

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-402

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22402

SUPPL #

HFD # 170

Trade Name <none>

Generic Name codeine sulfate
 [marketed, unapproved drug]

Applicant Name Roxane

Approval Date, If Known July 15, 2009

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1: An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

The Applicant relied on published articles to show efficacy for codeine. They are not requesting exclusivity.

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA

#(s).

NDA#	20232	FIORICET W/ CODEINE
NDA#	19429	FIORINAL W/CODEINE
NDA#	11483	SYNALGOS-DC
NDA#	12366	SOMA COMPOUND W/ CODEINE

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or

sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

For this application, efficacy was supported by literature articles submitted by the Applicant. Six of these articles were selected by the Agency to support approval, however other submitted articles could also support efficacy, but were not reviewed.

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

The Applicant relied on published articles to show efficacy for codeine. They are not requesting exclusivity.

- b) For each investigation identified as "essential to the approval", does the investigation

duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES ! NO
! Explain:

Investigation #2 !
IND # YES ! NO
! Explain:

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

/s/

Matthew Sullivan
7/16/2009 12:00:07 PM

Sharon Hertz
7/16/2009 12:20:59 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-402

Supplement Number: _____

NDA Supplement Type (e.g. SE5): _____

Division Name: DAARP

PDUFA Goal Date: 8/2/09

Stamp Date: 7/2/2008

Proprietary Name: _____

Established/Generic Name: Codeine sulfate

Dosage Form: tablets

Applicant/Sponsor: Roxanne

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

Indication: treatment of mild to moderately severe pain

Q1: Is this application in response to a PREA PMR?

Yes Continue

No Please proceed to Question 2.

If Yes, NDA/BLA#: _____

Supplement #: _____

PMR #: _____

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. Skip to signature block.

* Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. Skip to signature block.

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

Yes: (Complete Section A.)

No: Please check all that apply:

Partial Waiver for selected pediatric subpopulations (Complete Sections B)

Deferred for some or all pediatric subpopulations (Complete Sections C)

Completed for some or all pediatric subpopulations (Complete Sections D)

Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [#]	Ineffective or unsafe [†]	Formulation failed [‡]
<input checked="" type="checkbox"/>	Neonate	0 wk. 0 mo.	__ wk. 1 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

The metabolic pathways to metabolize codeine are not mature before one month of age.

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	__ yr. 1 mo.	_____	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

b(4)

b(4)

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	_____	Yes <input type="checkbox"/>	No <input type="checkbox"/>

b(4)

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	_____

b(4)

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL. (cderrmh@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:				
Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	_____	<input type="checkbox"/>	<input type="checkbox"/>

b(4)

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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

/s/

Matthew Sullivan
7/14/2009 02:29:37 PM

Roxane Laboratories, Inc.
NDA - Codeine Sulfate Tablets, USP, 15 mg, 30 mg and 60 mg
Module 1: Administrative Information and Prescribing Information

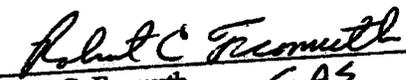
A. Certification of Compliance with Generic Drug Enforcement Act

In compliance with the Generic Drug Enforcement Act of 1992, Roxane Laboratories, Inc. hereby certifies that (1) we did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)], in connection with this application, and (2) there have been no convictions of the applicant and affiliated persons at Roxane Laboratories, Inc. responsible for the development or submission of the application in the last five years.


Elizabeth Ernst
Director, Drug Regulatory Affairs and Medical Affairs
Roxane Laboratories, Inc.

6/24/08
Date

In compliance with the Generic Drug Enforcement Act of 1992, Boehringer Ingelheim Roxane, Inc. (BIRI) hereby certifies that (1) we did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)], in connection with this application, and (2) there have been no convictions of the applicant and affiliated persons at BIRI responsible for the development or submission of the application in the last five years.


Robert C. Fromuth
President and COO
Boehringer Ingelheim Roxane Laboratories, Inc.

4/31/09
Date

B. U.S. Agent Letter of Authorization

Not applicable.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION		
NDA # 22402 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: <none> Established/Proper Name: Codeine sulfate Dosage Form: tablets		Applicant: Roxane Agent for Applicant (if applicable):
RPM: Matthew Sullivan		Division: Division of Anesthesia, Analgesia and Rheumatology Products
<p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Tylenol with Codeine #3 (ANDA 85-055)</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>Single entity codeine, rather than in combination</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: July 14, 2009</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
♦ User Fee Goal Date Action Goal Date (if different)		August 2, 2009 July 15, 2009
♦ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None

The Application Information section is (only) a checklist. The Contents of Action Package section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ Promotional Materials (accelerated approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application² Characteristics</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC</p> <p>Comments: _____</p>	
<p>❖ Date reviewed by PeRC (required for approvals only) If PeRC review not necessary, explain: _____</p>	<p>March 11, 2009</p>
<p>BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (approvals only)</p>	<p><input type="checkbox"/> Yes, date</p>
<p>❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (approvals only)</p>	
<p>• Office of Executive Programs (OEP) liaison has been notified of action</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>• Press Office notified of action (by OEP)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>• Indicate what types (if any) of information dissemination are anticipated</p>	<p><input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other</p>

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDA only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)). 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>CONTENTS OF ACTION PACKAGE</p>	
<p>❖ Copy of this Action Package Checklist³</p>	<p>Sullivan</p>
<p>Officer/Employee List</p>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Action Letters</p>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) AP: July 15, 2009</p>
<p>Labeling</p>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>July 10, 2009</p>
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>July 2, 2008</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<p>❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<p><input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None</p>

³ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	July 10, 2009
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent division proposal for (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	July 10, 2009
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA July 2, 2009 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC February 23, 2009 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Review(s) (<i>indicate date(s)</i>) • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	<none proposed>
Administrative / Regulatory Documents	
Administrative Reviews (e.g., RPM Filing Review/Memo of Filing Meeting) (<i>indicate date of each review</i>)	March 26, 2009
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html <ul style="list-style-type: none"> • Applicant in on the AIP • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Postmarketing Requirement (PMR) Studies 	<input type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing communications (<i>if located elsewhere in package, state where located</i>) 	In Outgoing Communications section
<ul style="list-style-type: none"> • Incoming submissions/communications 	
<ul style="list-style-type: none"> ❖ Postmarketing Commitment (PMC) Studies 	<input type="checkbox"/> None

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.
 Version: 9/5/08

<ul style="list-style-type: none"> Outgoing Agency request for postmarketing commitments (if located elsewhere in package, state where located) 	In Outgoing Communications section
<ul style="list-style-type: none"> Incoming submission documenting commitment 	
<ul style="list-style-type: none"> Outgoing communications (letters (except previous action letters), emails, faxes, telecons) 	various
<ul style="list-style-type: none"> Internal memoranda, telecons, etc. 	
<ul style="list-style-type: none"> Minutes of Meetings 	
<ul style="list-style-type: none"> PeRC (indicate date; approvals only) 	<input type="checkbox"/> Not applicable March 11, 2009
<ul style="list-style-type: none"> Pre-Approval Safety Conference (indicate date; approvals only) 	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> Regulatory Briefing (indicate date) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (indicate date) 	<input type="checkbox"/> No mtg January 24, 2007
<ul style="list-style-type: none"> EOP2 meeting (indicate date) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	
<ul style="list-style-type: none"> Advisory Committee Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> 48-hour alert or minutes, if available 	
Decisional and Summary Memos	
<ul style="list-style-type: none"> Office Director Decisional Memo (indicate date for each review) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Division Director Summary Review (indicate date for each review) 	<input type="checkbox"/> None Hertz: July 16, 2009
<ul style="list-style-type: none"> Cross-Discipline Team Leader Review (indicate date for each review) 	<input type="checkbox"/> None Fields: July 15, 2009
Clinical Information⁵	
<ul style="list-style-type: none"> Clinical Reviews 	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (indicate date for each review) 	
<ul style="list-style-type: none"> Clinical review(s) (indicate date for each review) 	Yancey: December 22, 2008
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (indicate date for each review) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Safety update review(s) (indicate location/date if incorporated into another review) 	
<ul style="list-style-type: none"> Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not 	Fields: July 15, 2009
<ul style="list-style-type: none"> Clinical reviews from other clinical areas/divisions/Centers (indicate date of each review) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review) 	<input type="checkbox"/> Not needed Hunter: March 16, 2009
<ul style="list-style-type: none"> Risk Management <ul style="list-style-type: none"> Review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) REMS Memo (indicate date) REMS Document and Supporting Statement (indicate date(s) of submission(s)) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators) 	<input checked="" type="checkbox"/> None requested

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology <input checked="" type="checkbox"/> None	
• Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None Agarwal: April 3, 2009
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None Yau: March 31, 2009
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None Mellon: July 15, 2009
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None Delatte: June 2, 2009
Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None Al Hakim: July 13, 2009
• CMC/product quality review(s) (indicate date for each review)	<input type="checkbox"/> None Nashed: July 9, 2009
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None
Environmental Assessment (check one) (original and supplemental applications)	

<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
♦ NDAs: Methods Validation	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
♦ Facilities Review/Inspection	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) 	Date completed: March 9, 2009 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>) 	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental 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) Or 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.
- (3) Or 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) And 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.
- (3) And 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) Or 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.
- (3) Or 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 ODE's ADRA.

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

/s/

Matthew Sullivan

7/23/2009 11:53:17 AM

Sullivan, Matthew

From: Greeley, George
Sent: Wednesday, July 15, 2009 2:40 PM
To: Sullivan, Matthew
Cc: Stowe, Ginneh D.
Subject: NDA 22-402 Codeine Sulfate

Importance: High

Hi Matt,

The Codeine Sulfate partial waiver/deferral/plan was reviewed by the PeRC PREA Subcommittee on March 11, 2009. The Division recommended a partial waiver from 0<1 month because evidence strongly suggests that the product would be ineffective and unsafe in all pediatric subpopulations and a deferral from 1 month to ~~_____~~ because the product is ready for approval in adults. The PeRC agreed with the Division to grant a partial waiver and deferral for this product.

b(4)

The PeRC requested that the pediatric page be modified to reflect the reason for the waiver be that evidence strongly suggests that product would be ineffective in all pediatric subpopulations.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

 Please consider the environment before printing this e-mail.

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

/s/

Matthew Sullivan
7/15/2009 03:07:39 PM
CSO

PMR/PMC Development Template

PMR/PMC Title: Collect long-term data for hardness and friability generated during release and stability testing of commercial drug product tablets.

PMR/PMC Schedule Milestones:

Study Completion: by June 1, 2012

Final Report Submission: by July 1, 2012

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., 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).

Long-term data needed.

2. If required, characterize the PMR. Check all that apply and add text where indicated. *If not a PMR, skip to 3. Not Applicable*

- Which regulation?

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- Describe the particular review issue leading to the PMR

- If the PMR is a FDAAA safety study/clinical trial, describe the risk

- If the PMR is a FDAAA safety study/clinical trial, does it:

- 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?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not Applicable

4. If not required by regulation, characterize the review issue leading to this PMC

The controls for monitoring of hardness and friability of the tablets were implemented during the NDA review cycle and long-term data are needed to revise interim acceptance criteria for harness and friability.

5. What type of study or clinical trial is required or agreed upon (describe)?

Required:

- Pharmacoepidemiologic study (list risk to be evaluated)
- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)
- Subpopulation (list type)
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)
- Meta-analysis or pooled analysis of previous studies/clinical trials

NDA 22402

- 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)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)
- Other (provide explanation)

CMC Comment to the Action Letter

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

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

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or 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.

**Ali Al Hakim, Ph.D., Branch Chief, Division of Pre-Marketing Quality Assessment,
ONDQA**

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

/s/

Eugenia Nashed
7/15/2009 12:24:53 PM
CHEMIST

Ali Al-Hakim
7/15/2009 12:30:02 PM
CHEMIST

Larissa Lapteva
7/15/2009 12:36:53 PM
MEDICAL OFFICER

PMR/PMC Development Template

PMR/PMC Title: Agreement to collect long-term data for dissolution.

PMR/PMC Schedule Milestones:

Study Completion: by June 1, 2012

Final Report Submission: by July 1, 2012

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., 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).

Long-term data needed.

2. If required, characterize the PMR. Check all that apply and add text where indicated. *If not a PMR, skip to 3. Not Applicable*

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

- 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?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not Applicable

4. If not required by regulation, characterize the review issue leading to this PMR/PMC

The dissolution method was changed/improved during the NDA review cycle and long-term data are needed to revise interim acceptance criteria for dissolution of tablets.

5. What type of study or clinical trial is required or agreed upon (describe)?

Required:

- Pharmacoepidemiologic study (list risk to be evaluated)
- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)
- Subpopulation (list type)
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (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)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)
- Other (provide explanation)

CMC Comment to the Action Letter

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

- a. You agree to submit dissolution profile data generated during release and stability testing of commercial drug product, for a minimum of 20 production batches, i.e., first 10 batches of the 15 mg tablets and first 5 batches of each of the 30 mg and 60 mg tablets). The dissolution profiles will include adequate number of data points to allow comparison of the profiles, e.g., 10 min, 15 min, 30 min and 45 min. A statistical evaluation of batch to batch variability, between different drug product strengths and within the same batch during stability storage, sorted by the type of container closure, will be provided.**
6. Is the PMR/PMC clear and feasible?
- Are the schedule milestones and objectives clear?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or 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.

Ali Al Hakim, Ph.D., Branch Chief, Division of Pre-Marketing Quality Assessment, ONDQA

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

/s/

Eugenia Nashed
7/15/2009 12:20:47 PM
CHEMIST

Ali Al-Hakim
7/15/2009 12:29:43 PM
CHEMIST

Larissa Lapteva
7/15/2009 12:38:11 PM
MEDICAL OFFICER

Attachment B: Sample 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: Efficacy, safety and pharmacokinetic (single and multiple dose) study of Codeine sulfate in pediatric patients with mild to moderately severe pain in pediatric patients 12-17 years old.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	<u>11/2009</u>
Study/Clinical trial Completion Date:	<u>04/2010</u>
Final Report Submission Date:	<u>10/2011</u>
Other:	_____

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 were 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."

To obtain pharmacokinetic, efficacy and safety data in pediatric patients ages 12-17 to inform dosing in this age group.

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.

Pediatric patients ages 12-17 years.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- 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)
 - 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)

Attachment B: Sample 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: Efficacy, safety and pharmacokinetic (single and multiple dose) study of Codeine sulfate in pediatric patients with mild to moderately severe pain in pediatric patients 2 to 12 years old.

PMR/PMC Schedule Milestones: Final protocol Submission Date: 01/2010
Study/Clinical trial Completion Date: 06/2010
Final Report Submission Date: 12/2011
Other: _____

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 were ready for approval in adults
Necessary to commence studies in older children prior to younger age group for safety reasons

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."

To obtain pharmacokinetic, efficacy and safety data in pediatric patients ages 2 to 12 years to inform dosing in this age group.

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.

Pediatric patients ages 2 to 12 years.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- 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)
 - 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)

Attachment B: Sample 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: Efficacy, safety and pharmacokinetic (single and multiple dose) study of Codeine sulfate in pediatric patients with mild to moderately severe pain in pediatric patients 1 month to 2 years old.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>05/2010</u>
	Study/Clinical trial Completion Date:	<u>10/2010</u>
	Final Report Submission Date:	<u>04/2012</u>
	Other:	_____

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 were ready for approval in adults
Necessary to commence studies in older children prior to younger age group for safety reasons

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."

To obtain pharmacokinetic, efficacy and safety data in pediatric patients ages 1 month to 2 years to inform dosing in this age group.

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.

Pediatric patients ages 1 month to 2 years.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- 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)
 - 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)

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

/s/

Matthew Sullivan
7/14/2009 06:24:48 PM
CSO

Ellen Fields
7/15/2009 11:33:49 AM
MEDICAL OFFICER

Larissa Lapteva
7/15/2009 11:56:26 AM
MEDICAL OFFICER

505(b)(2) ASSESSMENT

Application Information		
NDA # 22402	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: <none proposed> Established/Proper Name: Codeine sulfate Dosage Form: tablets Strengths: 15, 30 and 60 mg		
Applicant: Roxane Laboratories		
Date of Receipt: July 2, 2008		
PDUFA Goal Date: August 2, 2009 (3-month extension from May 2, 2009)		Action Goal Date (if different): July 15, 2009
Proposed Indication(s): Treatment of mild to moderate 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)
Tylenol with Codeine #3 (ANDA 85-055)	Safety of single-entity codeine
Published literature	Support of efficacy, and for non-clinical pharmacology and toxicology

*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)

Comparative BA study between codeine (30 mg) tablets and Tylenol #3 (30 mg).

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)
Tylenol with Codeine #3	ANDA 85-055	Y

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 supplement, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?
- N/A YES NO
- 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: Trigesic with Codeine

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 is for single-entity codeine. All previously approved codeine products, including the listed drug, are as part of a combination with another active ingredient.

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): <None listed>

- 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

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

/s/

Matthew Sullivan
7/14/2009 01:46:56 PM
CSO

PMR/PMC Development Template

NDA 22-402

PMR/PMC Title:

Conduct an in vitro genetic toxicology study to detect point mutations with the isolated drug substance impurity codeine methyl ether, tested up to the limit dose for the assay.

PMR/PMC Schedule Milestones:

Protocol Submission: December 1, 2009

Study Completion Date: July 1, 2010

Final Report Submission: December 31, 2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., 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).

Safety qualification (minimal genetic toxicology screen and repeat dose toxicity study) of this impurity was deemed acceptable to be completed post-marketing given the purported long history of CME being present in currently marketed unapproved product and other codeine containing products and the lack of indirect evidence to suggest that the impurity represents a significant safety risk. However, since the specification requested of NMT — exceeds the ICH Q3A qualification threshold of NMT 0.15%, this impurity should be definitively qualified. Should the qualification data suggest a safety concern with this currently marketed unapproved product, the adequacy of the proposed specification should be reconsidered, by either the drug substance manufacturer or a drug product sponsor since the current level of the impurity exceeds the recommended ICH Q3A qualification threshold.

b(4)

2. If required, characterize the PMR. Check all that apply and add text where indicated. *If not a PMR, skip to 3.*

- Which regulation?

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- Describe the particular review issue leading to the PMR

The proposed drug substance specification for CME of NMT — exceeds the ICH Q3A qualification threshold of NMT 0.15%. Likewise, the drug product specifications also list codeine methyl ether as NMT — which also exceeds the ICH Q3B qualification threshold of NMT 0.2%. Other than the claim that the impurity has likely been in codein

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b(4)

containing products since they have been marketed, NDA 22-402 does not contain any justification for these specifications.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

As mentioned above, CME exceeds the ICH Q3A and Q3B qualification thresholds in the proposed specifications; however, its genotoxic potential and repeat-dose toxicity have not been evaluated.

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

- 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?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable.

4. If not required by regulation, characterize the review issue leading to this PMC

Not applicable.

5. What type of study or clinical trial is required or agreed upon (describe)?

Required:

- Pharmacoepidemiologic study (list risk to be evaluated)
- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)
- Subpopulation (list type)
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (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)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)
- Other (provide explanation)

6. Is the PMR/PMC clear and feasible? Yes.

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or 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.

NDA 22-402

PMR/PMC Title:

Conduct an in vitro genetic toxicology study to detect chromosome aberrations with the isolated drug substance impurity codeine methyl ether, tested up to the limit dose for the assay.

PMR/PMC Schedule Milestones:

Protocol Submission: December 1, 2009

Study Completion Date: July 1, 2010

Final Report Submission: December 31, 2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., 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).

Safety qualification (minimal genetic toxicology screen and repeat dose toxicity study) of this impurity was deemed acceptable to be completed post-marketing given the purported long history of CME being present in currently marketed unapproved product and other codeine containing products and the lack of indirect evidence to suggest that the impurity represents a significant safety risk. However, since the specification requested of NMT exceeds the ICH Q3A qualification threshold of NMT 0.15%, this impurity should be definitively qualified. Should the qualification data suggest a safety concern with this currently marketed unapproved product, the adequacy of the proposed specification should be reconsidered by either the drug substance manufacturer or a drug product sponsor since the current level of the impurity exceeds the recommended ICH Q3A qualification threshold.

b(4)

2. If required, characterize the PMR. Check all that apply and add text where indicated. *If not a PMR, skip to 3.*

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

The proposed drug substance specification for CME of NMT exceeds the ICH Q3A qualification threshold of NMT 0.15%. Likewise, the drug product specifications also list codeine methyl ether as NMT, which also exceeds the ICH Q3B qualification threshold of NMT 0.2%. NDA 22-402 does not contain any justification for these specifications.

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b(4)

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

As mentioned above, CME exceeds the ICH Q3A and Q3B qualification thresholds in the proposed specifications; however, its genotoxic potential and repeat-dose toxicity have not been evaluated.

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

- 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?

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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?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable.

4. If not required by regulation, characterize the review issue leading to this PMC

Not applicable.

5. What type of study or clinical trial is required or agreed upon (describe)?

Required:

- Pharmacoepidemiologic study (list risk to be evaluated)
- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
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- Drug interaction or bioavailability studies or clinical trials
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- Additional data or analysis required for a previously submitted or expected study (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)
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- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)
- Other (provide explanation)

6. Is the PMR/PMC clear and feasible? Yes.

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or 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.

NDA 22-402

PMR/PMC Title:

Conduct a 90-day repeat dose toxicology study in a single species with the isolated drug substance impurity codeine methyl ether.

PMR/PMC Schedule Milestones:

Protocol Submission: December 1, 2009

Study Completion Date: July 1, 2010

Final Report Submission: December 31, 2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., 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).

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b(4)

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- **Which regulation?**

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- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

The proposed drug substance specification for CME of NMT — exceeds the ICH Q3A qualification threshold of NMT 0.15%. Likewise, the drug product specifications also list codeine methyl ether as NMT —, which also exceeds the ICH Q3B qualification threshold of NMT 0.2%. Other than the claim that the impurity has likely been in codeine containing products since they have been marketed, NDA 22-402 does not contain any justification for these specifications.

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- 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
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3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable.

4. If not required by regulation, characterize the review issue leading to this PMC

Not applicable.

5. What type of study or clinical trial is required or agreed upon (describe)?

Required:

- Pharmacoepidemiologic study (list risk to be evaluated)
- Registry studies

- Primary safety study or clinical trial (list risk to be evaluated)
- Subpopulation (list type)
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
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- Pharmacokinetic studies or clinical trials
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- Additional data or analysis required for a previously submitted or expected study (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)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)
- Other (provide explanation)

6. Is the PMR/PMC clear and feasible? Yes.

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or 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.

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

/s/

R. Daniel Mellon
7/13/2009 04:41:04 PM
PHARMACOLOGIST

Larissa Lapteva
7/15/2009 11:57:04 AM
MEDICAL OFFICER

Sullivan, Matthew

From: elizabeth.ernst@boehringer-ingenelheim.com
Sent: Thursday, July 09, 2009 4:44 PM
To: Sullivan, Matthew
Cc: elizabeth.ernst@boehringer-ingenelheim.com
Subject: FW: Codeine Post-approval Commitments

Dear Matt,

Roxane Laboratories commits to provide the following information post-approval on or before July 1, 2012:

Dissolution

Roxane Laboratories will perform dissolution profile testing at 10, 15, 30, and 45 minutes on 10 lots of Codeine Tablets, 15 mg, 5 lots of Codeine Tablets, 30 mg, and 5 lots of Codeine Tablets, 60 mg on release and stability (time points 3, 6, 9, 12, and 18 months). This data will be compiled and statistically evaluated for submission to the FDA. All of this will occur for submission on or before July 1, 2012.

Hardness and Friability

Roxane Laboratories will provide available release and stability hardness and friability data by July 1, 2012. In the submission we will evaluate and report on any trends in results. This will include a proposal for tightening the acceptance criteria based on the evaluation of the data available.

If you have any questions please let me know.

Regards

Elizabeth Ernst
Director of Regulatory & Medical Affairs
Roxane Laboratories
614-272-4785 phone
614-276-2470 fax

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

/s/

Matthew Sullivan
7/10/2009 11:57:54 AM
CSO

From: Sullivan, Matthew
To: "elizabeth.ernst@boehringer-ingenelheim.com";
Subject: more labeling comments
Date: Thursday, July 09, 2009 11:04:00 AM

Here are (hopefully) the last ones:

Revise the drug product carton, and blister and container labels to include the following:

- Remove USP from the drug product name
- Increase the prominence of the nonproprietary name
- Increase the prominence of Rx and Class II designations

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

From: Sullivan, Matthew
To: "elizabeth.ernst@boehringer-ingenelheim.com";
Subject: RE: Response for NDA 22-402 Codeine Sulfate Tablets, 15 mg, 30 mg and 60 mg-I think we figured it out
Date: Tuesday, July 07, 2009 10:41:00 AM

Liz -

As I mentioned on the phone, we're in agreement with the CMC changes as noted below.

Additionally, here are the labeling comments from OSE:

1. ✓

b(4)

2. Increase the prominence of the product strength on the unit-dose blister labels.

I'm checking with everyone now to make sure there are no other issues outstanding.
Matt

From: elizabeth.ernst@boehringer-ingenelheim.com [mailto:elizabeth.ernst@boehringer-ingenelheim.com]
Sent: Tuesday, July 07, 2009 10:08 AM
To: Sullivan, Matthew
Cc: elizabeth.ernst@boehringer-ingenelheim.com
Subject: FW: Response for NDA 22-402 Codeine Sulfate Tablets, 15 mg, 30 mg and 60 mg-I think we figured it out

Dear Matt,

Please confirm with the chemist our understanding of what the FDA wants:

RLI and the FDA have agreed to the following dissolution specification Q of _____ in 30 minutes. In addition, RLI will agree to the following:

b(4)

A PAS will be submitted by July 1, 2012 and will include the following dissolution data:

Dissolution profile data generated at release and stability will include a minimum of 3 data points for a profile to be established RLI is suggesting 10 min, 15 min, 30 min and 45 min). A statistical evaluation of batch to batch variability will be provided.

This data will be generated in order for us to demonstrate that the product does not have dissolution variability and that the dissolution profiles are consistent across production batches”

FDA has requested to profile data on a minimum of 10 production lots for release and stability. Can the FDA confirm that they will accept data from 10 lots of the 15 mg and only 5 lots for each of the 30 mg and 60 mg tablets since these dosage forms are dose proportional).

If the FDA agrees with this approach then RLI will initiate the spec and stability protocol changes so that we can send updated versions to the FDA by the EOB.

Please advise ASAP so we can proceed.

As always feel free to call me.

Regards

Liz

-----Original Message-----

From: Ernst,Elizabeth ROX-US-C

Sent: Tuesday, July 07, 2009 6:51 AM

To: Annibaldi,Matthew ROX-US-C; Smith,Sarah ROX-US-C

Subject: FW: Response for NDA 22-402 Codeine Sulfate Tablets, 15 mg, 30 mg and 60 mg

-----Original Message-----

From: Sullivan, Matthew [mailto:Matthew.Sullivan@fda.hhs.gov]

Sent: Monday, July 06, 2009 7:15 PM

To: Ernst,Elizabeth ROX-US-C

Subject: RE: Response for NDA 22-402 Codeine Sulfate Tablets, 15 mg, 30 mg and 60 mg

OK, I think we're all on the same page – I hope.

➤ Yes, the "is acceptable" was missing in my "however" sentence - mea culpa. Please make sure that the data in PAS include dissolution profiles, as elaborated in my prior comments.

Does that help to complete the picture?

From: elizabeth.emst@boehringer-ingenelheim.com [mailto:elizabeth.emst@boehringer-ingenelheim.com]
Sent: Monday, July 06, 2009 6:05 PM
To: Sullivan, Matthew
Subject: RE: Response for NDA 22-402 Codeine Sulfate Tablets, 15 mg, 30 mg and 60 mg

sounds good! Would appreciate it. I am kind of out of the loop and a bit confused. If possible RLI would like to commit to a single profile vs a tiered one.

I would be more than happy to talk to the chemist tomorrow.

Regards

Liz

-----Original Message-----

From: Sullivan, Matthew [mailto:Matthew.Sullivan@fda.hhs.gov]
Sent: Monday, July 06, 2009 5:57 PM
To: Ernst,Elizabeth ROX-US-C
Subject: RE: Response for NDA 22-402 Codeine Sulfate Tablets, 15 mg, 30 mg and 60 mg

Hi Liz -

Sorry for the back and forth. I'm out of the office and just able to check email sporadically. I'm in the office tomorrow and we can try to get it squared away then. We really do need to get this tied up tomorrow, if possible, though.

I'll forward your thought (That the FDA will agree to the O~~-----~~ at 30minutes if we commit to providing data to them as a PAS by 7/1/2012 which contains all available dissolution data for lots manufactured and placed on stability. If that is the correct

b(4)

interpretation then yes RLI will revise the specs and stability protocol and submit to the FDA ASAP.) and see it is OK with the reviewer.

Otherwise, I really can help with the comments.. I just don't speak chemistry. We can try to do a Telecon tomorrow if needed.

Matt

From: elizabeth.ernst@boehringer-ingelheim.com [mailto:elizabeth.ernst@boehringer-ingelheim.com]
Sent: Monday, July 06, 2009 5:26 PM
To: Sullivan, Matthew
Cc: elizabeth.ernst@boehringer-ingelheim.com
Subject: RE: Response for NDA 22-402 Codeine Sulfate Tablets, 15 mg, 30 mg and 60 mg

I am sorry Matt but I am confused as well. I think what the reviewer is saying is that the FDA will agree to the Q¹ at 30 minutes if we commit to providing data to them as a PAS by 7/1/2012 which contains all available dissolution data for lots manufactured and placed on stability.

b(4)

If that is the correct interpretation then yes RLI will revise the specs and stability protocol and submit to the FDA ASAP.
Can you confirm?

Is that your understanding of the message below? I tried to call you and left you a VM to obtain clarification.

Please advise and we will begin making the changes to the documents so I can send them by tomorrow.

Regards

Liz

-----Original Message-----

From: Sullivan, Matthew [mailto:Matthew.Sullivan@fda.hhs.gov]
Sent: Monday, July 06, 2009 4:24 PM
To: Ernst, Elizabeth ROX-US-C

Cc: Posey, Corina ROX-US-C

Subject: RE: Response for NDA 22-402 Codeine Sulfate Tablets, 15 mg, 30 mg and 60 mg

Liz -

This is somewhat greek to me, but it's out comments on your excel sheet that you sent earlier this afternoon.

Matt

We have reviewed the submitted data and can see that none of the lots will fail any of the proposed specs on stage _____ tested), with the exception of "red" lot 757627A, which probably will have to have additional 12 tablets tested (stage _____, to pass Q_____ at 30 min.

b(4)

b(4)

However, the applicant's proposal of the interim acceptance criteria (Q_____ at 30 min), providing that they will submit an agreement to submit PAS, by Jul 1, 2012, which contains available dissolution data and representative dissolution profiles for release and stability testing, as outlined in my prior comment.

b(4)

Due to changes in specs, an updated dp release and stability specs have to be submitted as well.

From: elizabeth.ernst@boehringer-ingenelheim.com [mailto:elizabeth.ernst@boehringer-ingenelheim.com]

Sent: Monday, July 06, 2009 1:49 PM

To: Sullivan, Matthew

Cc: corina.posey@boehringer-ingenelheim.com; elizabeth.ernst@boehringer-ingenelheim.com

Subject: RE: Response for NDA 22-402 Codeine Sulfate Tablets, 15 mg, 30 mg and 60 mg

Matt please review the data and give me a call to discuss.

Tx

Liz

-----Original Message-----

From: Sullivan, Matthew [mailto:Matthew.Sullivan@fda.hhs.gov]

Sent: Monday, July 06, 2009 12:57 PM

To: Annibaldi, Matthew ROX-US-C

Cc: Ernst, Elizabeth ROX-US-C; Posey, Corina ROX-US-C

Subject: RE: Response for NDA 22-402 Codeine Sulfate Tablets, 15 mg, 30 mg and 60 mg

Hi Matt –

Thanks. In order to fully complete the CMC review, we really need a final response by first thing tomorrow morning. The CMC review is later this week, and any open items may affect the approvability of the application.

Thanks, and please let me know when we can expect your response.

Matt

PS I also have a couple of carton and container comments that I'll be sending along in a few minutes. They don't require a response by tomorrow, but should be addressed in the next few days.

From: Matthew.Annibaldi@boehringer-ingenelheim.com [mailto:Matthew.Annibaldi@boehringer-ingenelheim.com]

Sent: Monday, July 06, 2009 11:41 AM

To: Sullivan, Matthew

Cc: elizabeth.ernst@boehringer-ingenelheim.com; corina.posey@boehringer-ingenelheim.com

Subject: RE: Response for NDA 22-402 Codeine Sulfate Tablets, 15 mg, 30 mg and 60 mg

I am putting together a meeting with the team this afternoon and will work quickly to resolve the issues below. When I can best predict when a response will be made

(this week), I will send you the target date.

Thanks,

Matt Annibaldi
DRA-MA
Ext. 4159

-----Original Message-----

From: Sullivan, Matthew [mailto:Matthew.Sullivan@fda.hhs.gov]
Sent: Thursday, July 02, 2009 3:58 PM
To: Annibaldi, Matthew ROX-US-C
Cc: Ernst, Elizabeth ROX-US-C; Posey, Corina ROX-US-C
Subject: RE: Response for NDA 22-402 Codeine Sulfate Tablets, 15 mg, 30 mg and 60 mg

Hi Matt –

Another clarification:

The specific language about the future dissolution data is missing. We have asked about collecting dissolution profiles on release and stability and submit these with evaluation by July 1, 2012. Alternatively, the applicant may implement C_{30} at 30 min acceptance criteria, as recommended by ONDQA BioPharm expert, based on the currently available data. b(4)

The response is proposing dissolution method collecting only 2 data points, at 15 min and 45 min - this will not create a profile- as a minimum another data point has to be added at 30 min.

Also, stating that "This information can be submitted ... by Jul 1, 2012" is not satisfactory. We need data and specs evaluation that will be submitted by Jul 1, 2012.

Please see a copy of my prior comment on the subject:

Re 3b: Agreement should outline the specific data to be submitted, i. e., side-by-side dissolution profiles collected during release and

stability testing, with statistical evaluation of batch-to-batch variability of dissolution profiles, for each type of container closure. Depending on the consistency of the provided data and assuming substantially reduced dissolution variability (the profile is established and consistent for 10 production batches), Roxane Labs may seek revision of the dissolution acceptance criteria to a single time point, e. g., Q_{30} at 30 min.

b(4)

Alternative Solution: The Applicant may implement the recommended above single point Dissolution controls (C_{30} at 30 min) now and report the regular dissolution data in the annual report.

b(4)

From: Matthew.Annibaldi@boehringer-igelheim.com [mailto:Matthew.Annibaldi@boehringer-igelheim.com]
Sent: Thursday, July 02, 2009 2:23 PM
To: Sullivan, Matthew
Cc: elizabeth.ernst@boehringer-igelheim.com; corina.posey@boehringer-igelheim.com
Subject: Response for NDA 22-402 Codeine Sulfate Tablets, 15 mg, 30 mg and 60 mg

Mr. Sullivan

Attached is our response to the deficiencies noted in the E-mail received on June 26th, 2009. I have attempted to fax this deficiency to 301-796-9722 and we have received an error message. If you need a faxed copy, please let me know and verify the fax number listed and I will send ASAP. A hard copy has been sent via fed-ex today as well.

Thank you,

Matthew Annibaldi
Roxane Laboratories Inc.
Drug Regulatory Affairs and Medical Affairs
Phone: 614-241-4159

-----Original Message-----

From: Sullivan, Matthew [mailto:Matthew.Sullivan@fda.hhs.gov]

Sent: Wednesday, July 01, 2009 8:46 AM
To: Annibaldi, Matthew ROX-US-C
Cc: Ernst, Elizabeth ROX-US-C; Posey, Corina ROX-US-C
Subject: RE: Update for NDA 22-402

Hi Matt –

We've reviewed your email from yesterday, and have a couple of comments:

We would like to see the following/similar language present in the revised specs and agreements.

1. In the dp specs table, asterisks by the Hardness, Friability and Dissolution attributes, and a footnote informing that that:

*These are interim acceptance criteria due to the limited data available. The supplemental application, with supporting release and stability data, re-evaluating the interim acceptance criteria will be submitted by July 1, 2012.

2. *Re 3b:* Agreement should outline the specific data to be submitted, i.e., side-by-side dissolution profiles collected during release and stability testing, with statistical evaluation of batch-to-batch variability of dissolution profiles, for each type of container closure. Depending on the consistency of the provided data and assuming substantially reduced dissolution variability (the profile is established and consistent for 10 production batches), Roxane Labs may seek revision of the dissolution acceptance criteria to a single time point, e. g., Q ~~at~~ at 30 min. b(4)

Alternative Solution: The Applicant may implement the recommended above single point Dissolution controls (Q ~~at~~ at 30 min) now and report the regular dissolution data in the annual report. b(4)

From: Matthew.Annibaldi@boehringer-ingenelheim.com [mailto:Matthew.

Annibaldi@boehringer-ingelheim.com]

Sent: Tuesday, June 30, 2009 2:18 PM

To: Sullivan, Matthew

Cc: elizabeth.ernst@boehringer-ingelheim.com; corina.posey@boehringer-
ingelheim.com

Subject: Update for NDA 22-402

Attached is the current status of the response to your e-mail questions from June 26th.

I would like to bring you attention to a few specific questions as for the progress and comments have been updated.

Question 1: We wish to tighten the total aerobic microbial count to ~~_____~~. We will not be adding the total combined yeast and molds to the API specification as these were not on the previous specification.

b(4)

Question 2: We will specify that the bulk hold time allowable for the blend will be no more than ~~_____~~. The bulk hold time for the compressed tablets will be ~~_____~~. We commit to providing updated documentation as soon as possible.

b(4)

Question 3: The dissolution specification Roxane Laboratories' proposes is as follows:

After evaluation of the data that is available, Roxane Laboratories Proposes the following tentative specifications for all strengths using pooled samples:

- Q of ~~_____~~ in 15 minutes (the S1 testing limit is then ~~_____~~ LA)
- Q of ~~_____~~ in 45 minutes (the S1 testing limit is then ~~_____~~ LA)

b(4)

The above specifications have been selected for the following reasons:

1. Pooled sampling is statistically equivalent to individual tablets. The variability evaluation of the tablets will be captured in the content uniformity testing at release.
2. The 15 minute time point is proposed for the two step dissolution due to the fact that at 25 RPM the 10 minute time point lacks the hydrodynamics to produce a reliable quality assessment of the product. The 15 minute time point does produce a reliable quality measurement of the product.

The above proposed specifications are tentative and Roxane Laboratories commits to evaluating this specification and proposal of a final testing specification in the same supplement that will contain the final specifications

for hardness and friability which is due by July 1, 2012

b(4)

If we can obtain concurrence on the above specification, the Codeine product specification will then route and be approved tomorrow with all stability documents updated in accordance with the limits proposed.

Additional updates:

We have again contacted the API supplier both via phone and e-mail and await acceptance of the FDA agreed upon limits.

I will continue to update you on our progress and will have a majority of the responses complete by Thursday.

Thank you,

Matt Annibaldi
DRA-MA
Ext. 4159

From: Sullivan, Matthew
To: elizabeth.ernst@boehringer-ingenelheim.com;
Subject: Need Codeine "milestone" dates
Date: Thursday, July 02, 2009 5:09:00 PM

Liz - we're going to ask you to complete the following studies post-approval:

The proposed specification for the drug substance impurity codeine methyl ether (CME) of NMT exceeds the ICH Q3A (R2) qualification threshold. CME has been reported to be a known impurity of codeine; however, the sponsor has not provided adequate safety qualification for this impurity. Therefore, the Sponsor must submit adequate safety qualification data for this impurity. b(4)

Adequate safety qualification must include:

- Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
- Repeat dose toxicology of 90-days duration to support the proposed indication. b(4)

We need to get proposed "milestone" timelines for each of these (although you could combine them into one if you wanted to). Please provide the following dates:

- Final protocol submission
- Study/Trial Completion date
- Final report submission

Thanks,
Matt

Matthew W. Sullivan, M.S.

**Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov**

From: Sullivan, Matthew
To: "elizabeth.ernst@boehringer-ingenheim.com";
Subject: Codeine CMC Information Request
Date: Thursday, June 25, 2009 5:53:00 PM

Liz -

We have some additional CMC-related items that have come up during the review of the CMC amendments. We'd really like to get a response to these by early next week (say, noon Tuesday) so we can begin to wrap everything up on our side.

Please let me know if that is feasible, or if anything is going to take longer.

Matt

1. Tighten the acceptance criteria for total drug substance impurities and microbial limits to reflect the batch results. Submit revised acceptance specification sheet for the drug substance. We note that the acceptance criteria for total impurities in drug substance (excluding codeine methyl ether) are proposed as NMT _____ whereas the results for process validation batches vary from _____ to _____ refer to data submitted in amendment dated Mar 25, 2009. b(4)

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

3. Submit revised drug product Specification to include the following.

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

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

10 min: _____ Label Claim
45 min: NLT _____ Label Claim

b(4)

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

7
2

c. The Hardness and Friability data collected for the drug product stability lots (refer to Table 2 in submission dated Mar 25, 2009) demonstrate substantial variability within each lot and between different lots, i.e., Δp for 30 mg lot (757701B; 6 months 40/75), and Δp for 60 mg lot (657557A; 24 months RT). It is not clear if the observed changes are due to the variability in manufacturing or due to the changes occurring in tablets during storage, since no release data were provided. Provide an agreement to submit, by July 1, 2012, available release and stability data for Hardness and Friability of drug product with a statistical evaluation of observed variability trends. The submission should include a proposal for tightening the currently proposed interim acceptance criteria for Hardness and Friability, as warranted by the data. Include a footnote, in the revised release and stability specifications, indicating that the Hardness and Friability acceptance criteria are interim and will be re-evaluated by July 1, 2012.

b(4)

4. Submit revised drug product stability protocol, which includes the following.

a. Stability specification sheet, i.e., a table with full list of tested-on-stability attributes, corresponding analytical method numbers and stability acceptance criteria, as requested in Comment #6 of Jan 2009 letter. Include changes to the specifications as requested in this communication.

b. Revised Commitment #4 stating the current expiry period and detail mechanism for extending the expiry period. Based on the 12 months real time stability data submitted for the primary stability batches, the current expiry period can be extrapolated maximum to 18 months. It can be prolonged by submission of the complete stability data collected on the commercial product according to the revised stability protocol, as requested in this communication. In view of the recent changes to the formulation and manufacturing, changes to the analytical methods, and incomplete stability data set for several stability-indicating attributes, the extension of the drug product expiry period beyond 24 months can be achieved only via submission and approval

b(4)

of a prior-approval supplement.

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

From: Sullivan, Matthew
To: "elizabeth.ernst@boehringer-ingenelheim.com";
Subject: pharm/Tox question N 22402
Date: Monday, June 01, 2009 3:31:00 PM

Hi Liz --

Can you guys answer this?

Has codeinone been in the [currently marketed unapproved] codeine products at
— or greater prior to this NDA application?

b(4)

Thanks
matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

From: Sullivan, Matthew
To: elizabeth.ernst@boehringer-ingenelheim.com;
Subject: Codeine: Pharm Tox Information Request 3/26/09
Date: Thursday, March 26, 2009 3:56:00 PM

Liz -

From the Pharm / Tox team:

Your proposed drug substance specification for codeine methyl ether of NMT ~~exceeds~~ the ICH Q3A qualification threshold of NMT 0.15%. Likewise, your drug product specifications also list codeine methyl ether as NMT ~~exceeds~~, which also exceeds the ICH Q3B qualification threshold of NMT 0.2%. Your NDA does not contain any justification for these specifications. As noted at the time of the pre-NDA meeting, you must submit adequate justification for the safety of the proposed specifications. Adequate qualification for impurities typically includes data from the following studies:

b(4)

b(4)

- Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
- Repeat dose toxicology of 90-days duration to support the proposed ~~indication~~ indication.

b(4)

Literature references or other data, if available, may be adequate in lieu of the above studies; however, final determination of the acceptability of the justification can only be provided upon review of the submitted response.

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245

Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

From: Sullivan, Matthew
To: elizabeth.ernst@boehringer-ingenheim.com;
Subject: Age groups for codeine pediatric plan
Date: Wednesday, March 11, 2009 11:34:00 AM

Hi Liz –

Minor item regarding the pediatric plan. We'd like to have you split the youngest group at 2 years instead of _____ as shown below. b(4)

Please resubmit your peds plan with these new age groups. Also, for clarity, please explicitly state which group is "Study #1", etc, so that we have documented when we should expect your protocol and final study report.

Thanks
Matt

- Infant: 1 month to 2 years
- Children: 2 to 12 years
- Adolescent: 12 years to _____ years. b(4)

In addition to the above description of the study (ies) required under PREA, submit a timeline for the study (ies) which should include the following dates:

- **Protocol submission**
- **Study start**
- **Final study report submission**

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
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Phone 301-796-1245
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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.**

/s/

Matthew Sullivan
7/10/2009 11:48:01 AM
CSO

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

- Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, _____ Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) 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 . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO

- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO

- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 75 764

- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) January 24, 2007 NO

If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 8, 2008

NDA #: 22 402

DRUG NAMES: codeine sulfate tablets

APPLICANT: Roxane Laboratories, Inc

BACKGROUND: This is a marketed, unapproved drug. Codeine is approved, but not as (Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	C. Yancey
Secondary Medical:	E. Fields
Statistical:	D. Price
Pharmacology:	M. Delatte
Statistical Pharmacology:	D. Mellon
Chemistry:	J. Nashed
Secondary Chemistry:	A. Al Hakim
Environmental Assessment (if needed):	
Biopharmaceutical:	S. Agarwal
Secondary Biopharmaceutical:	S. Doddapaneni
DSI:	
Regulatory Project Management:	M. Sullivan
Other Consults:	

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site audit(s) needed? YES NO
If no, explain: No Clinical Studies submitted
- Advisory Committee Meeting needed? YES, date if known _____ NO
- 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? N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
BIOPHARMACEUTICS		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• Biopharm. study site audits(s) needed?	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
PHARMACOLOGY/TOX	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• GLP audit needed?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
CHEMISTRY		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• Establishment(s) ready for inspection?	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
	• Sterile product?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
	If yes, was microbiology consulted for validation of sterilization?	YES <input type="checkbox"/>	NO <input type="checkbox"/>

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

- Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
- If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
- If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
- If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
- Convey document filing issues/no filing issues to applicant by Day 74.

M. Sullivan
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

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 ODE's Office of Regulatory Policy representative.

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/s/

Matthew Sullivan
3/26/2009 01:30:57 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 22-402

Roxane Laboratories, Inc.
1809 Wilson Road
Columbus, OH 43228

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

Dear Ms. Ernst:

Please refer to your new drug application (NDA) submitted July 1, 2008, received July 2, 2008, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for codeine sulfate tablets.

On February 23, 2009, we received your February 20, 2009, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is August 2, 2009.

If you have any questions, call Matt Sullivan, Regulatory Project Manager, at 301-796-1245.

Sincerely,

{See appended electronic signature page}

Sara Stradley, M.S.
Chief, Project Management Staff
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sara Stradley
3/25/2009 10:21:32 AM

From: Al Hakim, Ali H
To: Sullivan, Matthew;
cc: Nashed, Eugenia M; Christodoulou, Danae D;
Subject: FW: CMC draft comments to the IR letter for the applicant
Date: Friday, January 30, 2009 1:37:39 PM
Attachments: IR letter comments.doc

Matt,

Please see attached CMC questions for the NDA 22-402 (Codeine Sulfate).
Jean, just minor edit for Q7. The rest looks fine.

Thanks
Ali

From: Nashed, Eugenia M
Sent: Friday, January 30, 2009 12:23 PM
To: Al Hakim, Ali H
Cc: Christodoulou, Danae D
Subject: CMC draft comments to the IR letter for the applicant

Hello Ali,

Please see my draft comments attached and let me know if you propose any changes. Matt is standing-by and hopefully we can expedite it today. I am requesting response by COB Feb 16.

Thank you ... Jean

1. Submit revised acceptance testing specification sheet for the incoming drug substance, codeine sulfate trihydrate. Provide list of all tested attributes, individual numbers for analytical methods/SOPs (to allow tracking of future changes to the methods), and data-based acceptance criteria. Specify the party responsible for testing. Include full list of individual impurities and residual solvents that may be present in the final product. Note that each impurity at, and above 0.05% need to be reported, and each impurity at, or above 0.10% need to be identified. Attach a list with chemical names and structures for all identified impurities. Upgrade the analytical method for assay to a validated HPLC method. Also, include testing for heavy metals and bioburden.
2. Provide a side-by-side comparison of the acceptance/retest testing and results from COAs for the representative batches of drug substance used in the manufacture of drug product used in biostudies and to-be-marketed drug product. A concise tabular format according to the revised specifications, as described in item #1 of this letter, is preferred for the ease of review.
3. Deficiency letters dated January 23 and 29, 2009, were issued to the holder of DMF _____ and DMF _____, respectively. Note that adequate status for each supporting DMF is required before the approval of NDA application.
4. Submit revised regulatory specifications sheet for the drug product (refer to section 3.2.P.5.1, pages 374-377 of your NDA application) to include the following.
 - a. A full list of individual impurities and residual solvents that may be present in the final product. For the impurities/solvents originating from the drug product ingredients, which do not increase during drug product manufacture or storage, the testing does not have to be performed on the drug product but need to be listed for a reference, and the acceptance criteria may be based on the acceptance testing results for drug product ingredients. Attach, to the drug product specifications, a sheet with the chemical names and structures for all identified impurities.
 - b. Analytical methods and data-based acceptance criteria for the bioburden limits and moisture content in the drug product.
 - c. Revised dissolution method and/or the acceptance criteria for the drug product tablets to increase the discriminatory power of the method. Provide dissolution profiles for the drug product tablets (all strengths) tested by different methods/conditions to demonstrate the appropriateness of the selected method and acceptance criteria. Provide, a side-by-side comparative dissolution profiles, obtained with the upgraded method, for all strengths of drug product batches used in biostudies in comparison to the to-be-marketed drug product, and primary and supportive stability batches.

b(4)

- d. We recommend including testing for hardness and friability of drug product tablets during the release and stability testing, since the commercial manufacturing process is not validated yet for all strengths of the drug product. In addition, there are no controls implemented for the particle size distribution in the drug product ingredients or in the bulk blend. For the release specifications, the in-process data can be referenced.
5. Provide a table summarizing CMC differences for drug product tablets used in biobatches, to-be-marketed drug product, primary stability, and supportive stability batches, in respect to the following:
 - Source/impurity profile of drug product ingredients
 - Composition of drug product
 - Manufacturing process and in-process controls/testing
 - Specifications/analytical methods

Include the batch numbers and describe any changes briefly in the table. Also, provide references to the supportive data submitted along with the response to this comment, or submitted previously to the NDA.

6. Submit revised stability protocol for the drug product to include stability specifications sheet upgraded accordingly to requests in comment #4, of this letter. Include all stability-indicating attributes to control the strength, quality and purity of the tablets, with emphasis on impurity profile and dissolution.
7. Provide updated stability data for drug product batches representative of the commercial drug product (e.g., registration batches), and collected according to the revised stability protocol, as requested above. Submit data in a tabular format organized by the container closure system (blisters *versus* HDPE bottles) and storage conditions, for each stability-indicating attribute. Provide graphical representation for all pivotal stability attributes to facilitate the evaluation of any instability trends. We withhold comments on the expiry period until acceptable stability data for batches representative of commercial product, and collected according to the revised protocol are submitted and evaluated. However, note that the currently proposed expiry period of _____ is not supported by the submitted real time stability data.
8. The appearance of different strengths of the drug product tablets is confusingly similar. We recommend diversifying the appearance with changes to color, shape or embossing with the strength for all tablets.

b(4)

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/s/

Matthew Sullivan
1/30/2009 03:20:13 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-402

FILING COMMUNICATION

Roxane Laboratories Inc
1809 Wilson Rd
Columbus, OH 43228

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

Dear Ms Ernst:

Please refer to your new drug application (NDA) dated July 1, 2008, received July 2, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for codeine sulfate tablets, 15, 30, and 60 mg.

We also refer to your submission(s) dated July 23, and 30, and August 11, and 18, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is May 2, 2009.

We request that you submit the following information:

Additional real-time stability data on historical batches to support the proposed expiration dating.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond to the above request for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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/s/

Bob Rappaport
9/12/2008 05:22:03 PM

REQUEST FOR CONSULTATION

TO (Division/Office):
HFD-170, DAARP, PharmTox Review Team
Attn: Dan Mellon and Marcus Delatte

FROM:
Eugenia Nashed, Chemistry Reviewer, ONDQA,
HFD-820

DATE Sep 11, 2008	IND NO.	NDA NO. 22-402	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT 7/02/08
NAME OF DRUG Codeine Sulfate Tablets, 15 mg, 30 mg & 60 mg	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE Nov 14, 2008

NAME OF FIRM: Roxane Laboratories, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RICK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS:

Please evaluate the adequacy of Genetic Toxicity studies provided in DMF _____ for _____
 _____ DMF Holder _____ to support the safety of the proposed acceptance criteria for impurities.
 Refer to attached copies of drug substance and drug product specifications, and DMF amendment dated Jan 30, 2008, pp. 3-136.

b(4)

SIGNATURE OF REQUESTER Eugenia Nashed	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Ali Al-Hakim

9/11/2008 03:14:05 PM

DSI Consult: Request for Biopharmaceutical Inspections

DATE: August 15, 2008

TO: Dr. CT Viswanathan, Associate Director, Bioequivalence Branch
Division of Scientific Investigations, HFD-48
Office of Compliance/CDER

THROUGH: Sheetal Agarwal, PhD/ Clinical Pharmacology Reviewer /DCP 2/HFD-870
Lei Zhang, PhD/ Clinical Pharmacology Reviewer/DCP 2/HFD-870
Suresh Doddapaneni, PhD/ Clinical Pharmacology Team Leader/
DCP 2/HFD-870

FROM: Matthew Sullivan, Regulatory Health Project Manager/DAARP/HFD-170

SUBJECT: Request for Bioequivalence Study Site Inspections
NDA-22-402
Codeine Sulfate Tablets USP 15, 30, 60 mg

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

<i>CODE-T30- PVFS-1</i>	<p><u>STUDY SITE:</u> Cedra Clinical Research, LLC PI: Jolene K. Berg 2455 N.E. Loop 410 Suite 150 San Antonio, TX 78217 Phone: 210-635-1500 Fax: 210-635-1646</p>	<p><u>ANALYTICAL SITE:</u> ____ Assoc Gro Leader: _____ _____ Manager, Bioanalysis: _____ _____ _____ Phone: _____</p>
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b(4)

b(4)

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **February 1, 2009**. We intend to issue an action letter on this application by **April 17, 2009**. The PDUFA date is **May 2, 2009**.

Should you require any additional information, please contact Matthew Sullivan at **301-796-1245** or Dr. Sheetal Agarwal at **301-796-3861**.

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/s/

Matthew Sullivan
8/15/2008 12:27:47 PM

Suresh Doddapaneni
8/15/2008 12:29:43 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-402

NDA ACKNOWLEDGMENT

Roxane Laboratories, Inc.
1809 Wilson Road
Columbus, OH 43228

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

Dear Ms. Ernst:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Codeine Sulfate Tablets USP, 15 mg, 30 mg and 60 mg

Date of Application: July 1, 2008

Date of Receipt: July 2, 2008

Our Reference Number: NDA 22-402

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 31, 2008, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Matthew Sullivan
7/17/2008 11:08:58 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Office/Division): HFD-009 (Controlled Substances Staff) Corine Moody (WO 51, #5144)		FROM (Name, Office/Division, and Phone Number of Requestor): HFD-170, DAARP, Margarita Tossa on behalf of Matthew Sullivan (301) 796-4053		
DATE 7/10/08	IND NO.	NDA NO. 22-402	TYPE OF DOCUMENT New original NDA submission	DATE OF DOCUMENT 7/2/08
NAME OF DRUG Codeine Sulfate, Tablets, USP, 15 mg, 30 mg & 60 mg	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 10/10/2008 PDUFA goal date: 5/2/2009	
NAME OF FIRM: Roxane Laboratories, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END-OF-PHASE 2a MEETING <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY / EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
<input type="checkbox"/> PRIORITY P NDA REVIEW <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):				
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE 4 STUDIES <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST				
IV. DRUG SAFETY				
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS				
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL <input type="checkbox"/> NONCLINICAL				
COMMENTS / SPECIAL INSTRUCTIONS: Application: The new original NDA for Codeine Sulfate, Tablets, as a relief of mild to moderately severe pain. Division requests that you please review this NDA and provide your assessment. A desk copy will be forwarded next week. EDR location: \\FDSWA150\NONECTD\N22402\N_000\2008-07-01 The NDA filing meeting is scheduled for 8/8/2008 at 3:00 pm in room 3270.				
SIGNATURE OF REQUESTOR Margarita Tossa		METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER		PRINTED NAME AND SIGNATURE OF DELIVERER		

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/s/

Margarita Tossa
7/10/2008 01:49:12 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Office/Division): CDER/OSE/RMS Darrell Jenkins (WO 22, #4483)		FROM (Name, Office/Division, and Phone Number of Requestor): HFD-170, DAARP, Margarita Tossa on behalf of Matthew Sullivan (301) 796-4053		
DATE 7/10/08	IND NO.	NDA NO. 22-402	TYPE OF DOCUMENT New original NDA submission	DATE OF DOCUMENT 7/2/08
NAME OF DRUG Codeine Sulfate, Tablets, USP, 15 mg, 30 mg & 60 mg	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 10/10/2008 PDUFA goal date: 5/2/2009
NAME OF FIRM: Roxane Laboratories, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END-OF-PHASE 2a MEETING <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY / EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
<input type="checkbox"/> PRIORITY P NDA REVIEW <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):				
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE 4 STUDIES <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST				
IV. DRUG SAFETY				
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS				
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL <input type="checkbox"/> NONCLINICAL				
COMMENTS / SPECIAL INSTRUCTIONS: Application: The new original NDA for Codeine Sulfate, Tablets, as a relief of mild to moderately severe pain. Division requests that you please review this NDA and provide your assessment. A desk copy will be forwarded next week. EDR location: \\FDSWA150\NONECTDN22402\N_000\2008-07-01 The NDA filing meeting is scheduled for 8/8/2008 at 3:00 pm in room 3270.				
SIGNATURE OF REQUESTOR Margarita Tossa		METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER		PRINTED NAME AND SIGNATURE OF DELIVERER		

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/s/

Margarita Tossa
7/10/2008 01:45:46 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 75,764

Roxane Laboratories, Inc.
1900 Arlingate Lane
Columbus OH, 43228

Attention: Elizabeth A. Ernst
Associate Director, Regulatory Affairs

Dear Ms Ernst:

Please refer to your Pre-Investigational New Drug Application (PIND) file for codeine sulfate tablets.

We also refer to the meeting between representatives of your firm and the FDA on January 24, 2007, to discuss a possible 505(b)(2) application for codeine sulfate tablets.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Industry Meeting Minutes

MEETING DATE: January 24, 2007

TIME: 3:00 to 4:00 pm

LOCATION: FDA White Oak Campus
 Silver Spring, MD

APPLICATION: PIND 75,764

STATUS OF APPLICATION: Pre-IND file

PRODUCT: Codeine sulfate tablets

INDICATION: Relief of mild to moderate pain

SPONSOR: Roxane Laboratories, Inc

TYPE OF MEETING: Type B, Pre-IND

MEETING CHAIR: Mwango Kashoki, M.D., MPH, Division of Anesthesia,
 Analgesia and Rheumatology Products (DAARP)

MEETING RECORDER: Matthew Sullivan, M.S., Regulatory Project Manager,
 DAARP

FDA Attendees	Title
Bob Rappaport, M.D.	Director, DAARP
Sharon Hertz, M.D.	Deputy Director, DAARP
Ali Al Hakim, Ph.D.	Pharmaceutical Assessment Lead, ONDQA
Dan Mellon, Ph.D.	Supervisor, Pharmacology/Toxicology, DAARP
BeLinda Hayes, Ph.D.	Pharmacology/Toxicology Reviewer, DAARP
David Lee, Ph.D.	Clinical Pharmacology Reviewer, OCP
Mwango Kashoki, M.D., MPH	Medical Team Leader, DAARP
Yasmin Choudhry, M.D.	Medical Officer, DAARP
Dionne Price, Ph.D.	Team Leader (acting), Statistics, DAARP
Matthew Sullivan, M.S.	Regulatory Project Manager, DAARP
Shanna Oldewurtel	Pharmacy Student
Sally Loewke, M.D.	Medical Officer, Office of New Drugs, Immediate Office
Janice Weiner, J.D., M.P.H.	Regulatory Counsel, Office of Regulatory Policy
Roxane Laboratories Attendees	Title
Elizabeth Ernst	Associate Director, Regulatory Affairs

Marilynn Davis	Regulatory Manager
Gregory Hicks, Pharm.D.	Clinical Research Manager
Mukul Agrawal, Ph.D.	Clinical Research Manager
	Consultant
	Consultant
	Consultant
	Consultant

b(4)

Meeting Objective(s): To discuss questions related to a possible 505(b)(2) application for codeine sulfate tablets.

Opening Discussion: Following introductions, the discussion focused on Roxane Laboratories' questions that were included in the December 15, 2006, meeting package. The questions are presented in italicized text and Division responses are in bold. Discussion is presented in normal text. The Division's responses were sent to the sponsor on January 22, 2007.

Question 1. Is it agreeable that _____

b(4)

FDA RESPONSE:

b(4)

1 Page(s) Withheld

 ✓ Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

b(4)

Post-Meeting Note:

b(4)

_____ we recommend that the sponsor consider relying on published literature for nonclinical pharmacology and toxicology information to support the safety of their proposed codeine sulfate product.

Question 2. Does the Agency agree with Roxane's proposal to update the clinical data summary and labeling sections, based on a review of the literature, since the

b(4)

FDA RESPONSE:

See above response to Question 1.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 3. Does the Agency agree that Roxane will update pediatric information _____

b(4)

FDA RESPONSE:

_____ requirements of PREA. To address these requirements you must provide single- and multiple-dose pharmacokinetic trials in children, as well as sufficient data on safety and analgesic efficacy. The data must reflect pediatric patients of all ages, and doses and formulations appropriate for pediatric patients.

b(4)

You may request a deferral of pediatric studies at the time of your marketing application, but you will need to support why a deferral is appropriate.

b(4)

Discussion:

The Sponsor requested _____

b(4)

_____ However, the Sponsor could request deferral of pediatric studies until after approval of the product in adults. The Sponsor could also submit a Proposed Pediatric Study Request, which could provide six months of exclusivity.

The Division further commented that PREA requires development of a dosage form appropriate for administration to pediatric patients. The Sponsor replied that Roxane used to market a codeine syrup, but discontinued this formulation due to _____

b(4)

The Division noted that single-entity products, such as the proposed codeine product, may have increased utility in the marketplace with the recent public discussion regarding the safety of combination products with acetaminophen.

Question 4. Does the Agency agree with Roxane's proposal to update the Nonclinical Pharmacology and Toxicology Summary and labeling sections with a review of available literature since _____ (2004)?

b(4)

FDA RESPONSE:

Yes. However, final review of the labeling will occur at the time of NDA submission. The Division requests that your NDA submission include copies of all English-language referenced literature citations.

ADDITIONAL COMMENTS:

- 1) Opioid drug products derived from thebaine (phenanthrene-derivatives) may contain impurities containing an α , β -unsaturated ketone moiety, which is a structural alert for mutagenicity. Therefore, the specification for these impurities in the drug substance should be reduced to a TDI of NMT _____ or adequate safety qualification should be provided. Consult with you _____ to decrease the limit of these impurities. b(4)
- 2) Adequate safety qualification for any potential genotoxic impurities should be provided with the NDA submission and should include:
 - a) Minimal genetic toxicology screen (two in vitro genetic toxicology studies (point mutation assay and chromosomal aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
 - b) Repeat dose toxicology of appropriate duration to support the proposed indication.
 - c) Should this qualification produce positive or equivocal results, the impurity specification should be set at NMT _____ or otherwise justified. Justification may require an assessment for carcinogenic potential either in a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.
 - d) NOTE: Guidance to Industry regarding setting acceptable specifications for potential genotoxic impurities is in development in CDER OND. The specifications above represent our current thinking on this topic at this time.
- 3) Adequate safety qualification should be provided for any new excipients. Please refer to Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005) which is available on the CDER web page at the following <http://www.fda.gov/cder/guidance/guidance.htm>.

Discussion:

The Sponsor asked whether submission of non-clinical literature would be necessary _____ The Sponsor stated that they had intended to perform a literature search from 1980 to the present, and inquired as to which literature references they should submit. The Division replied that all literature that is found to be relevant should be submitted. _____ b(4)

See Post-Meeting Note to Discussion of Question 1]

The Division reminded the Sponsor that the DMF referenced must be for the _____ as Roxane's product, and requested that the Sponsor confirm this and ensure that the referenced DMF is an active one. The Sponsor stated that they would do so. b(4)

The Sponsor stated that their API will be supplied by _____. The Division responded that they should include a letter of authorization to the DMF with their IND/NDA submission. The DMF will then be reviewed with _____ b(4)

Question 5. Does the Agency agree that the Human Pharmacokinetics and Bioavailability Summary will be based on the descriptive pharmacokinetic study conducted by Roxane, and that Roxane will develop a descriptive pharmacokinetic section of the labeling based on results of this study?

FDA RESPONSE:

From a biopharmaceutics perspective, the following information is needed:

1. Dose linearity information using 1x15 mg vs. 1x30 mg vs. 1x60 mg
2. Food effect from 60-mg strength tablet
3. Multiple dose from 15-mg strength tablet Q4h
4. Relative BA information using the listed drug(s) for which you are relying upon the Agency's finding of safety and/or effectiveness in support of your 505(b)(2) application.

Discussion:

The Sponsor concurred with the studies listed, and committed to perform them.

Question 6. Roxane proposes to reference information obtained from Roxane's history with the Codeine Sulfate 15 mg, 30 mg, and 60 mg Tablets. Is this acceptable for the Safety Update Report section of the NDA?

FDA RESPONSE:

The Integrated Summary of Safety can be composed of the information from Roxane's history with codeine sulfate tablets, the package inserts of the listed drug(s) upon which you are relying, and your literature review.

The Safety Update report can be restricted to Roxane's adverse event history with the codeine sulfate tablets.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 7. Does the Agency agree with Roxane's proposal as stated above for the Chemistry, Manufacturing, and Controls Summary?

FDA RESPONSE:

The proposed summary and related index (module 3) for the chemistry, manufacturing and controls is acceptable. However, the CMC test data and related information should include, but not be limited to, the following topics:

1. **Dosing of the drug product, which appears in the product labeling, should be based on its therapeutically active moiety. Therefore, in the proposed clinical studies, ensure that the drug dosing regimens are based on the free-form of the investigational drug rather than on its salt form.**
2. **Drug master file (DMF) or letter of authorization from the _____ (if applicable).**
3. **The CMC information for the drug substance and the drug product, e.g. manufacturing, composition/components, analytical methods, process controls and validation, impurity profile (reporting, identification, and qualification) stability, packaging, etc. should be submitted as per FDA and ICH guidelines. The stability study should be conducted as per ICH guideline ICH-Q1A including room temperature, intermediate and accelerated conditions.**
4. **Provide adequate amount of satisfactory and real time stability test data to cover the proposed expiry dating (at least 12 months of room temperature and 6 months of accelerated study conditions).**
5. **Submit a well documented pharmaceutical development report as per ICH-Q8 and highlight how critical quality attributes and critical process parameters are identified and controlled.**
6. **Ensure that all facilities are ready for inspection by the day the application is submitted, and include a statement confirming this in the NDA cover letter.**
7. **At the beginning of the CMC section, include a table of all facilities, include specifically what each facility does, the contact name and address, the CFN number, and the complete name and address of the facility.**

b(4)

Discussion:

The Sponsor sought agreement that, at the time of NDA submission, they could submit historical room-temperature stability data for one lot of each dosage strength, and 3 months of accelerated stability data. Additional 3 months of accelerated stability data would be submitted during the NDA review. The Division agreed to this proposal, as long as the Sponsor also provides adequate bridging data between the historical and to-be-marketed lots. The Sponsor concurred. The bridging data should be for both room temperature and accelerated conditions.

General Discussion:

The Sponsor was encouraged to request a Pre-NDA meeting with the Division prior to submission of the application for codeine sulfate tablets. The Division added that submission of the background meeting package of the published literature that the sponsor proposes to rely upon in support of its 505(b)(2) application would permit a preliminary evaluation of whether or not the literature is adequate. The Pre-NDA meeting would be scheduled with consideration for the time needed to review the package.

The Sponsor agreed that this plan was reasonable.

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this page is the manifestation of the electronic signature.**

/s/

Matthew Sullivan
2/9/2007 02:15:47 PM