

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202245Orig1s000**

**OTHER REVIEW(S)**

### 505(b)(2) ASSESSMENT

Application Information		
NDA # 202245	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Codeine sulfate Dosage Form: oral solution Strengths: 30mg/5mL		
Applicant: Roxane		
Date of Receipt: September 27, 2010		
PDUFA Goal Date: July 27, 2011		Action Goal Date (if different): <b>June 18, 2011</b>
Proposed Indication(s): relief of mild to moderately severe pain		

### GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Acetaminophen/codeine sulfate tablets (ANDA 85-055)	

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

**BA/BE studies used to bridge the two products.**

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If “NO,” proceed to question #5.*

*If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
<b>Acetaminophen/codeine sulfate tablets</b>	<b>85-055</b>	<b>Y</b>

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

**This application provides for a new dosage form (oral solution).**

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?  
YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?  
YES  NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO   
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?  
YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?  
YES  NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

**PATENT CERTIFICATION/STATEMENTS**

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed  *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

**Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KATHLEEN M DAVIES  
06/30/2011

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: Deferred pediatric study of pharmacokinetics and safety under PREA for the (b)(4) of mild to moderately severe pain when the use of an opioid analgesic is appropriate in pediatric patients ages 2 to 17 years

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>12/01/2011</u>
	Study/Trial Completion:	<u>09/01/2013</u>
	Final Report Submission:	<u>03/01/2014</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Studies are ready for approval in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

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3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A deferred safety and pharmacokinetic study in pediatric patients ages 2 to 17 years.
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Required

- Observational pharmacoepidemiologic study  
 Registry studies  
 Primary safety study or clinical trial  
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety  
 Thorough Q-T clinical trial  
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

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PMR/PMC Description: Deferred pediatric study of pharmacokinetics, and safety under PREA for the (b)(4) of mild to moderately severe pain when the use of an opioid analgesic is appropriate in pediatric patients ages one month to 2 years

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>12/01/2011</u>
	Study/Trial Completion:	<u>09/01/2013</u>
	Final Report Submission:	<u>03/01/2014</u>
	Other:	<u>MM/DD/YYYY</u>

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- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

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2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

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 Assess signals of serious risk related to the use of the drug?  
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- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A deferred safety and pharmacokinetic study in pediatric patients ages 1 month to 2 years
---

Required

- Observational pharmacoepidemiologic study  
 Registry studies  
 Primary safety study or clinical trial  
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety  
 Thorough Q-T clinical trial  
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
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  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
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- Meta-analysis or pooled analysis of previous studies/clinical trials
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  - Other (provide explanation)
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Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
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5. Is the PMR/PMC clear, feasible, and appropriate?

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PMR/PMC Description: Deferred pediatric study of efficacy and safety under PREA for the (b) (4) of mild to moderately severe pain when the use of an opioid analgesic is appropriate in pediatric patients ages one month to 2 years

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/01/2014</u>
	Study/Trial Completion:	<u>06/01/2016</u>
	Final Report Submission:	<u>12/01/2016</u>
	Other:	<u>MM/DD/YYYY</u>

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2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

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Required

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## PMR/PMC Development Template

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PMR/PMC Description: Submit a validated method for quantitative monitoring of the drug product color and update the drug product specifications with data-based acceptance criteria

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PMR/PMC Schedule Milestones: Final Protocol Submission: \_\_\_\_\_  
Study/Trial Completion: \_\_\_\_\_  
Final Report Submission: July 8, 2011  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Not a safety issue that would preclude approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

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***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

---

(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

---

PMR/PMC Description: Provide systematic release and stability data for the drug product, according to the updated specifications, and submit as a prior-approval supplement. 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. Revise, as needed, drug product specifications and stability protocol with detailed references to the validated analytical methods.

---

PMR/PMC Schedule Milestones: Final Protocol Submission: \_\_\_\_\_  
Study/Trial Completion: \_\_\_\_\_  
Final Report Submission: September 2012  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Not a safety issue that would preclude approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
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- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
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- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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KATHLEEN M DAVIES  
06/30/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

DATE: June 20, 2011

TO: Bob Rappaport, M.D.  
Director, Division of Anesthesia, Analgesia, and  
Addiction Products (HFD-170)

FROM: Charles R. Bonapace, Pharm.D.  
Bioequivalence Branch  
Division of Bioequivalence (BEQ) and Good Laboratory  
Practice (GLP) Compliance  
Office of Scientific Investigations (HFD-48)

Michael F. Skelly, Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence (BEQ) and Good Laboratory  
Practice (GLP) Compliance  
Office of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D.  
Acting Team Leader - Bioequivalence Branch  
Division of Bioequivalence (BEQ) and Good Laboratory  
Practice (GLP) Compliance  
Office of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 202-245, Codeine Sulfate  
Oral Solution, 30 mg/5 mL, Sponsored by Roxane  
Laboratories, Inc.

At the request of the Division of Anesthesia and Analgesia Products, the Division of Scientific Investigations (DSI) inspected one clinical site and one analytical site of the following bioequivalence study:

**Study Number:** CODE-S30-T30-PVFS-1

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

An inspection of the clinical portion of the study was conducted at the following site:

**Clinical Site:** CEDRA Clinical Research, LLC  
2455 N.E. Loop 410, Suite 150  
San Antonio, TX 78217

Following the audit of the clinical records at CEDRA Clinical Research, LLC [REDACTED] (b)(4), there were no significant objectionable observations and FDA Form 483 was not issued.

An inspection of the analytical portion of the study was conducted at the following site:

**Analytical Site:** [REDACTED] (b)(4)

Following the audit of the analytical records at [REDACTED] (b)(4) [REDACTED] (b)(4), there were no significant objectionable observations and FDA Form 483 was not issued.

**Conclusion:**

Based on the above audit findings, OSI recommends that the clinical data generated at CEDRA Clinical Research, LLC (San Antonio, TX) and analytical data generated at [REDACTED] (b)(4) [REDACTED] (b)(4) for Study CODE-S30-T30-PVFS-1 be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

---

Charles R. Bonapace, Pharm.D.  
Bioequivalence Branch  
Division of Bioequivalence (BEQ) and Good Laboratory Practice  
(GLP) Compliance  
Office of Scientific Investigations

---

Michael F. Skelly, Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence (BEQ) and Good Laboratory Practice  
(GLP) Compliance  
Office of Scientific Investigations

**Final Classifications:**

**NAI - CEDRA Clinical Research, LLC, San Antonio, TX**  
(FEI Number: 3006724658)

**NAI -** [REDACTED] (b) (4)  
[REDACTED] (b) (4)

cc: DARRTS

CDER DSI PM TRACK  
OSI/Ball/Salewski  
OSI/Haidar/Yau/Skelly/Dejernet/Bonapace/CF  
DAAAP/Rappaport/Davies  
HFR-CE2545/McNew  
HFR-SW150/Ngai  
Draft: CRB 6/20/11  
Edit: MFS 6/20/11  
DSI: 6159; O:\BE\EIRCover\202245.doc  
FACTS: 1258373

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/s/  
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CHARLES R BONAPACE  
06/20/2011

MICHAEL F SKELLY  
06/20/2011  
Skelly signing for myself and also on behalf of Martin K. Yau, Ph.D.

**MEMORANDUM**  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

**\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**Date:** June 13, 2011

**To:** Kathleen Davies – Regulatory Project Manager  
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

**From:** Twyla Thompson – Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications  
(DDMAC)

**Subject: DDMAC Draft Medication Guide Comments  
NDA 202245 Codeine Sulfate Oral Solution**

DDMAC has reviewed the proposed Medication Guide for Codeine Sulfate Oral Solution submitted for DDMAC review on January 4, 2011.

The following comments are provided using the substantially complete version of the labeling sent via email on June 10, 2011, by Kathleen Davies. DDMAC's comments on the proposed product labeling (PI) have been issued under separate cover. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

7 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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/s/  
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TWYLA N THOMPSON  
06/13/2011

**MEMORANDUM**  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

**\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**Date:** June 10, 2011

**To:** Kathleen Davies – Regulatory Project Manager  
Division of Anesthesia, and Analgesia Products (DAAP)

**From:** Mathilda Fienkeng – Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Subject:** **DDMAC draft labeling comments**  
**NDA 202245 Codeine Sulfate Oral Solution**

DDMAC has reviewed the proposed product labeling (PI), for Codeine Sulfate Oral Solution, submitted for DDMAC review on January 04, 2011. The following comments are provided using the substantially complete version of the labeling sent via email on June 10, 2011, by Kathleen Davies. DDMAC's comments on the proposed Medication Guide will be provided under separate cover.

DDMAC's comments are provided directly in the attached marked-up copy of the PI. If you have any questions about DDMAC's comments, please do not hesitate to contact Mathilda Fienkeng at 301-796-3692 or at [Mathilda.fienkeng@fda.hhs.gov](mailto:Mathilda.fienkeng@fda.hhs.gov).

13 pages of draft labeling has been withheld in full as B(4)  
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/s/  
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MATHILDA K FIENKENG  
06/10/2011



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** June 8, 2011

**To:** Bob Rappaport, M.D., Director  
Division of Anesthesia, Analgesia, and Addiction Products

**Through:** Michael Klein, Ph.D., Director  
Controlled Substance Staff

**From:** Alicja Lerner, M.D., Ph.D., Medical Officer  
Controlled Substance Staff

**Subject:** **NDA 202-245 Codeine Sulfate Oral Solution**  
**Indication:** Relief of mild to moderately severe pain  
**Dosages:** Codeine sulfate oral solution 30 mg/5mL  
**Company:** Roxane Laboratories, Inc.

**Materials reviewed:** NDA 201-194 is located in EDR (Receipt Date: Sept 27, 2010)  
<\\CDSESUB1\EVSPROD\NDA202245\202245.enx>

**Amendment**

We are retracting earlier recommendations to the sponsor listed in the review from May 27 2011.

One reason for the retraction relates to a possible anticipated DAWN access issue over the next 1 or 2 years. CSS may be able to still access national estimates but data trending may be difficult.

Regarding diversion data, we will rely on the DEA data bases.

Therefore, we do not need to depend on the sponsor to provide data regarding abuse and diversion of the drug.

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/s/  
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ALICJA LERNER  
06/08/2011

MICHAEL KLEIN  
06/08/2011



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** May 27, 2011

**To:** Bob Rappaport, M.D., Director  
Division of Anesthesia, Analgesia, and Addiction Products

**Through:** Michael Klein, Ph.D., Director  
Controlled Substance Staff

**From:** Alicja Lerner, M.D., Ph.D., Medical Officer  
Controlled Substance Staff

**Subject:** **NDA 202-245 Codeine Sulfate Oral Solution**  
**Indication:** (b) (4) of mild to moderately severe pain  
**Dosages:** Codeine sulfate oral solution 30 mg/5mL  
**Company:** Roxane Laboratories, Inc.

**Materials reviewed:** NDA 201-194 is located in EDR (Receipt Date: Sept 27, 2010)  
<\\CDSESUB1\EVSPROD\NDA202245\202245.enx>

**Table of Contents**

**A. BACKGROUND.....1**

**B. CONCLUSION.....2**

**C. RECOMMENDATIONS.....2**

**A. Background:**

This memorandum responds to the DAAAP consult regarding abuse potential of Codeine Sulfate Oral Solution 30 mg/5mL mL by Roxane. The sponsor submitted NDA 202-245 as a 505(b)(2) application. The Reference Listed Drug is Codeine sulfate tablets, 15 mg, 30 mg, and 60 mg, NDA 22-402 by Roxane Laboratories, which was approved on July 16, 2009. The sponsor is relying on the findings of safety and efficacy of the reference listed drug. A comparative bioavailability study bridging the oral solution formulation to RLD was conducted and is included in this NDA. Also, a complete Chemistry, Manufacturing and Controls (CMC) section is included in this application.

CSS Consult: NDA 202-245 Codeine Sulfate Oral Solution, 30 mg/5mL

Roxane Laboratories, Inc. requests a deferral of pediatric studies for this NDA for the following pediatric populations: infant (1 month to 2 years), children (2 to 12 years) and adolescent (12 years to < 16 years) with the intention to conduct these pediatric studies in Phase IV.

The bridging study CODE-S30-T30-PVFS-1 (A Single Dose, Two-Period, Two-Treatment, Two-Way Crossover Comparative Bioavailability Study of Codeine Sulfate Oral Solution and Tablets Under Fasted Conditions) was performed in 36 healthy volunteers. The study was conducted to assess comparative bioavailability of Codeine Sulfate Oral Solution 30 mg/mL and Codeine Sulfate Oral Tablet 30 mg, both products of Roxane Labs. The adverse events profile was similar in both groups. The sponsor states that Codeine Sulfate Oral Solution 30 mg/5 mL and Tablet 30 mg were bioequivalent with respect to codeine, morphine, morphine-3-glucuronide, and morphine-6-glucuronide.

Codeine Sulfate Oral Solution 30mg/5mL will be manufactured and packaged in bottles of 500 mL.

The sponsor has no questions specific for CSS, but DAAAP requests input from CSS regarding this NDA.

## **B. Conclusion**

The sponsor states that Codeine Sulfate Oral Solution 30 mg/5 mL and Tablet 30 mg are bioequivalent with respect to codeine, morphine, morphine-3-glucuronide, and morphine-6-glucuronide.

Codeine (and its salts) is listed as a Schedule II narcotic in the Controlled Substances Act.

## **C. Recommendation (to be relayed to the Sponsor)**

1. Conduct routine pharmacovigilance of this drug and report all cases of potential abuse, misuse or overdose (intentional or unintentional including cases leading to death).
2. 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.

CSS Consult: NDA 202-245 Codeine Sulfate Oral Solution, 30 mg/5mL

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/s/  
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ALICJA LERNER  
05/27/2011

MICHAEL KLEIN  
05/27/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**PATIENT LABELING REVIEW**

Date: May 27, 2011

To: Bob Rappaport, MD, Director  
Division of Anesthesia, Analgesia, and Addiction Products  
(DAAAP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN  
Acting Team Leader, Patient Labeling Reviewer  
**Division of Risk Management (DRISK)**  
Barbara Fuller, RN, MSN, CWOCN  
Acting Team Leader, Patient Labeling Reviewer  
**Division of Risk Management**

From: Steve L. Morin, RN, BSN, OCN  
Patient Labeling Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Medication Guide and  
Instructions for Use )

Drug Name (established name): Codeine Sulfate Oral Solution

Application Type/Number: NDA 202245

Therapeutic Class: Opioid Analgesic  
(optional)

Applicant: Roxane Laboratories, Inc

OSE RCM #: 2011-40

## 1 INTRODUCTION

This review is written in response to a request by the Division of Anesthesia, Analgesia and Addiction Products (DAAAP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for Codeine Sulfate Oral Solution.

On September 27, 2010 Roxane Laboratories submitted 505(b)(2) New Drug Application (NDA) 202245 for Codeine Sulfate Oral Solution 30mg/5mL for (b)(4) of mild to moderately severe pain.

On December 6, 2010, the FDA requested that Roxane Laboratories submit a Risk Evaluation Mitigation Strategy (REMS) based on section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA).

On Friday, February 25, 2011, FDA published a draft Guidance that addresses when a Medication Guide will be required as part of a REMS. Based on the risks of a drug and public health concerns, FDA has the authority to determine whether a Medication Guide should be required as part of a REMS or should be required as labeling but not part of a REMS.

DRISK and DAAAP determined that a REMS for Codeine Sulfate Oral Solution is not necessary and that the Applicant can be released from their REMS requirements. The approval of NDA 202245 should include the action to eliminate the REMS.

DRISK conferred with DMEPA and a separate DMEPA review of the IFU was completed and submitted on May 13, 2011.

## 2 MATERIAL REVIEWED

- Draft Codeine Sulfate Oral Solution MG and IFU received on September 27, 2010, revised by the Review Division through the current review cycle, and provided to DRISK on May 12, 2011.
- Draft Codeine Sulfate Oral Solution prescribing information (PI) received September 27, 2010, revised by the Review Division throughout the current review cycle, and provided to DRISK on May 12, 2011.
- Approved Morphine Sulfate Oral Solution, comparator labeling dated May 2011.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG and IFU the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Verdana font, size 11.

In our review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The MG and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG and IFU are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/  
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STEVE L MORIN  
05/27/2011

LASHAWN M GRIFFITHS  
05/29/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label and Labeling Review**

Date: May 12, 2011

Reviewer(s): Richard Abate, RPh, MS, Safety Evaluator  
Division of Medication Prevention and Analysis

Team Leader Melina Griffis, RPh, Team Leader  
Division of Medication Prevention and Analysis

Division Director Carol Holquist, RPh, Director  
Division of Medication Prevention and Analysis

Drug Name and Strength: Codeine Sulfate Oral Solution, USP, 30 mg/5 mL

Application Type/Number: NDA 202245

Applicant/sponsor: Roxane Laboratories, Inc

OSE RCM #: 2010-2476

## 1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA's) evaluation of the proposed container labels, carton and insert labeling for Codeine Sulfate Oral Solution in NDA 202245. The review responds to a request from the Division of Analgesia, Anesthesia and Addiction Products (DAAAP) to review the labels and labeling and to provide comments for labeling negotiations with the Applicant. DMEPA evaluates the labels and labeling for vulnerabilities to confusion that may lead to medication errors.

### 1.1 REGULATORY HISTORY

This application was filed as a (505)(b)(2) for the use of Codeine Sulfate Oral Solution, USP. The reference listed drug serving as the basis for this application is Codeine Sulfate Tablets, USP NDA 022402. Codeine Sulfate Oral Solution is not currently marketed by any manufacturer.

### 1.2 PRODUCT INFORMATION

Codeine Sulfate Oral Solution is indicated for the (b)(4) of mild to moderately severe pain. The dose is 15 mg to 60 mg (2.5 mL to 10 mL) up to every four hours as needed. Doses above 60 mg (10 mL) may fail to give commensurate pain relief and may be associated with an increased incidence of undesirable side effects. Codeine Sulfate Oral Solution, USP will available in one concentration, 30 mg/5 mL. The oral solution is proposed to be packaged in bottles containing (b)(4). The applicant is co-packaging 5 mL oral syringes for patients to measure doses of the product.

## 2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis<sup>1</sup> and the principles of human factors, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted January 6, 2011.
- Carton Labeling submitted February 23, 2011.
- Insert Labeling submitted April 6, 2011 which is combined with Codeine Sulfate Tablets, USP.
- Patient instructions for use submitted April 6, 2011.

As wrong drug medications errors have resulted from confusion among the Roxane products<sup>2</sup> due to the similarity of the labels, we compared the proposed container label and carton labeling to the approved container labels for the Morphine Sulfate Oral Solution, 10 mg/5 mL and 20 mg/5 mL included in NDA 022195.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

<sup>2</sup> OSE review 2007-2786 and 2007-1808, Morphine Sulfate Labeling Review, Duffy, F. February 8, 2008.

### 3 DISCUSSION OF DEFICIENCIES IDENTIFIED

DMEPA identified the following deficiencies with the packaging, labels and labeling or areas that are vulnerable to confusion and lead to medication errors.

#### 3.1 PRODUCT DESIGN

The Applicant proposes to supply oral syringe to accurately measure doses of Codeine Sulfate Oral Solution. The intended instructions for use for this oral syringe include inserting the syringe into the bottle. The dimensions specified for the barrel diameter (14 mm) of the oral syringe should fit in the mouth of the 500 mL bottle as described in the Container Closure System of the Application. (b) (4)

The Applicant provided no dimensional information that describes the openings of commonly used amber bottles for dispensing so that oral syringe will fit when patients attempt to withdraw a dose as the instructions for use state.

In addition, since the repackaging of Codeine Sulfate Oral Solution is likely upon dispensing, the number of oral syringes to be co-packaged should be sufficient to provide each patient with a dosing device.

#### 3.2 CONTAINER LABELS

The similar presentation of the information on the container labels among Roxane products (i.e., trade dress) makes the proposed product look similar to the other Roxane marketed opioid oral solutions marketed in the 500 mL presentation. In addition, Codeine Sulfate Oral Solution uses the same color field, (b) (4), to present the product's strength as the Roxane's Morphine Sulfate Oral Solution 20 mg/5 mL<sup>3</sup> and Meperidine HCl Oral Solution, USP<sup>4</sup>. This color scheme is unacceptable (b) (4)

<sup>3</sup> NDA 022195 Annual report 2009, Roxane Laboratories.

<sup>4</sup> ANDA 088744 Annual Report 2010, Roxane Laboratories.

### 3.3 CARTON LABELING

The similarity of the trade dress of Roxane products is a source of confusion with the carton labeling as noted in Section 3.2. DMEPA notes that the fact that this 500 mL bottle is packaged in a carton helps to differentiate it from the other oral opioid solutions which do not include a carton with the 500 mL presentation. However, this minor differentiation will be lost once the bottle is removed from the carton and returned to the pharmacy shelf.

### 3.4 INSERT LABELING

The Dosage and Administration section presents the doses of an oral solution in milligrams alone.

### 3.5 THE PATIENT INSTRUCTIONS FOR USE

The patient instructions for use include a pictogram of the syringe that is intended to help provide directions on how to measure the oral solution accurately with this device. However, DMEPA believes the lack of units of measure on the oral syringe could be a source of confusion for patients.

## 4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed packaging, label, and labeling introduce vulnerability that can lead to medication errors because of lack of data confirming the provided oral syringe will work in bottle used to repack the product during dispensing, the common colors and presentation of information across the Roxane product line, and the lack of units of measurement in terms of volume may require recalculation of the dose. We recommend the following:

- A. Product Design
  - 1. DMEPA requests the Applicant provide dimensional information for amber plastic bottles commonly used to repack oral liquids during dispensing [REDACTED] <sup>(b) (4)</sup> to demonstrate the provided oral syringe will fit. Specifically, the mouth of the bottle must be > 14 mm.
  - 2. Provide enough oral syringes in the carton of Codeine Sulfate Oral Solution, USP so that each patient dispensed a portion of the bottle receives an oral syringe.
- B. Container Label
  - 1. The trade dress is too similar to your currently marketed products. Present the established name in a font color other than brown that adequately distinguishes Codeine Sulfate Oral Solution from the other opioid oral solutions you currently market in 500 mL.
  - 2. Use a larger font to display the center four digit drug portion of the NDC. (e.g., 0054-**0294**-63)

3. Revise the presentation of the strength so that it appears different from your other opioid oral solutions you currently market in 500 mL.
  4. Revise the presentation of the established name to appear on one line to improve readability.
- C. Carton Labeling
1. See Comments B1 through B3.
- D. Insert Labeling
1. If the package insert for Codeine Sulfate Oral Solution, USP is separated from Codeine Sulfate Tablets, DMEPA recommends including the doses in term of volume in the Highlights and Dosage and Administration sections of the labeling for Codeine Sulfate Oral Solution, USP. For example, “The dose is 15 mg to 60 mg (2.5 mL to 10 mL).”
- E. Patient Instructions for Use
1. Add a scale to the left of the pictogram of the syringe that includes the unit of measure (mL) with each whole number (i.e. 1 mL, 2 mL, 3 mL... etc) as marked on the syringe to clearly state what units the syringe measures.
  2. DMEPA defers changes to the language used in the Instructions for Use to the Patient Labeling Reviewer in DRISK.

If the Division has further questions or need clarifications, please contact Danyal Chaudhry, project manager, at 301-796-3813.

2 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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

RICHARD A ABATE  
05/13/2011

MELINA N GRIFFIS  
05/13/2011

CAROL A HOLQUIST  
05/13/2011

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 202245 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: codeine sulfate Dosage Form: oral solution Strengths: 30 mg/5 mL		
Applicant: Roxane Agent for Applicant (if applicable): N/A		
Date of Application: September 27, 2010 Date of Receipt: September 27, 2010 Date clock started after UN:		
PDUFA Goal Date: July 27, 2011		Action Goal Date (if different):
Filing Date: November 26, 2010		Date of Filing Meeting: November 9, 2010
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): (b) (4) of mild to moderately severe pain.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:  <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html</a>                      and refer to Appendix A for further information.</i></b>		
Review Classification:  <b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>  <b><i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i></b>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): N/A				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov/9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov/9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b>  <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="201 1440 1349 1577"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product have orphan exclusivity for the same indication? <b>Check the Electronic Orange Book at:</b>  <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></p>		<p>X</p>																		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?<sup>1</sup>            If not, explain (e.g., waiver granted).</p>	X			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?				
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?				
<b>Patent Information</b> (NDAs/NDA efficacy supplements only)	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the <b>APPLICANT</b>, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(l) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i> 11/16/2010</p>	X			

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <i>If no, request in 74-day letter</i>				
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>		X		REMS notification letter sent 12/6/2010: Medication Guide required for this product.
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request in 74-day letter.</i>	X			Submitted 10/21/2010.
Is the PI submitted in PLR format? <sup>4</sup>				

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?				
<i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			Consult sent 1/4/11.
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)				
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			Consult sent 11/22/10.
<b>OTC Labeling</b>	<input type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?				
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)				
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s) <b>Date(s):</b>			X	

<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> <i>If yes, distribute minutes before filing meeting</i>			X	PIND 75764 had a meeting for codeine tablets on 1/24/2007 which pertains to both this NDA and their approved NDA 22402.
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>			X	

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** November 9, 2010

**NDA #:** 202245

**PROPRIETARY NAME:** N/A

**ESTABLISHED/PROPER NAME:** Codeine Sulfate

**DOSAGE FORM/STRENGTH:** Oral Solution 30 mg/ 5 mL

**APPLICANT:** Roxane

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** (b) (4) of mild to moderately severe pain.

**BACKGROUND:** Roxane has an approved NDA 22402 (July 2009) for codeine sulfate tablets. Roxane submitted this 505(b)(2) application, referencing their approved NDA to provide for an oral solution of codeine sulfate.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kathleen Davies	Y
	CPMS/TL:	Sara Stradley	N
Cross-Discipline Team Leader (CDTL)	Ellen Fields		Y
Clinical	Reviewer:	Liz Kilgore	Y
	TL:	Ellen Fields	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial products)	Reviewer:		
	TL:		


Clinical Pharmacology	Reviewer:	Zhihong Li	N
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:	N/A	N
	TL:	Dionne Price (if needed)	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Marcus Delatte	Y
	TL:	Dan Mellon	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Eugenia Nashed	N
	TL:	Danae Christodoulou	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Richard Abate	N
	TL:	Melina Griffis	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	Alicja Lerner	N
	TL:	Mike Klein	N
Other reviewers	Mathilda Fienkeng, DDMAC		N
Other attendees	Sharon Hertz, Bob Rappaport		

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p>Comments: Not deemed necessary at this time.</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p>Comments: EER sent via CMC reviewer.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<b><u>CMC Labeling Review</u></b>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Sharon Hertz (subject to change)  <b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):  Comments:	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> </ul>

	<ul style="list-style-type: none"> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at:  <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a>]</p>
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KATHLEEN M DAVIES  
01/05/2011

**DSI CONSULT**  
**Request for Biopharmaceutical Inspections**

**DATE:** December 13, 2010

**TO:** Associate Director for Bioequivalence  
Division of Scientific Investigations, HFD-48

**THROUGH:** Bob Rappaport, M.D.  
Director, Division of Anesthesia and Analgesia Products

**FROM:** Kathleen Davies, Senior Regulatory Health Project Manager, Division of Anesthesia and Analgesia Products, HFD-170

**SUBJECT: Request for Biopharmaceutical Inspections**  
NDA 202-245  
Codeine Sulfate Oral Solution, 30 mg/5 mL  
Roxane Laboratories, Inc.

**Study/Site Identification:**

As discussed with you, the following studies/sites pivotal to approval have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
CODE-S30-T30-PVFS-1	PI: Mark T. Leibowitz, MD CEDRA Clinical Research, LLC 2455 N.E. Loop 410, Suite 150 San Antonio, TX 78217 Phone: 210-635-1500 Fax: 210-635-1646	(b) (4)

**International Inspections:**

**(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)**

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

\_\_\_\_\_ Other (please explain):

**Goal Date for Completion:**

We request that the inspections be conducted and the Inspection Summary Results be provided by **May 9, 2011**. We intend to issue an action letter on this application by **July 27, 2011**.

Should you require any additional information, please contact Kathleen Davies, Senior Regulatory Health Project Manager, at 301-796-2205.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KATHLEEN M DAVIES  
12/14/2010