA. Statistical analysis evaluation has not been performed by the applicant. Photostability testing has not been reported. In addition, in-use stability data and in-use shelf life has not been provided and should be requested.

**Labeling**

Labeling information of the container labels and packaging insert should be assessed with respect to CMC related information. SPL labeling has not been included and should be requested from the applicant.

### C. Critical issues for review and recommendation

During assessment of the CMC information provided in this NDA, the primary reviewer should consider addressing issues identified above and other related ones, summarized here, for their impact on drug product quality and performance throughout the shelf-life:

1. Updates to the drug substance DMF (b) (4) should be assessed.
2. Limits of impurities and related substances in the drug substance as per ICH Q3A(R), in consultation with the Toxicology Division (b) (4) for compliance with ICH Q3C.
3. The suitability of the compendial specifications of excipients for drug product manufacturability, quality and performance should be assessed. A reference to a drug Master File for the Orange Flavor should be requested, and the DMF should be assessed.
4. Details of the manufacturing process of the drug product (b) (4)
5. Drug product specifications, e.g., impurity/degradant limits as per ICH Q3B(R), (b) (4) limits (a structural alert), and unidentified impurity limits, in consultation with the Toxicology Division.
6. The suitability of the HPLC method for related substances to detect (b) (4) and unidentified impurities.
7. The proposed codeine sulfate oral solution expiration dating of (b) (4) months. (b) (4)
8. Photostability testing of the drug product has not been reported and should be requested. Codeine is photosensitive.
9. In-use stability data, to support in-use shelf life and conditions for the multi-dose presentations of 500 ml.
10. No justification for extractables/leachables has been provided. Compliance of all packaging components to appropriate CFR regulations for indirect food additives, should be requested.
11. Labeling in Structured Product Labeling (SPL) format has not been provided and should be requested.

### D. Comments for 74-day Letter:

1. Provide a DMF reference for the Orange Flavor.
2. Provide photostability data as per ICH Q1B.
3. Provide an extractables/leachables evaluation of the container/closure system with the oral solution with adequate justification of any findings. Alternatively, provide data describing compliance of the components to indirect food additive regulations to support compatibility of the container/closure with the aqueous oral solution.
4. Propose an in-use period (shelf-life) for your drug product, and provide in-use stability data to support the in-use period.

E. **Recommendation for fileability:** The NDA is fileable based on CMC data on three NDA batches, with 6-month long term/6-month accelerated stability data for drug product packaged in the proposed commercial presentation. The NDA is suitable for evaluation and assessment based on FDA and ICH guidelines for submitting CMC information for New Drug Applications.

**Recommendation for Team Review:** The NDA is not recommended for a team review.

**Consults:**

- 1. Toxicology** (to be determined and initiated by the primary reviewer.)
- 2. Biopharmaceutics, ONDQA** (Angelica Dorantes was notified; However, Clinical Pharmacology will perform review of the relative bioavailability study.)
- 3. Microbiology** (to be determined and initiated by the primary reviewer.)

Microbiology consult was not deemed necessary. However, it may be initiated by the primary reviewer after evaluation of the firm's specifications, antimicrobial effectiveness testing and supporting data.

Danae D. Christodoulou, Ph.D.  
CMC Lead

11/10/2010  
Date

Prasad Peri, Ph.D.  
Branch VIII Chief, ONDQA

\_\_\_\_\_  
Date

NDA Number: 202245

Supplement Number and Type:

Established/Proper Name:

Codeine sulfate oral solution

Applicant: Roxane

Letter Date: 09/27/2010

Stamp Date: 09/27/2010

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

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		FDA Correspondences dated 10/16/2007, 9/20/2007 and 5/17/2010

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		(M3)
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			NA

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <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		<p>(b) (4) DMF (b) (4)</p>
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <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		<p>Clarifications and communications with OC.</p>
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <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		<p>Clarifications and communications with OC.</p>

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		X	
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\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Referenced to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Referenced to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Referenced to DMF (b) (4)
15.	Does the section contain controls for the DS?	X		Specifications included in the NDA
16.	Has stability data and analysis been provided for the drug substance?			Referenced to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?	X		Relative BE study has been performed
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	NA (Solution Oral Dosage Form)

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	2	(b) (4)	Codeine Sulfate USP	4/21/2009	API
	3		(b) (4)	1/25/2007	(b) (4)
	3			8/5/2008	(b) (4)
	3			4/12/2010	
	3			8/4/2009	
	3		(b) (4)	6/9/2008	
	3		(b) (4)	2/26/2007	
	3		(b) (4)	7/31/2009	(b) (4)
	4		XBF-709818 Orange	1/11/2011	Flavorant (AMENDED)

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>			Based on pre-NDA agreements and sufficient data
35.	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.	X		Describe filing issues here or on additional sheets
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	X		See p. 9, above

*{See appended electronic signature page}*

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Name of

PAL: Danae Christodoulou 11/10/10  
 Division of Pre-Marketing Assessment III  
 Office of New Drug Quality Assessment

Date

*{See appended electronic signature page}*

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Name of

Branch Chief (Acting): Prasad Peri  
 Division of Pre-Marketing Assessment III  
 Office of New Drug Quality Assessment

Date

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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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DANAE D CHRISTODOULOU  
04/19/2011  
Initial Quality Assessment

PRASAD PERI  
04/19/2011  
I concur