CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202245Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	NDA 202-245
Priority or Standard	Standard
Submit Date(s)	September 27, 2010
Received Date(s)	September 27, 2010
PDUFA Goal Date	July 27, 2011
Division / Office	Anesthesia, Analgesia and Addiction Products (DAAAP)
Reviewer Name(s)	Elizabeth Kilgore, M.D.
Review Completion Date	June 9, 2011
Established Name	Codeine Sulfate Oral Solution
Therapeutic Class	Opioid analgesic
Applicant	Roxane Laboratories, Inc.
Formulation(s)	Oral Solution 30 mg/5 mL
Dosing Regimen	15 to 60 mg (2.5mL to 10mL) up to every 4 hours as needed
Indication(s)	(b) (4) of mild to moderately severe pain where the use of an opioid analgesic is appropriate
Intended Population(s)	Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval is recommended for Codeine Sulfate Oral Solution, 30mg/5mL, for the indication of (b) (4) of mild to moderately severe pain based on the following determinants:

Efficacy: NDA 202-245 was submitted under 505(b)(2) with reference to the listed Codeine Sulfate Tablets 15 mg, 30 mg and 60 mg (NDA 22-402) approved 7/16/09.

Efficacy for NDA 22-402 was supported by the findings from the Agency's analysis of an extensive literature review for codeine.

For this submission, the Applicant's Phase 1 bioavailability/bioequivalence study showed that Codeine Sulfate Solution 30mg/5mL and Codeine Sulfate Tablets 30 mg are bioequivalent with respect to the active ingredient codeine, and the metabolites morphine, morphine-3-glucuronide, and morphine-6-glucuronide.

Safety: The safety findings in NDA 202-245 are consistent with the known safety profile of codeine from the approved Codeine Tablet NDA, relevant published literature, and postmarketing information.

Risk Mitigation: The risks of this drug appear manageable with the product label and a Medication Guide which addresses the risk of medication errors.

1.2 Risk Benefit Assessment

The overall benefit associated with immediate-release oral codeine sulfate solution outweighs the risks associated with its use.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A Risk Evaluation and Mitigation Strategy (REMS) is not required for this product.

1.4 Recommendations for Postmarket Requirements and Commitments

In order to comply with the Pediatric Research Equity Act (PREA), the Applicant submitted a pediatric plan. The plan is identical to that submitted with NDA 22-402 (codeine tablets). The plan includes PK, safety and efficacy studies in pediatric patients from age one month to two years, and PK and safety in pediatric patients ages 2 to 17 years. As per the current Division policy, efficacy findings from adults may be extrapolated to pediatric patients over the age of two years. Studies in pediatric patients under the age of one month are waived due to the timing of the development of the metabolic pathway for codeine, and the inability of patients less than one month of age to metabolize codeine.

The Applicant requested deferral of pediatric studies for Codeine Sulfate Oral Solution 30 mg/5mL for the following pediatric populations because the product was ready to be approved in adults:

- Infant (1 month to 2 years)
- Children (2 to 12 years)
- Adolescent (12 years to < 16 years)

The Applicant's proposed pediatric plan with timelines is shown below:

Table 1. Proposed Codeine Pediatric Assessment Timelines

Codeine	Final Protocol	FDA Comments	First Patient In	Last Subject Out	Final Report
Safety and PK Study for peds from 2 to 17	1 Dec 2011	1 Mar 2012	1 Sep 2012	1 Sep 2013	1 March 2014
Safety and PK Study for peds under 2	1 Dec 2011	1 Mar 2012	1 Sep 2012	1 Sep 2013	1 March 2014
Safety and Efficacy Study for peds under 2	1 Sept 2014[1]	1 Dec 2014	1 Jun 2015	1 Jun 2016	1 Dec 2016

[1]We will require FDA's comments on the results of the under 2 year old PK/Safety study before this protocol (under 2 year old Safety and Efficacy study) can be finalized. If greater review time is required by the agency, remaining dates for the Safety and Efficacy Study for the under 2 year olds would shift accordingly.

(Source: Applicant's Table, 9//27/10 cover letter)

The Applicant's proposed pediatric plan was presented to the Agency's Pediatric Review Committee (PeRC) on 5/11/11 and was found to be acceptable.

2 Introduction and Regulatory Background

2.1 Product Information

Codeine Sulfate Oral Solution is a clear, reddish-orange to (b) (4) orange solution which is to be manufactured in one strength of 30mg/5mL. The active ingredient is codeine. The components and composition of the product are shown in Table 2 below:

Table 2. Components and Composition of Codeine Sulfate Oral Solution 30mg/5mL

Ingredients	Purpose	Quality Standard	Dosage (Amount per 5 mL)	Quantity (Amount per (b) (4)
Codeine Sulfate, USP	Active Ingredient	USP; BIRI Spec. No. 6081700R-01-05	30 mg	
Sorbitol Solution, USP (b) (4)	(b) (4)	USP		(b) (4)
Glycerin, USP		USP		
Ascorbic Acid, USP		USP		
Citric Acid (b) (4) USP (b) (4)		USP		
Disodium Edetate, USP		USP		
Sucralose, NF (b) (4) (b) (4)		NF		
Sodium Benzoate, NF (b) (4)		NF		
FD&C Yellow No. 6 (b) (4)	Coloring	BIRI Spec. No. 6108000R-01-01		
FD&C Red No. 40	Coloring	BIRI Spec. No. 6105600R-01-01		
Orange Flavor, XBF-709818	Flavor	BIRI Spec. No. 6194600R-01-01		
Water, (b) (4) USP	(b) (4)	USP		
Theoretical Weight	-	-	2330.85 mg	(b) (4)

(Source: Applicant's Table, NDA Submission, Module 3:Quality; Section 3.2 Drug Product)

- Drug description: Aqueous oral solution
- Dose strengths: 30mg/5mL
- Dosing regimen: 15 to 60 mg (2.5 to 10mL) up to every 4 hours as needed
- Established name: Codeine Sulfate Oral Solution
- Proposed Tradename: Codeine Sulfate Oral Solution
- Pharmacologic class: Opioid analgesic

Codeine is prepared from [redacted] (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Multiple products are available for the treatment of moderate-to-severe pain, including immediate and extended-release opioids, prescription strength NSAIDs, tramadol, and tapentadol.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient in this product is codeine. Codeine Sulfate Tablets (NDA 22-402) approved in July, 2009, was the first approved single-entity codeine product.

The following is taken verbatim from the Medical Officer review for NDA 22-402, Codeine Sulfate Tablets:

Codeine and its' phosphate or sulfate salts are used in a variety of pharmaceutical products as an analgesic, sedative, hypnotic, anti-peristaltic, and anti-tussive therapeutic agent.

The Agency has approved 62 combination products with codeine across 56 NDAs. The potential advantage of combining two analgesics, which act by different mechanisms of action, is the increased analgesic efficacy. Examples of these approved combination products with codeine as a tablet or capsule include:

- 200 mg mg aspirin, 325 mg carisoprodol and 16 mg codeine phosphate as an oral tablet [redacted] (b) (4)
- 50 mg butalbital, 325 mg acetaminiophen, 40 mg caffeine and 30 mg codeine phosphate as an oral capsule (Fioricet with Codeine, NDA 020-232);
- 325 mg aspirin, 50 mg butalbital, 40 mg caffeine and 30 mg codeine phosphate as an oral capsule (Fiorinal with Codeine, NDA 019-429);

- 300 mg acetaminophen and 30 mg codeine phosphate as an oral tablet (Tylenol with Codeine, NDA 085-055); and
- 325 mg aspirin, 200 mg carisoprodol, and 16 mg codeine phosphate oral tablet (Soma Compound with Codeine, NDA 012-366).

Fewer combination products with codeine as an oral solution, suspension, and or syrup are available and approved. Examples of such approved formulations include:

- 10 mg/5 mL codeine phosphate, 30 mg/5 mL pseudoephedrine hydrochloride; 1.25 mg/5 mL triprolidine hydrochloride as an oral syrup (Actifed with Codeine, NDA 012-575);
- 10 mg/5 mL codeine phosphate, 30 mg/ 5 mL pseudoephedrine hydrochloride and 1.25 mg/5 mL triprolidine hydrochloride as an oral syrup (Triacin, NDA 088-704);
- 10.5 mg/5 mL codeine phosphate, 6.25 mg/ 5 mL promethazine hydrochloride as an oral syrup (Promethazine with Codeine, NDA 040-650) and
- 120 mg/5 mL acetaminophen and 12 mg/5 mL codeine as an oral suspension (Capital and Codeine, ANDA 085-883)

2.4 Important Safety Issues With Consideration to Related Drugs

The risks associated with the use of Codeine Sulfate Oral Solution appear similar to the risks of approved codeine tablets and other immediate-release and extended-release opioids. These risks include death, respiratory depression, withdrawal, physical dependence, misuse, abuse, diversion and overdosage (intended or accidental).

The class of opioids, in general, carries label warnings regarding concomitant use with CNS depressants such as alcohol, other opioids, anesthetic agents, sedative hypnotics and skeletal muscle relaxants which can potentiate respiratory depressant effects and increase the risk of adverse outcome.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- 9/20/07: Sponsor submitted Controlled Correspondence to the Agency which outlined their approach for filing NDA 202-245. Key points of the correspondence are as follows:
    - Clinical Data Summary and Labeling
        - Submit the clinical literature previously provided in support of codeine sulfate tablet and accepted by Agency in 7/17/07 correspondence
    - Pediatric Study Requirements
        - Deferral of pediatric studies until after approval of the product in adults

    - Nonclinical Pharmacology and Toxicology Summary and Labeling
        - Submit literature previously provided in support of Codeine Sulfate Tablet
    - Human PK and BA Summary
        - Conduct a dose linearity study using the Codeine Sulfate Tablet for comparison
    - Safety Update Report
        - Literature search of relevant published information regarding the safety of Codeine
    - Chemistry, Manufacturing and Controls Summary
        - Sponsor plans to manufacture one registration lot with 3 months accelerated stability with the commitment to add the 6 month accelerated data when it becomes available. If this option is not acceptable, the Sponsor would manufacture three registration lots but wanted clarification on acceptability of using the same log of API for the three registration batches in support of the 505(b)(2) or if they would be required to use different API lots.
- 10/17/07: email correspondence from Agency to the Applicant stating:
    - Preliminary review of the information in 9/20/07 correspondence was adequate to support a 505(b)(2) application
    - No PIND meeting would be necessary
- 7/02/08: Applicant submitted NDA 22-402 (Codeine Sulfate Tablets)
- 7/16/09: NDA 22-402 was approved
- 9//27/10: Applicant submitted NDA 202245 (Codeine Sulfate Oral Solution)

2.6 Other Relevant Background Information

None applicable.

3 Ethics and Good Clinical Practice

3.1 Submission Quality and Integrity

The submission appeared to be of good quality, was well organized and easily navigated. A number of information requests were sent from various review disciplines. The Applicant responded and complied with all information requests with no outstanding requests at the time of this review.

3.2 Compliance with Good Clinical Practices

The Applicant's submission included a statement that the clinical pharmacology study was conducted in accordance with Good Clinical Practices (GCP), including the archiving of essential documents.

The Division of Scientific Investigations (DSI) was to conduct a routine inspection at one clinical site. The inspection was delayed due to the inspector's illness, and the status of the inspection date is pending at the time of this review.

3.3 Financial Disclosures

The Applicant conducted one key study to assess the comparative bioavailability of Roxane Laboratories' Codeine Sulfate Oral Solution 30 mg/5 mL to Roxane Laboratories' Codeine Sulfate 30 mg Tablets. The Applicant provided the financial certification for the principal investigator which confirmed that the Investigator had no financial arrangements with the Sponsor.

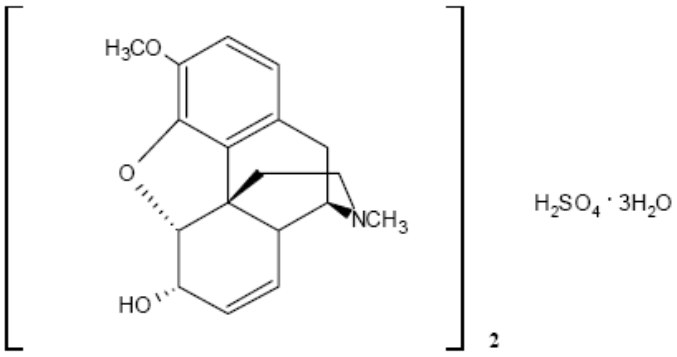
4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The drug substance is Codeine Sulfate, USP with a formula of $(C_{18}H_{21}NO_3)2\bullet H_2SO_4 \bullet 3H_2O$) and the chemical name of Morphinan-6α-ol, 7, 8-didehydro-4, 5-epoxy-3-methoxy-17-methyl-,(5α, 6α)-,sulfate (2:1)(salt), trihydrate. The molecular weight is 750.85 g/mol.

The structure for codeine sulfate is shown below in Figure 1.

Figure 1. Codeine Sulfate, USP



(Source: Applicant's Figure, NDA Submission, Module 3, Quality)

There were a number of information requests sent from the Agency's Chemistry, Manufacturing and Controls (CMC) reviewer to the Applicant throughout the review cycle.

As stated in the CMC Executive Summary review of Dr. Eugenia M. Nashed, dated 5/27/11, the information requests pertained to the following:

> 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.

The following recommendations and conclusions were made by CMC:

- The Application is recommended for approval from the CMC perspective, based on provided data and commitments.
- Based on the 12 months of stability data submitted 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 as of 1/24/11. The supporting DMFs have adequate status as of 5/2/11.

These Phase 4 CMC (Post-Marketing) Commitments, Agreements and/or Risk Management Steps have been forwarded to the Applicant:

- 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.
- 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.
- Provide a 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.
- Submit, revised as needed, drug product specifications and stability protocol with detailed references to the validated analytical methods.

4.2 Clinical Microbiology

According to the Microbiology review by Dr. Jessica Cole dated 5/2/11, this product is a non-sterile, (b) (4) aqueous solution for oral use; the drug product components are controlled to minimize the presence of microbes (b) (4) The Application was recommended for approval.

4.3 Preclinical Pharmacology/Toxicology

The Applicant intends to rely on the Agency's prior findings of preclinical pharmacology/toxicology safety for approved Codeine Sulfate Tablets.

As taken from the Pharmacology Toxicology review of Marcus Delatte, PhD, prior to the approval of Codeine Sulfate Tablets, the Sponsor agreed to postmarketing requirements to qualify the drug substance impurity (b) (4) ((b) (4) since its proposed specification of NMT (b) (4) exceeded the ICH Q3A(R2) qualification threshold. (b) (4) has been reported to be a known impurity of codeine; however, the Sponsor did not provide adequate safety qualification for this impurity at the time of the application review period.

The Sponsor provided data from rats in two separate repeat-dose toxicology studies; as well as data from four genetic toxicology studies in this submission to fulfill the Pharmacology Toxicology postmarketing requirement.

See Dr. Delatte's review for a detailed Pharmacology Toxicology discussion.

There were no approvability issues from Pharmacology Toxicology and no labeling changes that differed from the codeine tablet label.

4.4 Clinical Pharmacology

The Applicant submitted one bioavailability study with this NDA. The Applicant intends to rely on the Agency's prior clinical pharmacology findings of approved Codeine Sulfate Tablets.

The Agency has determined that Codeine Sulfate Oral Solution and it's metabolites are bioequivalent to the approved Codeine Sulfate Tablets (NDA 22-402). The reader is referred to the Clinical Pharmacology review of Dr. Sheetal Agarwal for further details.

As shown in Table 3 below, and as taken verbatim from Dr. Agarwal's review, "the statistical analysis results for the assessment of bioequivalence between Codeine Oral Solution 30mg and Codeine Tablet 30mg showed that the ratio of the geometric means for log transformed Cmax and AUC values as well as its corresponding 90% confidence intervals fell within the range of 80% to 125%".

Table 3. PK Parameters for Codeine in Study S30-T30-PVFS (N=36)

Parameter*	Solution 30 mg	Tablet 30 mg
Cmax (ng/mL)	74.4 ± 18.8 (36)	71.4 ± 21.2 (36)
Tmax (h)	1.00 (36) [0.25 – 2.50]	1.00 (36) [0.50 – 2.50]
AUC(0-t) (h×ng/mL)	279 ± 76.9 (36)	270 ± 76.6 (36)
AUC(inf) (h×ng/mL)	285 ± 77.1 (36)	274 ± 77.5 (35)
λz (h^{-1})	0.2826 ± 0.0343 (36)	0.2929 ± 0.0422 (35)
t½ (h)	2.49 ± 0.33 (36)	2.42 ± 0.39 (35)
Ln(Cmax)	4.28 ± 0.26 (36)	4.22 ± 0.33 (36)
Ln[AUC(0-t)]	5.60 ± 0.26 (36)	5.56 ± 0.29 (36)
Ln[AUC(inf)]	5.62 ± 0.26 (36)	5.57 ± 0.29 (35)

*Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported.

(Source: Dr. Sheetal Agarwal's Table, Clinical Pharmacology review, p.8)

The PK parameters for Codeine in Study S30-T30-PVFS are shown in Table 4.

Table 4. PK parameters for Codeine in Study S30-T30-PVFS

Parameter	Geometric Mean Ratio (%)*	
	Estimate	90% Confidence Interval
Cmax	105.98	99.29 → 113.13
AUC(0-t)	104.06	99.26 → 109.09
AUC(inf)	104.27	99.51 → 109.26

(Source: Dr. Sheetal Agarwal's Table, Clinical Pharmacology review, p.8)

Labeling changes by Clinical Pharmacology included (b) (4) The reader is referred to Dr. Agarwal's review for details.

There were no other substantial labeling changes in the Clinical Pharmacology section of the proposed label.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

One (1) Phase 1, single-dose, comparative bioavailability study in normal, healthy male and female subjects was conducted between the 30 mg Codeine Sulfate Tablet and 30mg/5mL Codeine Sulfate Oral Solution formulation in order to support the 505(b)(2) NDA application for Codeine Sulfate Oral Solution. Details of the study are described in detail in Dr. Agarwal's review and summarized in Table 5, below:

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Table 5. Clinical Trials Submitted with NDA 202-245 (Study No. CODE-S30-T30-PVFS1)

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	CODE-S30-T30-PVFS-1	5.3.1	comparative bioavailability under fasting conditions	Cross-over	Codeine sulfate 30 mg / 5 mL solution and 30 mg tablet, single dose, oral	36	Healthy Subjects	Single dose	Complete; Abbreviated

(Source: Applicant's submission, Module 5: Clinical Study Reports)

5.2 Review Strategy

The primary sources for this clinical review included the following:

- Applicant's NDA submission for 202-245 (Codeine Sulfate Solution)
- Relevant sections of Applicant's NDA submission for NDA 22-402 (Codeine Sulfate Tablets)
- Medical Officer (Clinical) Review by Dr. Carolyn Yancey for NDA 22-402, dated 12/22/08
- Cross-Discipline Team Leader Review of Dr. Ellen Fields for NDA 22-402, dated 7/15/09
- Deputy Division Director Summary Review by Dr. Sharon Hertz for NDA 22-402 dated 7/16/09
- Currently approved label for Codeine Sulfate Tablets (NDA 22-402)
- Referenced literature and postmarketing data

5.3 Discussion of Individual Studies/Clinical Trials

Background: The Applicant conducted one bioavailability (BA) study in order to support the 505 (b)(2) NDA application for Codeine Sulfate Oral Solution, 30 mg/5mL.

Title: A Single Dose, Two-Period, Two-Treatment, Two-Way Crossover Comparative Bioavailability Study of Codeine Sulfate Oral Solution and Tablets Under Fasted Conditions

Objective: To determine the comparative bioavailability of Roxane Laboratories' Codeine Sulfate 30 mg/5mL Oral Solution to Codeine Sulfate 30 mg Tablets under fasted conditions

Design: Open-label, randomized, two-treatment, two-period, two-sequence crossover study

Population: The study was to have enrolled 36 opioid-naïve, healthy adult subjects

Duration: 9 days (two treatment periods with a 7-day washout between the periods)

Key Inclusion criteria:

1. Male and female subjects between the ages of 18 and 45 years (inclusive)
2. Body mass Index (BMI) between 18 and 30 kg/m^2
3. Female subjects of childbearing potential – not surgically sterile or at least 2 years postmenopausal – must agree to utilize one of the following forms of contraception from screening through complete of the study: abstinence, hormonal (oral, implant, transdermal, vaginal or injection) for at least 3 months prior to the first dose of the study, barrier (condom with spermicide, diaphragm with spermicide), IUD,or vasectomized partner (6 months minimum)
4. No clinically significant abnormal findings on the physical examination, medical history, or clinical laboratory results during screening.
5. Opioid naïve defined as:
    a. Not currently taking opioids
    b. No prior addiction to or abuse of opioids
    c. No exposure to any opioids, including intermittent or short-term (5 days or less) such as that used in the immediate post-op surgical or dental procedure setting, within the last 3 years. Exposure to short-term use in this type of setting greater than 3 years prior to screening is acceptable.

Key Exclusion criteria:

1. History of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease or any other condition, which, in the opinion of the Investigator, would jeopardize the safety of the subject or impact the validity of the study results
2. History of allergic or adverse responses to codeine, opioids, or any comparable or similar product
3. Prior abnormal diet or have had substantial changes in eating habits within 30 days prior to study initiation
4. Prior blood donation of one pint or more within 30 days prior to study initiation
5. Use of any over-the-counter (OTC) medication, including vitamins, herbal products, and dietary supplements, within 7 days prior to or during the study
6. Use of any prescription medication within 7 days prior to or during the study, with the exception of hormonal contraceptives for women of childbearing potential, or hormone replacement therapy

7. Treatment with any known enzyme altering drugs such as barbiturates, phenothiazines, cimetidine, carbamazepine, phenytoin, rifampin, rifabutin, glucocorticoids, diltiazem, ketoconazole, MAOI, antidepressants, neuroleptics, verapamil, quinidine, erythromycin, etc., within 30 days prior to or during the study
8. Female subjects who were lactating
9. Positive serum pregnancy test for female subjects
10. Positive blood screen for HIV, Hepatitis B and Hepatitis C
11. Positive screen for alcohol, drugs of abuse, or cotinine and history or presence of alcoholism or drug abuse within 6 months prior to the study start

Study Overview: This was an open-label, single dose PK study to assess the PK of codeine after single oral doses of Codeine Sulfate Solution 30 mg/5mL and Codeine Tablets 30 mg on two occasions performed at one study site in normal healthy volunteers.

- Enrollment
- Randomization
  - 1:1 to Codeine Sulfate Solution or Codeine Tablet
- Treatments
  - Treatment A (1st period)
    - Codeine Sulfate 30 mg/5 mL oral solution, 1 x 5 mL (30 mg) dose under fasting conditions
      - Minimum 7-day washout
  - Treatment B (2nd period)
    - Codeine Sulfate 30 mg tablets, 1 x 30 mg dose, under fasting conditions
- PK sampling (total of 44 blood samples=264 mL)
  - collected before and 5, 10, 15, 30, 45 minutes after and;
  - collected 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hours after dosing

Procedures:
The Schedule of Activities is shown in Table 6, followed by a bulleted summary of the key procedures performed during the study.

Table 6. Schedule of Activities

Procedure	Screen[1]	Each Dosing Period				End of Study Or Early Termination
	Day -21 → -1	Day 0, 7	Day 1, 8	Day 2, 9	Day 3, 10	Day 10
Informed Consent	X					
Medical History	X					
Physical Exam	X					X
Clinical Lab Tests	X					X
12-Lead ECG	X					X
Vital Signs	X		X[2]			X
HIV and Hepatitis Tests	X					
Alcohol, Drug, and Cotinine Screen	X	X				
Serum Pregnancy Test[3]	X	X				X
Admission to Clinical Site		X				
Single Dose of Drug			X			
PK Samples[4]			X	X	X	
Release from Clinical Site					X	X
Monitor and Record Adverse Events			X	X	X	X

[1] Within 21 days of the first dose (Day 1)
[2] Vital signs will be measured before each dose and at specified times after dosing
[3] For female subjects, results must be negative before drug is administered to the subject
[4] PK samples will be collected before dosing and at specified times after dosing

(Source: Applicant's Table, Study Protocol, p. 45)

Key Procedures:

- Check in
  - Urine testing for alcohol, drugs of abuse, and cotinine
  - Female subjects undergo a serum pregnancy test
- Confinement
  - Subjects are to be admitted to the study unit prior to the beginning of the fasting period in the evening prior to drug administration and will remain in the unit until the 48-hour blood sample is collected
- Fasting/Meals
  - Snack will be served the evening of check in
  - Subjects are required to fast overnight for at least 10 hours prior to dosing
  - Water is allowed ad lib except for one hour prior through one hour post dose
  - Standard meals will be provided at approximately 4 and 9 hours after drug administration and at other appropriate times thereafter

    - During confinement, meals plans will be identical for all periods
- Drug Administration
    - Treatment A
    - Treatment B
- Blood (PK) sampling
    - Blood (plasma) pharmacokinetic characteristics were assessed after each dose of study medication.
    - Blood samples were drawn prior to dose administration and at 5, 10, 15, 30, 45 minutes, and 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hours after dose administration.
- Safety Procedures:
    - Sitting vital signs (blood pressure, pulse, respiratory rate, temperature, pulse oximetry) were evaluated at screening, prior to each dose administration, and at end of study
    - Sitting vital signs consisting of blood pressure, pulse, respiratory rate, and pulse oximetry were measured at approximately 1, 2, 4 and 6 hours after dosing
    - 12-lead ECG at Screening and End of Study or Early Termination
- Laboratory Parameters
    - Hematology, serum chemistry, and urinalysis tests were performed at screening and at the end-of-study visit
    - HIV and hepatitis tests were performed at screening
    - Urine alcohol, drug, and tobacco screens were performed at screening and at each check-in
- End of Study/Early Termination
    - Physical examination; Safety and Laboratory Assessments

6 Review of Efficacy

Efficacy Summary

The efficacy for Codeine Sulfate Oral Solution (NDA 202-245) is based on the efficacy of Codeine Sulfate Tablets (NDA 22-402) approved 7/16/09.

Codeine sulfate tablets were approved under standard review for drugs already marketed, but without an approved NDA. Given the long history of codeine use in the United States, the extensive amount of published literature previously reviewed by the Agency for approval of NDA 22-402, and the Agency's prior communication to the Applicant that NDA 202-245 could be submitted as a 505(b)(2), the Applicant submitted no new clinical efficacy studies in support of this application.

The efficacy of single-entity codeine tablets (NDA 22-402) was based on published literature.

6.1 Indication

The proposed indication is for the (b) (4) of mild to moderately severe pain where the use of an opioid analgesic is appropriate.

6.1.1 Methods

No efficacy studies were submitted. Relevant data from the Applicant's Phase 1 bioavailability/bioequivalence study is provided in the applicable sections of this review.

7 Review of Safety

Safety Summary

The Applicant plans to rely upon the known safety profile of codeine from the approved Codeine Tablets (NDA 22-204), relevant published literature, and postmarketing information.

As taken from the Cross-Discipline Team Leader's review for Codeine Sulfate Tablets, NDA 22-204:

> Safety for single-entity codeine sulfate is supported by the Agency's prior findings of safety for the reference product Tylenol with Codeine #3 (acetaminophen 500mg/codeine phosphate 30mg). Tylenol with Codeine #3 is an oral combination product approved for the relief of mild to moderately severe pain. The applicant has provided support for the use of the referenced product through a relative bioavailability study
>
> Common adverse events associated with codeine are similar to those of other opioids and include lightheadedness, dizziness, sedation, nausea, vomiting, abdominal pain and constipation. Serious adverse events include overdose, severe respiratory depression, coma and death.
>
> Codeine sulfate is a Schedule II controlled substance and like all opioids, its' use can result in abuse, misuse, psychological and or physical dependence, and tolerance.
>
> A safety issue unique to codeine relates to its' use in nursing mothers. On August 17, 2007, an FDA Alert was issued regarding a very rare, but serious side effect in nursing infants whose mothers are taking codeine and are ultra-rapid metabolizers of codeine. Evidence suggests that individuals who are ultra-rapid metabolizers (those with a specific CYP2D6 genotype) may convert codeine to its active metabolite, morphine, more rapidly and completely than other people. In nursing mothers, this metabolism can result in higher than expected serum

and breast milk morphine levels. One published case report of an infant death raised concern that nursing babies may be at increased risk of morphine overdose if their mothers are taking codeine and are ultra-rapid metabolizers of the drug.

Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may experience overdose symptoms. Signs of morphine overdose in infants include increased sleepiness, difficulty breastfeeding or breathing, or decreased tone. Nursing mothers may also experience overdose symptoms such as extreme sleepiness, confusion, shallow breathing or severe constipation.

The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5% to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

As a result of this phenomenon, appropriate language has been added to the labels of all products containing codeine regarding ultra-rapid metabolizers and the prescribing of codeine to nursing mothers.

7.1 Methods

After review of the safety data from the Phase 1 PK study included in the submission for this NDA, this reviewer concludes that the safety findings of codeine sulfate oral solution 30 mg/5 mL appear, in general, to be consistent with the safety findings of the approved codeine sulfate oral tablets.

The adverse events observed in this study were not unexpected given the nature of the study drug as an opioid analgesic. The incidence of treatment-emergent adverse events was comparable in both formulations studied.

There were no subjects who experienced adverse events leading to death, serious adverse events or study discontinuation.

Most AEs were mild and the most commonly reported adverse events reported were headaches (n = 5), nausea (n = 5), dizziness (n = 4), and somnolence (n = 4) which are known and expected adverse events associated with codeine use.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Refer to Section 5 (Sources of Clinical Data) for a listing and brief description of the Codeine Sulfate Oral Solution bioavailability study.

Study CODE-S30-T30-PVFS-1, titled A Single Dose, Two-Period, Two-Treatment, Two-Way Crossover Comparative Bioavailability Study of Codeine Sulfate Oral Solution and Tablets Under Fasted Conditions, was conducted in the United States at one site initiated on 3/17/10 and completed on 3/26/10. The report date was 4/20/10 with one amendment to the report on 5/5/10 to include updated protocol deviations and meal deviation tables.

There was one administrative Protocol Amendment submitted to the Agency on 2/23/10, which informed that the principal investigator had changed. This administrative change should not have affected the safety or other relevant aspects of the study.

7.1.2 Categorization of Adverse Events

The Applicant reported that adverse events (AEs) from the Phase 1 PK study were coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 9.1). The Applicant's approach to safety coding appeared adequate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Since there was only one study there were no pooled safety data included in this submission.

7.2 Adequacy of Safety Assessment

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure: Subjects were exposed to a single dose on one occasion of Test Product (Codeine Sulfate Oral Solution) or Listed Product (Codeine Sulfate Tablets) using a cross-over study design. The total dose administered to each subject who completed both study periods was 60 mg of codeine sulfate.

Demographics: The subjects in the safety data base were evenly matched in terms of key demographics of age, sex, race, weight. Of the 36 subjects enrolled, 19 were male and 17 were female. The age range was from 19 to 42 years of age. Further details regarding the demographics are shown in Table 7.

Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study

Best Available Copy

Study No. CODE-S30-T30-PVFS-1		Treatment Groups	
		Test Product Oral Solution N =36	Reference Product Tablet N =36
Age (years)	Mean ± SD	26 ± 6	26 ± 6
	Range	19 - 42	19 - 42
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18 – 40	35 (97.22%)	35 (97.22%)
	41 – 64	1 (2.78%)	1 (2.78%)
	65 – 75	0 (0.00%)	0 (0.00%)
	> 75	0 (0.00%)	0 (0.00%)
Sex	Female	17 (47.22%)	17 (47.22%)
	Male	19 (52.78%)	19 (52.78%)
Race	Asian	0 (0.00%)	0 (0.00%)
	Black	10 (27.78%)	10 (27.78%)
	Caucasian	24 (66.67%)	24 (66.67%)
	Hispanic	0 (0.00%)	0 (0.00%)
	Other	2 (5.56%)	2 (5.56%)
BMI (kg/m^2)	Mean ± SD	25.0 ± 3.1	25.0 ± 3.1
	Range	19.0 - 29.9	19.0 - 29.9
Height (cm)	Mean ± SD	172.7 ± 8.8	172.7 ± 8.8
	Range	151.5 - 192.5	151.5 - 192.5
Weight (kg)	Mean ± SD	74.6 ± 10.6	74.6 ± 10.6
	Range	52.5 - 100.2	52.5 - 100.2

(Source: Applicant's table, Summary of Clinical Safety, p. 1)

Disposition

There were no dropouts or replacements in study CODE-S30-T30-PVFS-1. The Applicant reported that 36 subjects were enrolled and all subjects completed both periods of the study and comprised the analysis population.

7.2.2 Explorations for Dose Response

Not applicable.

7.2.3 Special Animal and/or In Vitro Testing

The currently approved Codeine Sulfate Oral Tablet label specifically addresses teratogenicity, fertility, genotoxicity and carcinogenicity.

There were no Phase 2 or 3 special animal and/or in vitro testing performed for this submission. Pertinent sections of the currently approved Codeine Sulfate Tablet were referenced by the Applicant and reviewed as appropriate.

7.2.4 Routine Clinical Testing

The routine clinical testing performed during the Phase 1 study appears adequate. Safety testing included vital signs at screening, prior to each dose administration, at specified times after dosing and at discharge.

Study exit clinical laboratory tests included serum pregnancy tests for female subjects, ECGs vital signs and physical examinations.

7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to the Clinical Pharmacology review of Dr. Sheetal Agarwal for information regarding the metabolic clearance and interaction findings for codeine sulfate tablets and oral solution.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable.

7.3 Major Safety Results

There were no deaths, serious adverse events or discontinuations due to adverse events.

A total of 34 adverse events (AEs) were reported by 16 of the 36 subjects over the course of the study.

Of the 34 treatment-emergent AEs, 26 (76%) were mild and 8 (23%) were moderate.

One subject had a clinically significant AE of a mild bruise on the left arm at the discharge physical examination (unlikely causality to study drug).

7.3.1 Deaths

There were no deaths reported in the Phase 1 bioequivalence study.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events (SAEs) reported in the Phase 1 bioequivalence study.

7.3.3 Dropouts and/or Discontinuations

There were no dropouts or discontinuations.

7.3.4 Significant Adverse Events

There were no significant or unexpected significant adverse events.

7.3.5 Submission Specific Primary Safety Concerns

Opioids produce a wide spectrum of pharmacologic effects including analgesia, dysphoria, euphoria, somnolence, respiratory depression, diminished gastrointestinal motility, altered circulatory dynamics, histamine release and physical dependence.

Nausea, vomiting, orthostatic hypotension, constipation, and respiratory depression are commonly reported with opioids and are appropriately labeled.

This study was comprised of healthy volunteers. Expected AEs would be those seen in prior Codeine Sulfate Tablet studies and approved opioid labeling.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In general, the incidence of AEs was comparable in both the study drug (Codeine Oral Solution) and comparator drug (Codeine Oral Tablet).

The only clinically important AE seen in the Oral Solution group not seen in the reference group was pruritus of face and neck in one subject in the Oral Solution compared to zero subjects in Tablet. Causality to study drug can not be assigned since the AE was not serious and no narrative was provided. Pruritus is currently a common AE labeled in the Codeine Tablet label.

Adverse events of dizziness, headache, nausea and somnolence occurred in 2 subjects each in the Codeine Oral Solution group, with similar incidence of occurrence in the Codeine Oral Tablet group (reference). There were no unexpected or unlabeled AEs except for ecchymosis right forearm in one subject and bilateral tinnitus in one subject in the Oral Solution group. Causality of these adverse events to study drug can not be

determined given the limited amount of information available regarding the AEs. It is unlikely that these two unlabeled AEs need to be addressed in the proposed label for Codeine Oral solution.

The most frequently occurring observed AEs in the listed product (Codeine Tablets) include drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, sweating, and constipation. As taken verbatim from the currently approved Codeine Sulfate Tablets label:

> **Currently Approved Codeine Sulfate Tablets Label:**
>
> **Section 6 ADVERSE REACTIONS**
> Serious adverse reactions associated with codeine are respiratory depression and, to a lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest. The most frequently observed adverse reactions with codeine administration include drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, sweating, and constipation.
>
> Other adverse reactions include allergic reactions, euphoria, dysphoria, abdominal pain, and pruritis.
>
> Other less frequently observed adverse reactions expected from opioid analgesics, including codeine sulfate, include:
> *Cardiovascular system:* faintness, flushing, hypotension, palpitations, syncope
> *Digestive System:* abdominal cramps, anorexia, diarrhea, dry mouth, gastrointestinal distress, pancreatitis
> *Nervous system:* anxiety, drowsiness, fatigue, headache, insomnia, nervousness, shakiness, somnolence, vertigo, visual disturbances, weakness
> *Skin and Appendages:* rash, sweating, urticaria

As shown in Table 8, below, the safety findings of the study population were consistent with the current labeling and codeine literature.

Table 8. Incidence of Adverse Events in Individual Studies (Oral Solution Compared to Tablet)

Body System / Adverse Event	Reported Incidence by Treatment Groups Fasted Bioequivalence Study Study No. CODE-S30-T30-PVFS-1	
	Test Product Oral Solution N =36	Reference Product Tablet N =36
Abdominal cramps	1 (3%)	0 (0%)
Bilateral tinnitus	1 (3%)	0 (0%)
Bruise left arm	0 (0%)	1 (3%)
Chest pain	1 (3%)	1 (3%)
Cold sore	1 (3%)	0 (0%)
Diaphoresis	0 (0%)	1 (3%)
Dizziness	2 (6%)	2 (6%)
Ecchymosis right forearm	1 (3%)	0 (0%)
Feeling flushed	0 (0%)	1 (3%)
Headache	2 (6%)	3 (8%)
Hypotension	0 (0%)	1 (3%)
Nausea	2 (6%)	3 (8%)
Paresthesis	0 (0%)	1 (3%)
Probable Insect Bite	1 (3%)	0 (0%)
Pruritis face and neck	1 (3%)	0 (0%)
Somnolence	2 (6%)	2 (6%)
Substernal chest tightness	0 (0%)	1 (3%)
Vasovagal reaction	0 (0%)	1 (3%)
Vomiting	1 (3%)	0 (0%)
Total*	11 (31%)	9 (25%)

(Source: Applicant's table, Summary of Clinical Safety, p. 1)

7.4.2 Laboratory Findings

According to the Applicant's submission, clinical laboratory tests (chemistry, hematology and urinalysis) were performed at screening and at the end of the study.

Serology tests (Hepatitis B, Hepatitis C and HIV) were performed on all subjects at screening. Urine alcohol, drug, and cotinine tests were performed at screening and check-in for each study period.

Serum pregnancy tests were done at screening, check-in for each study period, and at the end of the study.

The Applicant reported that no AEs were related to abnormal laboratory evaluations. There were no clinically important abnormal laboratory values noted upon review of the submitted data.

7.4.3 Vital Signs

The Applicant reported that sitting vital signs (blood pressure, pulse, and temperature) were measured at screening, prior to each dose administration, approximately 1, 2, 4 and 6 hours after dosing, and at discharge.

There was one clinically important adverse change in vital signs in subject 105, who experienced a clinically significant AE of hypotension (lowest 75/40 and 73/42 mm/Hg) within the first two hours after dosing with predose BP of 124/70. The BP returned to a normal range of 111/70 within 2 hours post dose. Associated decrease in pulse (52/53 bpm) and respiration from baseline was noted with the drop in blood pressure. However, there was no meaningful change in pulse oxygen saturation which remained at the predose level of 98%. The patient reportedly had no other associated systemic complaints.

7.4.4 Electrocardiograms (ECGs)

There were no clinically important changes in ECGs according to the Applicant, although ECG tracings were not included in the submission.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

There were no other safety explorations in this Phase 1, bioequivalence study. The Applicant will rely upon approved Codeine Sulfate Tablets labeling and literature.

7.5.1 Dose Dependency for Adverse Events

This was not explored in the submission.

7.5.2 Time Dependency for Adverse Events

Not applicable.

7.5.3 Drug-Demographic Interactions

The following information is taken from the approved Codeine Sulfate Tablet label:

Pediatric Use
The safety and effectiveness and the pharmacokinetics of codeine sulfate in pediatric patients below the age of 18 have not been established. FDA has not required pediatric studies in ages birth to one month because there is evidence strongly suggesting that codeine would be ineffective in this pediatric group since the metabolic pathways to metabolize codeine are not mature.

Geriatric Use
Codeine may cause confusion and over-sedation in the elderly. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

7.5.4 Drug-Disease Interactions

The following information is taken from the approved Codeine Sulfate Tablet label:

Renal Impairment
Codeine pharmacokinetics may be altered in patients with renal failure. Clearance may be decreased and the metabolites may accumulate to much higher plasma levels in patients with renal failure as compared to patients with normal renal function. Start these patients cautiously with lower doses of codeine sulfate or with longer dosing intervals and titrate slowly while carefully monitoring for side effects.

Hepatic Impairment
No formal studies have been conducted in patients with hepatic impairment so the pharmacokinetics of codeine in this patient population are unknown. Start these patients cautiously with lower doses of codeine sulfate or with longer dosing intervals and titrate slowly while carefully monitoring for side effects.

7.5.5 Drug-Drug Interactions

The following information is taken from the approved Codeine Sulfate Tablet label:

CNS Depressants

Concurrent use of other opioids, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, or other tranquilizers or alcohol) concomitantly with codeine sulfate tablets may result in additive CNS depression, respiratory depression, hypotension, profound sedation, or coma. Use codeine sulfate with caution and in reduced dosages in patients taking these agents.

Mixed Agonist/Antagonist Opioid Analgesics

Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should NOT be administered to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic such as codeine sulfate. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

Anticholinergics
Anticholinergics or other medications with anticholinergic activity when used concurrently with opioids analgesics including codeine sulfate, may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

Antidepressants
Use of MAO inhibitors or tricyclic antidepressants with codeine sulfate may increase the effect of either the antidepressant or codeine. MAOIs markedly potentiate the action of morphine sulfate, the major metabolite of codeine. Codeine should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

Metabolic Enzymes
Patients taking cytochrome P-450 enzyme inducers or inhibitors may demonstrate an altered response to codeine, therefore analgesic activity should be monitored. Codeine sulfate is metabolized by the cytochrome P-450 3A4 and 2D6 isoenzymes. *[see Clinical Pharmacology (12)]* The concurrent use of drugs that preferentially induce codeine *N*demethylation (cytochrome P-450 3A4) may increase the plasma concentrations of codeine's inactive metabolite norcodeine. Drugs that are strong inhibitors of codeine *O*-demethylation (cytochrome P-450 2D6) may decrease the plasma concentrations of codeine's active metabolites, morphine and morphine-6-glucuronide. The contribution of these active metabolites to the overall analgesic effect of codeine is not fully understood, but should be considered.

Drug-Laboratory Test Interaction
Codeine sulfate tablets may cause an elevation of plasma amylase and lipase due to the potential of codeine to produce spasm of the sphincter of Oddi. Determination of these enzyme levels may be unreliable for some time after an opiate agonist has been given.

7.6 Additional Safety Evaluations

There were no additional safety evaluations in this Phase 1, bioequivalence study. The Applicant will rely upon Codeine Sulfate Tablets labeling and literature.

7.6.1 Human Carcinogenicity

No evaluations of human carcinogenicity were conducted,

7.6.2 Human Reproduction and Pregnancy Data

The following information is taken from the approved Codeine Sulfate Tablet label:

Teratogenic Effects, Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Codeine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Codeine has been shown to have embryolethal and fetotoxic effects (reduced fetal body weights and delayed or incomplete ossification) in the hamster, rat and mouse models at approximately 2-4 times the maximum recommended human dose of 360 mg/day based on a body surface area comparison. Maternally toxic doses that were approximately 7 times the maximum recommended human dose of 360 mg/day, were associated with evidence of resorptions and incomplete ossification, including meningioencephalocele and cranioschisis. In contrast, codeine did not demonstrate evidence of embrytoxicity or fetotoxicity in the rabbit model at doses up to 2 times the maximum recommended human dose of 360 mg/day based on a body surface area comparison

Nonteratogenic Effects
Neonatal codeine withdrawal has occurred in infants born to addicted and non-addicted mothers who had been taking codeine-containing medications in the days prior to delivery. Typical symptoms of narcotic withdrawal include irritability, excessive crying, tremors, hyperreflexia, seizures, fever, vomiting, diarrhea, and poor feeding. These signs occur shortly after birth and may require specific treatment.

Codeine (30 mg/kg) administered subcutaneously to pregnant rats during pregnancy and for 25 days after delivery increased neonatal mortality at birth. This dose is 0.8 times the maximum recommended human dose of 360 mg/day on a body surface area comparison.

7.6.3 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no reported cases of drug abuse, overdose, or dependence in this submission. Signs or symptoms of withdrawal or rebound were not reported, although the study was not designed to identify these specific AEs. These issues are addressed in the product label.

Consultation was obtained from the Division with the Agency's Controlled Substances Staff (CSS). Initial recommendations from Dr. Alicja Lerner, primary reviewer for CSS, noted in a 5/27/11 Memorandum the following points which were to be communicated to the Applicant:

- Conduct routine pharmacovigilance of this drug and report all cases of potential abuse, misuse or overdose (intentional or unintentional including cases leading to death).

- Submit a summary of analysis in two years of all available data (including DAWN and AERS) and relevant information on drug diversion from the US market for the product, Codeine Sulfate Oral Solution.

After further internal discussion, CSS modified their recommendations and, in a 6/8/11 Memorandum, the above bulleted recommendations to the Applicant were retracted due to the following:

- There is a possible anticipated DAWN access issue expected to occur over the next one to two years. CSS may be able to still access national estimates but data trending may be difficult.
- CSS will rely on DEA data bases regarding diversion data.

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

In response to an Information Request, the Applicant's submission included Postmarketing safety data for Codeine Sulfate Tablets covering a period from July 1, 2009 through May 31, 2011. No new or unexpected adverse events were reported during this period.

The Applicant reported that a total of 79 individual case safety reports for NDA 22-402 (Codeine Sulfate Tablets) had been received since approval 7/16/09. There were 38 reportable serious individual case safety reports submitted to the Agency. Of those, published scientific literature (foreign and domestic) was the source of 33 individual cases.

According to the Applicant, there were 9 fatal cases, with published literature being the source of all 9 cases. Two of these cases involved drug abuse and drug diversion that were reported spontaneously from local news media with the product in both cases reported as "codeine-based cough syrup."

A review was conducted by this reviewer of the Agency's internal Annual Report for NDA 22-402 covering the period July 1, 2009 through June 30, 2010 and periodic (quarterly) Adverse Event Reports up to May 6, 2011. There have been no new adverse events reported which would affect labeling or change the overall safety profile of codeine sulfate tablets.

9 Appendices

9.1 Literature Review/References

The Applicant reported that a literature review had been conducted which covered the period from 01/01/09 to 06/30/10 to support NDA 202-245. According to the Applicant, there were no unpublished clinical trials on codeine. Published literature was obtained via a search of MEDLINE for literature published during the reporting period which was pertinent to codeine. In response to an Information Request, the Applicant's submission included a list of citations, abstracts and the full articles from the stated periods.

The Applicant reported that there were no new safety findings which would affect labeling.

9.2 Labeling Recommendations

The label was submitted in PLR format and is under review at this time. No proprietary name was proposed for this product.

The Controlled Substance Staff is in agreement with the proposed drug abuse and dependence sections of the label. Labeling changes were made to (b) (4) consistent with updated class-wide labeling for opioids.

The label is essentially identical to that for the tablets (b) (4) This label will also include a medication guide for the purpose of mitigating dosing errors with the liquid formulation.

9.3 Advisory Committee Meeting

There was no Advisory Committee Meeting for this NDA.

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

/s/

ELIZABETH M KILGORE
06/09/2011

ELLEN W FIELDS
06/09/2011
I concur with Dr. Kilgore

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202-245 **Applicant: Roxane Laboratories** **Submission Date: 9/27/2010**

Drug Name: Codeine Sulfate **NDA/BLA Type: 505(b)(2)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X 505 (b)(2)			Reference NDA 22-402 for Codeine Sulfate Tablets
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	BA Study
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? **Pivotal Study #1:** CODE-S30-T30-PVFS-1 **Indication:**			X	BA Study

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 2869050

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:			X	Only 1 BA study was performed
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	BA Study
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	Not required
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	BA Study
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	No deaths, SAEs or dropouts due to AEs

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	BA Study
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	No deaths, SAEs, or dropouts due to AEs
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Elizabeth Kilgore	11/24/10
Reviewing Medical Officer	Date
Clinical Team Leader	Date

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

/s/

ELIZABETH M KILGORE
11/24/2010

ELLEN W FIELDS
11/28/2010
This application is filable from the clinical perspective