

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-402

CHEMISTRY REVIEW(S)

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 22402/000	Sponsor:	ROXANE
Code:	170		1400 SOUTH ORANGE AVE
Priority:	7S		ORLANDO, FL 32806
Stamp Date:	02-JUL-2008	Brand Name:	CODEINE SULFATE TABLETS 15,30,60 MG
PDUFA Date:	02-AUG-2009	Estab. Name:	
Action Goal:		Generic Name:	CODEINE SULFATE TABLETS 15, 30,60 MG
District Goal:	03-MAR-2009	Dosage Form:	(TABLET)
		Strength:	15, 30, 60 MG

FDA Contacts:	M. SULLIVAN	Project Manager	(HFD-170)	301-796-1245
	E. NASHED	Review Chemist	(HFD-820)	301-796-2410
	D. CHRISTODOULOU	Team Leader		301-796-1342

Overall Recommendation: ACCEPTABLE on 09-MAR-2009 by M. STOCK (HFD-320) 301-796-4753

Establishment: CFN: _____ FEI: _____
 _____ b(4)

DMF No: _____ **AADA:** _____

Responsibilities: _____
 _____ b(4)
Ve: _____ **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-AUG-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: _____ FEI: _____
 _____ b(4)
 _____ b(4)

DMF No: _____ **AADA:** _____

Responsibilities: _____

Profile: _____ **OAI Status:** NONE b(4)

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-AUG-2008

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 1510690 FEI: 1510690
ROXANE LABORATORIES INC
1809 WILSON RD
COLUMBUS, OH 432289579

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-JAN-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 1527529 FEI: 1527529
ROXANE LABORATORIES INC
330 OAK ST
COLUMBUS, OH 432154320

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORIES "ALSO"
(DRUGS) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-MAR-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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/s/

NICKEISHA S BURFORD
09/18/2009

NDA 22-402

Codeine Sulfate Tablets, 15 mg, 30 mg, and 60 mg

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

Applicant: Roxane Laboratories, Inc.
1809 Wilson Rd., Columbus
OH 43228

Indication: Relief of mild to severe pain in adults.

Presentation: The drug product consists of white, _____ (15 mg and 30 mg) or _____ (60 mg), biconvex un-coated tablets. The tablets are scored and debossed with strength-designation number (15, 30 or 60). The commercial drug product tablets are packaged in _____ bottles (100 tablets), or in _____ blister cards (4 cards of 25 tablets per pack).

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EER Status:	Recommendations:	Acceptable
Consults:	EA -	Categorical exclusion provided
	CDRH-	N/A
	Statistics -	N/A
	Methods Validation -	Not recommended
	Biopharm-	Acceptable
	Microbiology -	Acceptable
	Pharm/toxicology -	Acceptable

Original Submission: 01-July-2008

Re-submissions: N/A

Post-Approval CMC Agreements: An agreement was reached with the sponsor to collect additional data within the first 2.5 years of manufacturing and submit a prior approval supplement (PAS) by July 01, 2012, to revise and improve the interim acceptance criteria for dissolution, hardness and friability. Also, any extension of the expiry period beyond 24 months is possible *via* PAS only.

Background:

The application is filed as a 505(b)(2), standard review. Reference Listed Drug (RLD) is Tylenol with Codeine No.30, 300mg: 30 mg, ANDA 85-055, by Ortho McNeil Janssen. Codeine Sulfate Tablets, USP is a marketed, unapproved product. Roxane submitted the current NDA to obtain FDA approval for legal

marketing of their product. Based on the marketing history of this drug, Roxane submitted only limited data to support this NDA, i.e., three registration/primary stability batches, with 6 month long term and accelerated storage data provided in the original submission. Although there were recently minor changes in the drug formulation and manufacturing process, the manufacturing site and scale for the to-be-marketed drug are the same as for the currently marketed drug product.

The API is a Schedule II controlled substance due to the potential for drug abuse.

The review clock for this application was extended due to submission of a major amendment containing supporting stability data (12 months label storage) late in the review cycle.

Drug Substance:

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

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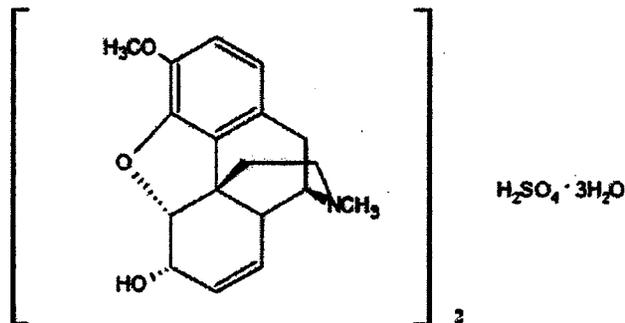
Codeine sulfate trihydrate is a fine crystalline powder with specific rotation of -112.5° to -115.0°, and pH 5.0. It is soluble in water and insoluble in chloroform and ether.

The safety of the drug substance and drug product impurities which either possess structural alert for carcinogenicity/genotoxicity (i.e., codeinone, NMT 0.15% in drug substance and NMT _____ in drug product, α,β - unsaturated ketone structural alert), or occur above the ICH-recommended level (i.e., codeine methyl ether, NMT _____ in drug substance), is considered adequate by the Pharm.Tox. review team, as documented in reviews dated Mar 10, and May 22, 2009, which were filed in response to the CMC consult dated Sep 11, 2008.

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Chemical structure, chemical name, molecular formula and molecular weight:



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

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

Molecular weight: 750.85 g/mol

The drug substance specifications include identification, specific rotation, acidity, water, readily carbonizable substances, residue on ignition, residual _____ heavy metals, microbial limits, residual solvents, impurities, and assay. The originally submitted specifications were updated during the review process to add controls for heavy metals, microbial limits, HPLC assay, and the acceptance criteria for total impurities were tightened, from NMT _____ to NMT _____. b(4)

Conclusion: The drug substance is satisfactory.

Drug Product:

The manufacturing process of the tablets is a relatively simple and consists of a _____ . Each tablet contains 15 mg, or 30 mg, or 60 mg of codeine sulfate, in addition to standard NF/USP grade excipients, which include microcrystalline cellulose _____, pregelatinized starch _____, colloidal silicon dioxide _____, and stearic acid. In addition, _____, NF was used in 15 mg tablets, but it is absent in the registration and commercial drug product batches. The dosage strengths are not compositionally proportional and contain _____ API by weight for 15 mg tablets, and _____ API by weight for the 30 mg and 60 mg tablets. The review dated Apr 3, 2009, by Dr. Sheetal Agarwal, found the submitted bioequivalence studies adequate to support the NDA application. b(4)

Drug product specifications include in process testing for blend uniformity, and release/stability acceptance criteria for description, identification (release only), moisture content, hardness, friability, dissolution, uniformity of dosage units, assay, degradation products, microbial limits, and _____. The originally submitted drug product specifications were updated substantially during the review process to add controls for testing moisture content, hardness, friability and microbial limits. In addition, the analytical method for testing dissolution was changed and acceptance criteria were revised. Due to the limited data available for hardness, friability and dissolution, additional data will be collected post-approval and submitted as PAS by July 1, 2012. b(4)

Based on the 12 months of incomplete stability data submitted up to date, an

expiry period for drug product is limited to 18 months, when stored — Any extension beyond 24 months may be achieved *via* PAS only.

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Conclusion: The drug product is satisfactory.

Overall Conclusion: From a CMC perspective, the application is recommended for approval. Refer to the Post-Approval Agreements, above.

Ali Al-Hakim, Ph.D.
Branch Chief,
DPA I/ONDQA

Container labels

b(4)

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

/s/

Ali Al-Hakim
7/13/2009 11:42:53 AM
CHEMIST

NDA 22-402

**Codeine Sulfate Tablets USP, 15 mg, 30 mg and 60 mg
(formulated with codeine sulfate trihydrate, USP)**

Roxane Laboratories, Inc.

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

Division of Anesthesia, Analgesia and Rheumatology Drug Products



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Chemistry Review Data Sheet

1. NDA 22-402
2. REVIEW #: 1
3. REVIEW DATE: 30-Jun-2009
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	01-Jul-2008	03-Jul-2008	26-Aug-2008
Amendment BC	20-Feb-2009	23-Feb-2009	03-Mar-2009
Amendment BC	02-Mar-2009	03-Mar-2009	10-Mar-2009
Amendment AC	25-Mar-2009	26-Mar-2009	31-Mar-2009
Amendment BC	22-Apr-2009	23-Apr-2009	30-Apr-2009
Amendment BC	29-Jun-2009		29-Jun-2009
Amendment BC	30-Jun-2009		30-Jun-2009
Amendment BC	02-Jul-2009		02-Jul-2009
Amendment BC	06-Jul-2009		06-Jul-2009
Amendment BC	07-Jul-2009		08-Jul-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Roxane Laboratories, Inc.

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

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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 tablets
- 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 Tablets (IR)

12. STRENGTH/POTENCY: 15 mg, 30 mg and 60 mg of codeine sulfate, per tablet

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

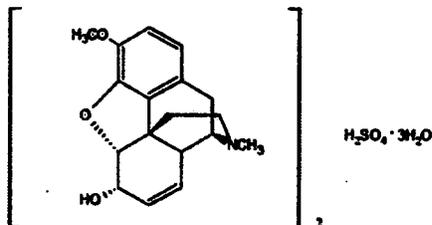
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed

Not a SPOTS product

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

Codeine Sulfate Trihydrate

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

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
					Adequate	July 2009	Deficiency Letter Jan 28, 2009. Response acceptable from CMC perspective. See review of PharmTox data by Delata/Meion.
					Adequate	July 2009	Deficiency Letter Jan 23, 2009. Response acceptable.
					Adequate		Meets the requirements in 21 CFR 175.300
					Adequate		Meets the requirements in 21 CFR 177.1520
					Adequate		Meets the requirements in 21 CFR 177.1520
					Adequate		Meets the requirements in 21 CFR 177.1520
					Adequate		Meets the requirements in 21 CFR 177.1520
					Adequate		Meets the requirements in 21 CFR 177.1520 and CFR 73.1575
					Adequate		Meets the requirements in 21 CFR 177.1520
					Adequate		Meets the requirements in 21 CFR 177.1520 and CFR 73.1575
					Adequate		Meets the requirements in 21 CFR 177.1520

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

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6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other 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 EER	None GMP inspections of the manufacturing and testing facilities	Aug 18, 2008	AC 09-Mar-2009	Status for all manufacturing and testing facilities was assigned by DO based on file review. A Gmp inspection at _____ (CFN # _____ drug substance manufacturer) was conducted 4/23-24/08 and was classified VAL
Pharm/Tox	Safety of the proposed acceptance criteria for impurities Evaluation (Amend. 1/30/08)	Sep 11, 2008	AC 22-May-2009	The PT team found problems with the <i>in vitro</i> chromosomal aberration assay method and requested to repeat the study to conduct <i>in vivo</i> genetic toxicology studies - Review for _____, dated Mar 10, 2009, in DARRTS. The evaluation of data supporting the safety acceptance criteria for codeine methyl ether (NMT _____) and codeinone impurity (NMT 0.15%, structural alert for genotoxicity/carcinogenicity) is delineated in PT review dated May 22, 2009, by Delatte/Mellon team, with input from Dr. David Jacobson-Kram (DARRTS).
Biopharm	Dissolution	Jun 2009	AC, with agreement to collect more data	Dr. Patrick Marroum recommends tightening of the proposed acceptance criteria for dissolution (Q 75% at 45 min) to C _____ based on currently available data
Methods Validation DMEPA	Labeling review		AC 02-Jul-2009	Will be initiated, as needed, upon completion of the review Recommendation to increase prominence of nonproprietary name and strength - Labeling review by Arnwine/Toyer, dated Jul 2, 2009.
EA				Categorical exclusion accepted based on the information provided in module 1.12.14.
Microbiology	Microbial specifications	Jun 2009	AC	Dr. David Hussong has recommended tightening of the proposed acceptance criteria for total aerobic microbial count (TAMC NMT _____) and for total combined yeasts and molds (TCYM NMT _____). The response dated Jul 2, 2009, with acceptance criteria for TAMC NMT _____ and for TCYM NMT _____, was found acceptable.

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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 extensive agreements provided by the applicant – refer to section I.B., below in this review. The safety of the drug substance and drug product impurities is addressed in the PharmTox reviews dated Mar 10, and May 22, 2009, based on the CMC consult dated Sep 11, 2008 –refer to section II.A., below.

The overall EER status for this NDA is acceptable (AC) as of Mar 9, 2009. The supporting DMFs have adequate status as of Jul 7, 2009.

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 moisture content, hardness, friability and adequate method for dissolution testing of the tablets. In response to our comments (IR letter dated Jan 2009, teleconference on Mar 16, 2009, and additional IR dated Jun 25, 2009), the applicant has implemented testing for the above attributes and proposed interim acceptance criteria due to the limited data available. An agreement was reached to collect additional data within the first 2.5 years of manufacturing, submit it in a prior approval supplement (PAS) by Jul 1, 2012, in order to improve the interim acceptance criteria for dissolution, hardness and friability. Also, the drug product expiry period was limited to 18 months (from the originally proposed _____ due to the lack of representative stability data – refer to section II.C., below in this review.

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Agreements

We acknowledge the interim acceptance criteria established for testing of drug product dissolution, hardness and friability and remind you of the agreement to submit a prior approval supplement by July 1, 2012, with the final data-reflecting regulatory specifications for dissolution, hardness and friability, as outlined in the following agreements.

1. You agree to submit dissolution profile data generated for a minimum of 20 production batches (first 10 batches for the 15 mg tablets and first 5 batches for each of the 30 mg and 60 mg tablets) during release and stability testing of commercial drug product. The dissolution profiles will include adequate number of data points to allow for comparison of the profiles, e.g., 10 min, 15 min, 30 min and 45 min. A statistical evaluation of batch

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to batch variability, between different drug product strengths and within the same batch during stability storage, sorted by the type of container closure, will be provided.

2. You agree to submit available data for hardness and friability generated during release and stability testing of commercial drug product tablets. A statistical evaluation of batch to batch variability, between different drug product strengths and within the same batch during stability storage, sorted by the type of container closure will be provided.

We remind you of the agreement that any extension of drug product expiry period beyond 24 months may be accomplished only *via* a prior approval supplement with adequate supporting data. The currently approved expiry period for drug product is 18 months, starting from the first use of drug substance in the drug product manufacturing process. The drug product expiry period may be extended to 24 months based on acceptable stability data collected according to the approved stability protocol, in accord with 21 CFR 314.70.

II. Summary of Chemistry Assessments

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

The drug product contains codeine sulfate trihydrate, which is present in unapproved product, Codeine sulfate tablets, USP, marketed by the applicant. The indication is for the relief of mild to severe pain in adults. The API is a Schedule II controlled substance due to the potential for drug abuse.

This NDA dated Jul 1, 2008, was filed as a 505(b)(2) application, standard review. The reference listed drug (RLD) is Tylenol with codeine No. 3 tablets, 300 mg:30 mg, approved under ANDA 85-055 (Ortho McNeil Janssen). The review clock for this application was extended due to submission of supporting stability data late in the review cycle.

Drug substance

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

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Codeine sulfate trihydrate is a fine crystalline powder with specific rotation of -112.5° to -115.0°, 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 (i.e., codeinone, NMT 0.15% in drug substance and NMT _____

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in drug product, α, β - unsaturated ketone structural alert), or occur above the ICH-recommended level (i.e., codeine methyl ether, NMT _____ in drug substance), is addressed in the PharmTox reviews dated Mar 10, and May 22, 2009, based on the CMC consult dated Sep 11, 2008. b(4)

Drug Product

The drug product consists of white _____ (15 mg and 30 mg) or _____ (60 mg), biconvex un-coated tablets. The tablets are scored and debossed with strength-designation number (15, 30 or 60) on one side, and debossed with numbers 54/613, 54/783, and 54/412, respectively, on the other side. b(4)

Each tablet contains 15 mg, or 30 mg, or 60 mg of codeine sulfate, in addition to standard NF/USP grade excipients, which include microcrystalline cellulose _____, pregelatinized starch _____, colloidal silicon dioxide _____, and stearic acid. In addition, _____ was used in 15 mg tablets, but it is absent in the registration and commercial drug product batches. The dosage strengths are not compositionally proportional and contain _____ API by weight for 15 mg tablets, and _____ API by weight for the 30 mg and 60 mg tablets. This information was forwarded to the ClinPharm review team for consideration during review. The review dated Apr 3, 2009, by Dr. Sheetal Agarwal, found the submitted bioequivalence studies adequate to support the NDA application. b(4)

The drug product is manufactured by a _____ Supportive stability batches for the 15 mg strength tablets were manufactured with a different blending process/equipment, which was in use until Jul 2000. The manufacturing is carried by the applicant (BIRI) at Columbus, Ohio, with additional distribution center in Reno, Nevada. b(4)

The commercial drug product tablets are packaged in _____ bottles (100 tablets), or in _____ blister cards (4 cards of 25 tablets per pack). b(4)

The release and stability controls for the drug product were revised significantly during the review process (see pending agreements). Based on the 12 months of incomplete stability data submitted up to date, and considering the recent changes in formulation and manufacturing, the expiry period for drug product is limited to 18 months, when stored at _____. b(4)

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

The drug product, Codeine sulfate tablets, 15 g, 30 mg and 60 mg, is intended for the relief of mild to moderately severe pain where the use of an opioid analgesic is appropriate. Codeine sulfate is an opioid agonist of the morphine-type and a Schedule II controlled substance.

The usual adult dosage for tablets is 15 mg to 60 mg repeated up to every four hours as needed for pain. The maximum 24 hour dose is 360 mg.

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

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C. Basis for the CMC Recommendation

This NDA application is recommended for approval from the CMC perspective, based on extensive agreements provided by the applicant. 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 moisture content, hardness, friability, microbial load and adequate method for dissolution testing of the tablets. Also, only 6 months of incomplete stability data for registration batches was provided in the original submission. Stability update (12 months data for three registration batches) was submitted late in the review cycle, necessitating extension of the review clock.

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

- Sep 2008 – Request for representative stability data in the 74 day filing letter.
- Jan 2008 - IR letter requesting to address inadequate drug substance and drug product controls, including impurity profiles, microbial load, dissolution, hardness, friability and stability protocol and data.
- Mar 2009 – Teleconference with the applicant discussing inadequate response to Jan 2008 letter.
- Jun 2009 – Multiple discussions of applicant's amendments submitted from Mar – Jun 2009, requesting improvements of controls utilized during drug product manufacturing and during release and stability testing for drug product, as follow.

As of Jun 25, 2009, the following items were listed as deficiencies (see copy of comments to IR letter Jun 25, 2009, listed at the end of this review):

1. Revision of Drug Substance Specifications to tighten the acceptance criteria for impurities, as warranted by the data.
2. Reduction of the Holding Time for the bulk blend and bulk tablets, or providing adequate supporting data.
3. Revise Drug Product specifications to include data-based acceptance criteria for Microbial limits, Dissolution, and Hardness and Friability.
4. Revision of Drug Product Stability Protocol to include testing for all stability-indicating attributes and provide Stability Specification table with methods and acceptance criteria.

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5. Reduce drug product expiry period to 18 months, and agree to submit PAS with supporting data for extension beyond 24 months.

In subsequent amendments dated Jun 29, Jun 30, Jul 2, Jul 6, and Jul 7, 2009, issues #1 and 2 were resolved adequately and issues #3, 4, and #5 were partially resolved and finalized with agreements for collecting additional data and submitting re-evaluation of the interim controls in a PAS.

The acceptance criteria for total impurities in drug substance were reduced from NMT _____ to NMT _____. The total holding time for the bulk blend and the bulk tablets was reduced from _____ to _____ for the bulk blend, and _____ for the bulk tablets. Also, the microbial load acceptance criteria were tightened from the originally proposed NMT _____ CFU/g for total aerobic microbial count, and NMT _____ for the total Yeast and Molds, to NMT _____ and NMT _____ respectively.

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Due to the lack of adequate amount of supporting data the remaining items were addressed by the agreements, as listed in section I.B. of the Executive Summary, and at the end of this review..

- **Interim Acceptance criteria for Drug Product Dissolution.**

Based on the dissolution data submitted in the Feb-Jun amendments, the FDA review team proposed acceptance criteria of NLT _____ of the labeled amount dissolved in 30 min. The applicant submitted additional dissolution data in amendment dated Jul 6, 2009, demonstrating that one registration lot would fail the step two (S2) dissolution testing – see section P.5.1., of this review for details. The applicant proposed interim acceptance criteria of NL7 _____ of the labeled amount dissolved in 30 min, and provided an agreement to collect additional dissolution data and submit release and stability dissolution profiles obtained on 20 commercial batches, in a PAS to be submitted by Jul 1, 2012. Also, statistical evaluation of dissolution trends and proposal for data-reflecting acceptance criteria for dissolution will be submitted. See copy of the revised drug product Specifications and copy of Agreement listed at the end of this review and in section I.B. of the Executive Summary.

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- **Interim Acceptance criteria for Drug Product Hardness and Friability.**

The original application lacked data or specifications for testing drug product hardness and friability. Due to the high water content (NMT _____ on release and NMT _____ on stability) testing for hardness and friability during release and stability testing was strongly recommended to the applicant. Based on the data submitted in Mar 2009, an interim acceptance criteria were proposed by the applicant and an agreement was provided to collect additional data for Hardness and Friability, and reevaluate the acceptance criteria in PAS to be submitted by Jul 1, 2012. See copy of the revised drug product Specifications and copy of Agreement listed at the end of this review and in section I.B. of the Executive Summary.

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- **Reduction of the Expiry Period due to Inadequate Stability Data.**

The applicant requested _____ expiry period in the original application. The submitted stability data collected on the developmental and registration batches seem to indicate reasonably stable

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CHEMISTRY REVIEW #1

impurity profile for the drug product. However, only 12 months of data, collected according to incomplete stability protocol, is currently available for the registration drug product batches.

There are no systematic data available for moisture content, hardness, friability, and reliable data for dissolution. Refer to agreements requiring additional data to be collected for these attributes and submitted in a PAS by Jul 1, 2012, as listed above. However, fragmental data submitted to support the application indicate that the moisture content increases during storage (see label warning) and the dissolution profile seem to be related to the tablet hardness and moisture content. In summary, the stability trends occurring in the drug product need to be re-evaluated when adequate amount of stability data collected according to the approved stability protocol is available for the commercial drug product batches.

Based on the above and the recent changes to the formulation, manufacturing, and analytical methods, the expiry period for the drug product is limited to 18 months, with provision for extension to 24 months based on acceptable stability data collected according to the approved stability protocol, in accord with 21 CFR 314.70. Any extension beyond 24 months has to be submitted in a prior approval supplement. Refer to the drug product Stability Protocol, Stability Commitment #6, for the agreement provided by the applicant.

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

66 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Eugenia Nashed
7/9/2009 01:17:33 PM
CHEMIST

Ali Al-Hakim
7/9/2009 04:11:13 PM
CHEMIST

CHEMISTRY REVIEWER'S MEMORANDUM

Date: June 25, 2009
To: NDA 22-402
Through: Ali Al Hakim, PhD, Chief, Branch 2, Division I,
Office of New Drug Quality Assessment, HFD-820
From: Eugenia M. Nashed, PhD, CMC Reviewer, Branch 2, Division I,
Office of New Drug Quality Assessment, HFD-820
Product: Codeine Sulfate Tablets, 15 mg, 30 mg and 60 mg
Applicant: Roxane Laboratories, Inc.

Background

This NDA application dated Jul 1, 2008, is filed as a 505(b)(2), standard review. The reference listed drug (RLD) is Tylenol with Codeine No.3[®], 300mg:30 mg, ANDA 85-055, by Ortho McNeil Janssen. The review clock for this application was extended due to submission of the supporting stability data late in the review cycle.

The drug product consists of white, _____ (15 mg and 30 mg) or _____ (60 mg) biconvex uncoated tablets. It is manufactured by a _____
It is packaged in _____ bottles or in _____ blister cards.

b(4)

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

Sep 2008 – request for representative stability data
Jan 2008 – request to address inadequate drug substance and drug product controls (impurity profiles, dissolution, stability protocol and data)
Mar 2009 – teleconference with applicant discussing inadequate response to Jan 2008 letter

The comments below attempt to address outstanding CMC issues after evaluation of Applicant's response dated Mar 25, 2009.

Draft CMC Comments for the IR Letter (Jun 25, 2009)

1. Tighten the acceptance criteria for total drug substance impurities and microbial limits to reflect the batch results. Submit revised acceptance specification sheet for the drug substance. We note that the acceptance criteria for total impurities in drug substance (excluding codeine methyl ether) are proposed as NMT _____ whereas

b(4)

the results for process validation batches vary from _____ refer to data submitted in amendment dated Mar 25, 2009. b(4)

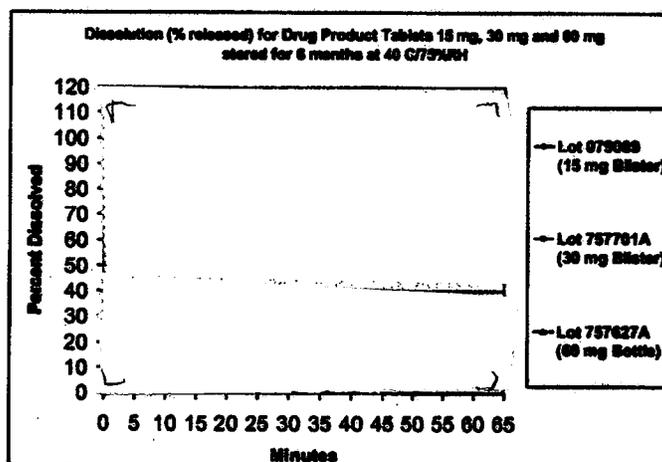
2. The proposed _____ holding time for the bulk blend in addition to _____ holding time for the bulk tablets adds up to _____ to the drug product manufacturing time. Shorten the proposed holding times or demonstrate with adequate stability data that the proposed holding times do not alter the quality, strength and purity of the drug product. Provide side-by-side results of the release and stability data collected on the fresh drug product and drug product manufactured with _____ blend and with bulk tablets held for _____. Note that the onset of the expiry period should coincide with the time of introducing the drug substance to the manufacturing process. b(4)

3. Submit revised drug product Specification to include the following.
a. Tighten the proposed acceptance criteria for Microbial Limits in drug product to NMT _____ for the total aerobic microbial count, NMT _____ for the total combined yeasts and molds, and 1 g sample show "Absence of *Escherichia coli*". Based on our discussion of water activity and microbial controls during teleconference on Mar 16, 2009, the future microbial testing on stability may be reduced upon approval of the supplemental submission with systematic data documenting low water activity, and manufacturing history demonstrating low microbial loads. b(4)

b. Revise the proposed acceptance criteria for drug product dissolution method to reflect the dissolution profile and assure routine quality control for batch-to-batch uniformity, e.g.:

10 min: _____, Label Claim
45 min: NLT _____ Label Claim b(4)

Refer to the chart below illustrating variability of the dissolution for the 15 mg tablets as compared to the 30 mg and 60 mg tablets and address the observed differences.



b(4)

- c. The Hardness and Friability data collected for the drug product stability lots (refer to Table 2 in submission dated Mar 25, 2009) demonstrate substantial variability within each lot and between different lots, i.e., 1.8 -3.0 Kp for 30 mg lot (757701B; 6 months 40/75), and 6.6-8.0 Kp for 60 mg lot (657557A; 24 months RT). It is not clear if the observed changes are due to the variability in manufacturing or due to the changes occurring in tablets during storage, since no release data were provided. Provide an agreement to submit, by July 1, 2012, available release and stability data for Hardness and Friability of drug product with a statistical evaluation of observed variability trends. The submission should include a proposal for tightening the currently proposed interim acceptance criteria for Hardness and Friability, as warranted by the data. Include a footnote, in the revised release and stability specifications, indicating that the Hardness and Friability acceptance criteria are interim and will be re-evaluated by July 1, 2012.
4. Submit revised drug product stability protocol, which includes the following.
- a. Stability specification sheet, i.e., a table with full list of tested-on-stability attributes, corresponding analytical method numbers and stability acceptance criteria, as requested in Comment #6 of Jan 2009 letter. Include changes to the specifications as requested in this communication.
 - b. Revised Commitment #4 stating the current expiry period and detail mechanism for extending the expiry period. Based on the 12 months real time stability data submitted for the primary stability batches, the current expiry period can be extrapolated maximum to 18 months. It can be prolonged by submission of the complete stability data collected on the commercial product according to the revised stability protocol, as requested in this communication. In view of the recent changes to the formulation and manufacturing, changes to the analytical methods, and incomplete stability data set for several

stability-indicating attributes, the extension of the drug product expiry period beyond 24 months can be achieved only *via* submission and approval of a prior-approval supplement.

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/s/

Eugenia Nashed
6/25/2009 05:31:13 PM
CHEMIST

Ali Al-Hakim
6/25/2009 05:32:54 PM
CHEMIST

Initial Quality Assessment
Division of Pre-Marketing Assessment I, Branch II
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Rheumatology Products

OND Division:	Anesthesia, Analgesia and Rheumatology	
NDA:	22-402	
Applicant:	Roxane Laboratories Inc.	
Stamp date:	July 8, 2008	
PDUFA Date:	May 8, 2008	
Trademark:	NA	
Established Name:	Codeine Sulfate Tablets, USP	
Dosage Form:	Tablets, 15, 30, 60 mg	
Route of Administration:	Oral	
Indication:	Management 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), standard review. Reference Listed Drug (RLD) is Tylenol with Codeine No.30, 300mg:30 mg, ANDA 85-055, by Ortho McNeil Janssen.

Codeine Sulfate Tablets, USP is a marketed, unapproved product. Roxane submitted the current NDA to obtain FDA approval and continue legal marketing of their product. Based on the marketing history of this drug, Roxane submitted a limited number of registration/primary stability batches, with 6 month long term and accelerated storage data to support this NDA. The formulation, manufacturing process, site and scale are the same as the marketed product. However, a new Drug Master File (DMF) which

b(4)

_____ was submitted in March 25, 2008 by _____ This DMF has not been reviewed previously

b(4)

Codeine Sulfate Tablets, USP is indicated for the management of mild to moderately severe pain and is dosed three times daily. Codeine Sulfate Tablets, USP 30 and 60 mg will be packaged in _____ bottles, sealed with _____, and a _____

b(4)

The proposed bottle is filled with tablet counts of 100 and contains a _____. The 15 and 30 mg strengths are packaged in 25x4 unit dose blisters.

B. Review, Comments and Recommendations

Drug Substance

_____ is described in DMF _____ LoA is provided in the NDA.

b(4)

Sections

_____ are included in the DMF. The DMF holder is the _____ (renamed _____) is _____

The type _____ DMF _____ should be reviewed and evaluated. The applicant claimed that the α,β -unsaturated ketone (ABUK) impurity, codeinone, was tested in a genetic toxicity screen and results were negative. This study should be consulted to the toxicology reviewer for assessment. The proposed specifications for impurities are:

b(4)

Codeine Methyl Ether: _____

codeinone: NMT 0.15% w/w

b(4)

Each unknown: NMT _____ w/w

Total impurities: NM _____ % w/w

The impact of physical properties of the drug substance, e.g., drug substance solubility, polymorphism, particle size distribution, etc., on the formulation _____ should be assessed. In addition, the suitability of the drug substance specifications for the formulation should be reviewed and assessed accordingly. It is recommended, that the drug substance acceptance specifications to be used as future manufacturer qualifying criteria, to be included in the NDA.

b(4)

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 α , 6 α)-, sulfate (2:1) (salt), trihydrate

Molecular Formula: (C₁₈H₂₁NO₃)₂ . H₂SO₄.3H₂O

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Danae Christodoulou
8/19/2008 06:47:10 PM
CHEMIST
Initial Quality Assessment

Ali Al-Hakim
8/20/2008 12:11:07 PM
CHEMIST