CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202245Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202245 SUPPL # HFD #

Trade Name

Generic Name codeine sulfate oral solution

Applicant Name Roxane

Approval Date, If Known 7/27/11

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?

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# 85-055 acetaminophen/codeine phosphate

NDA#	22402	Codeine sulfate tablets
NDA#	20232	Fioricet with codeine (phosphate) There are many approved Codeine containing products in addition to these

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:

(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:

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:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ☐ ! NO ☐

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

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Kathleen Davies
Title: Senior Regulatory Health Project Manager
Date: June 14, 2011

Name of Office/Division Director signing form: Sharon Hertz, MD
Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

KATHLEEN M DAVIES
06/30/2011

SHARON H HERTZ
06/30/2011

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 202245 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Established/Proper Name: codeine oral solution Dosage Form: 30mg/5mL		Applicant: Roxane Agent for Applicant (if applicable):
RPM: Kathleen Davies		Division: DAAAP

NDAs:
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(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 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

NDA 85-055/acetaminophen codeine phosphate tablets

Provide a brief explanation of how this product is different from the listed drug.

different dosage form

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check:

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.

❖ Actions	
• Proposed action • User Fee Goal Date is July 27, 2011	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain ____	☐ Received

[1] 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.

❖ Application Characteristics [2]

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☒ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments: MedGuide will not be a REMS as per the MedGuid Guidance issued 2/25/2011.

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation 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	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: 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.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (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.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (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.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (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.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs 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.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• 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.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• 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) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [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).	☒ No paragraph III certification Date patent will expire
• [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*)).*	☒ N/A (no paragraph IV certification) ☐ 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).*

(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? (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). *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*).* *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.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s)
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	x
• Example of class labeling, if applicable	

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

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	x
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEPA 5/12/11 ☒ DRISK 5/27/11 ☒ DDMAC 6/13/11, 6/10/11 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	 ☐ Not a (b)(2) 6/6/11 ☐ Not a (b)(2) 6/6/11
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 5/11/11 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ 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 *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	included

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 6/30/11
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None combined with DDSR
PMR/PMC Development Templates *(indicate total number)*	☐ None 5
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	N/A
• Clinical review(s) *(indicate date for each review)*	6/9/11
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	see clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ Not applicable 6/8/11, 5/27/11
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 6/2/11
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None 6/20/11
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 6/9/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 6/17/11
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 6/10/11, 5/28/11
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 5/4/11
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: 1/24/11 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☒ Not yet requested ☐ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix 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.

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/s/

KATHLEEN M DAVIES
06/30/2011

From: Davies, Kathleen
To: "elizabeth.ernst@boehringer-ingelheim.com";
Subject: NDA 202245/codeine - additional carton/container edits
Date: Friday, June 17, 2011 10:36:00 AM

Hi Liz,

Please refer to pending NDA 202245 for codeine oral solution. We did another QC of the carton/container submitted on 5/26/11 and noted some errors. Please revise as requested below. If you could get this back to us in the next few days (early next week), that would be greatly appreciated.

If you have any questions, let me know.

Thanks,
Kathleen

- *Remove the* (b) (4) *from the drug product name, throughout the labeling.*
- *Increase the prominence of drug product strength designation 30 mg/5 mL, e.g., change color from* (b) (4) *to brown.*
- *Increase the prominence (size, color) of R_x and Schedule II designations.*
- *Include a statement informing about the 40 days in-use expiry period for the drug product, e.g., Use or dispose within 40 days from the initial opening of the bottle.*
- *Correct the storage requirements to: Store at controlled room temperature: 20ºC to 25ºC (68ºF to 77ºF). Protect from light and moisture.*
- *Include, on the carton, information on the drug product composition.*
- *Include, on the carton, information on correct measuring of drug product volume to the black of o-ring with the included oral syringe. Refer to patient's instructions for details.*

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
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/s/

KATHLEEN M DAVIES
06/30/2011

From: Davies, Kathleen
To: "elizabeth.ernst@boehringer-ingelheim.com";
Subject: NDA 202245/codeine - please revise 356h and patent cert
Date: Monday, June 06, 2011 4:11:00 PM

Hi Liz,

Please refer to your pending NDA 202245 for codiene solution. We are reviewing your administrative materials and note that the 356h lists this NDA as a 505(b)(2), referencing NDA 22402, another 505(b)(2). For this NDA, you must rely on the listed drug relied upon in the original 505(b)(2) application, NDA 22402. Please resubmit your 356h and patent certification, correcting the RLD.

If you have any questions, please let me know.

Kathleen Davies, MS

Senior Regulatory Health Project Manager
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/s/

KATHLEEN M DAVIES
06/13/2011

From:	Davies, Kathleen
To:	"elizabeth.ernst@boehringer-ingelheim.com";
Subject:	NDA 202245/clinical IR
Date:	Thursday, June 02, 2011 2:26:00 PM

Hi Liz,

Please see question below from the clinical team for codeine.

In Module 5: Clinical Study Reports, Section 5.3.5.3, Reports of Analyses of Data from More Than One Study (including any Formal Integrated Analyses, MetaAnalysis, and Bridging Analysis), you note the following:

In addition, Roxane Laboratories, Inc. has performed a comprehensive search of published literature from 2009 to present to determine if there were any reported adverse events or relevant safety information that needed to be added to the most recent version of the RLD approved labeling for Codeine Sulfate Tablets ([Rev. 7/09]).

Adverse Events

There were no new adverse events or other safety information identified in the literature from 2009 to present.

Provide the published literature from 2009 to present which you referenced (or explain where in the submission this information is located) and provide your Postmarketing Safety data for the Codeine Sulfate Tablet since approval.

Kathleen Davies, MS

Senior Regulatory Health Project Manager
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/s/

KATHLEEN M DAVIES
06/13/2011

From: Davies, Kathleen
To: "elizabeth.ernst@boehringer-ingelheim.com";
Subject: NDA 202245/codeine - CMC commitment
Date: Wednesday, June 01, 2011 2:55:00 PM
Attachments: N202245 Phase 4 comm.doc

Hi Liz,

Please refer to your pending NDA 202245 for codeine solution. The CMC team has reviewed all of your information submitted and has a proposed [redacted] (b) (4) [redacted] (b) (4) Please review and let me know if you find it acceptable.

Kind Regards,

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
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/s/

KATHLEEN M DAVIES
06/10/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Wednesday, May 25, 2011 2:56 PM
To: 'elizabeth.ernst@boehringer-ingelheim.com'
Cc: Davies, Kathleen
Subject: RE: NDA 202-245 Information request-5-25-2011

Dear Ms. Ernst,

We are reviewing CMC aspect of your application and request additional information to complete the review. Provide a complete response to the following comments by **COB Friday, May 27, 2011**. Due to the review time constrains we may not be able to review any data incoming after 12 pm on May 31, 2011.

1. **Submit revised stability data to include a detailed description of the changes in drug product color (description). Include quantitative measurement results for color if available. Also, provide results of stability testing in the intermediate storage conditions if available.**

2. **We note variations in color and pH occurring during the storage of the drug product. Also, an appare increase in the API Assay occurring during storage at the labeled storage conditions for all three registration batches can not be attributed to the variation in the analytical method – refer to Figures # #4, #6, #8, #10 and #12, submitted in the stability report (Amendment dated Apr. 27, 2011). Explain chemical changes responsible for the above observations and evaluate the safety of the changes occurring in the drug product on stability. Propose and implement corrective actions to minimize or eliminate the observed changes.**

3. **The pH study report (refer to report BIRI TR 1674-008A01, submitted in amendment dated April 27, 201 does not support the proposed acceptance criteria for (b) (4) The report indicates "out-of-trend" resu for the pH as early as after six months of storage at (b) (4) (b) (4) the acceptance criteria for pH based on the available stability data (b) (4) an submit a justification confirming the proposed acceptance criteria.**

4. **Provide a commitment to develop and submit by a specified date, a validated quantitative method (e.g APHA) and data-based acceptance criteria for monitoring the color of the drug product. You may submit the method and supporting data in a post approval supplement**.

Please acknowledge the receipt.

Thank you

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
05/25/2011

From: Davies, Kathleen
To: "elizabeth.ernst@boehringer-ingelheim.com";
Date: Monday, May 02, 2011 2:43:00 PM

Hi Liz,

Please refer to your pending NDA 202245 for codeine oral solution. We reviewed your responses received on April 27 to our information request. For item 3, the request for in-use stability data needed to support the labeled in-use expiry, as previously requested November 27, 2010, we note that you will not have data submitted until June 10, 2011. Based on the GRMP timeline, primary reviews are due June 10. In order to complete the primary review on time, it will be necessary to have this data by close of business on Monday, May 16.

If you have any questions, please let me know.

Kind Regards,

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
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Center for Drug Evaluation and Research
(301) 796-2205 Office
(301) 796-9713 Fax

From: Davies, Kathleen
To: "elizabeth.ernst@boehringer-ingelheim.com";
Subject: RE:
Date: Tuesday, May 10, 2011 3:17:00 PM

Hi Liz,

Yes, I received the response to the NDA.

I have an additional question regarding your NDA. In your administrative section, you have provided a paragraph II certification, stating in your certification that there are no relevant patents. In filing the certification, Paragraph II refers to patents that are expired. Are there patents that are expired that are no longer impacting your application, or are there no relevant patents? Please clarify. If it is the latter, please re-certify your application by stating there are no relevant patents are per 21 CFR 314.50(i)(1)(ii).

Kathleen

From: elizabeth.ernst@boehringer-ingelheim.com [mailto:elizabeth.ernst@boehringer-ingelheim.com]
Sent: Monday, May 09, 2011 4:51 PM
To: Davies, Kathleen
Subject: RE:

Did you get our response?

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Monday, May 02, 2011 2:43 PM
To: Ernst,Elizabeth ROX-US-C
Subject:

Hi Liz,

Please refer to your pending NDA 202245 for codeine oral solution. We reviewed your responses received on April 27 to our information request. For item 3, the

request for in-use stability data needed to support the labeled in-use expiry, as previously requested November 27, 2010, we note that you will not have data submitted until June 10, 2011. Based on the GRMP timeline, primary reviews are due June 10. In order to complete the primary review on time, it will be necessary to have this data by close of business on Monday, May 16.

If you have any questions, please let me know.

Kind Regards,

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
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(301) 796-9713 Fax

From: Davies, Kathleen
To: "elizabeth.ernst@boehringer-ingelheim.com";
Subject: NDA 202245/codeine - medication guide and REMS
Date: Tuesday, May 17, 2011 1:31:00 PM

Hi Liz,

I just wanted to give you a heads up that, even though we issued a REMS notification letter for this product, a guidance was published February 2011 stating that not all medication guides required a REMS. The Division has determined that this application falls into that category. While a medication guide is still necessary for safe use of this product, it will not be evaluated under a REMS and will only be a part of labeling. You do not need to take any action at this time to withdraw the REMS; we will make note of it in your action letter.

If you have any questions, let me know.

Kind Regards,

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
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(301) 796-2205 Office
(301) 796-9713 Fax

From:	Davies, Kathleen
To:	"elizabeth.ernst@boehringer-ingelheim.com";
Subject:	NDA 202245/codeine - labeling comments
Date:	Thursday, May 19, 2011 1:10:00 PM

Hi Liz,

Please refer to your pending NDA 202245 for codeine. The Division of Medical Error Prevention and Analysis (DMEPA) have reviewed portions of the labeling section of your submission, and have identified the following deficiencies:

A. Product Design

1. Provide dimensional information for amber plastic bottles commonly used to repackage oral liquids during dispensing (b) (4) (b) (4) *to demonstrate the provided oral syringe will fit. Specifically, the mouth of the bottle must be greater than 14 mm.*

2. Provide enough oral syringes in the carton of Codeine Sulfate Oral Solution, USP so that each patient dispensed a portion of the bottle receives an oral syringe.

B. Container Label

1. The trade dress is too similar to your currently marketed products. Present the established name in a font color other than brown that adequately distinguishes Codeine Sulfate Oral Solution from the other opioid oral solutions you currently market in 500 mL.

*2. Use a larger font to display the center four digit drug portion of the NDC. (e.g., 0054-**0294**-63).*

3. Revise the presentation of the strength so that it appears different from your other opioid oral solutions you currently market in 500 mL.

4. Revise the presentation of the established name to appear on one line to improve readability.

C. Carton Labeling

See Comments B1 through B3.

D. Patient Instructions for Use

Add a scale to the left of the pictogram of the syringe that includes the unit of measure (mL) with each whole number (i.e., 1 mL, 2 mL, 3 mL... etc) as marked on the syringe to clearly state what units the syringe measures.

If you have any questions, please let me know.

Kind Regards,

Kathleen Davies, MS

Senior Regulatory Health Project Manager
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/s/

KATHLEEN M DAVIES
06/13/2011

Davies, Kathleen

From: Davies, Kathleen
Sent: Monday, April 18, 2011 10:29 AM
To: 'elizabeth.ernst@boehringer-ingelheim.com'
Subject: RE: NDA 202-245 Codeine OS - Request for concurrence by the CMC reviewer on one of the questions

Hi Liz,

Please find the CMC reviewer's response below. Let me know if you require additional clarification.

Kathleen

The acceptance criteria for degradants and impurities are established for the purpose of a) safety, and b) consistency of the manufacturing. The request to (b) (4) *the specification is based on our review of your existing data for this product, which indicates reasonably stable impurity profile, with Each, and with Total impurities NMT* (b) (4)*. The specification is driven by your ability to produce a consistent quality product based upon data submitted with your application, not based upon a specification for another existing approved product.*

If you believe that the data suggest that the proposed specification can not be (b) (4)*, you should provide clear justification for this position in your response. Also, submit supporting analysis of the updated stability data.*

From: elizabeth.ernst@boehringer-ingelheim.com [mailto:elizabeth.ernst@boehringer-ingelheim.com]
Sent: Thursday, April 14, 2011 8:08 AM
To: Davies, Kathleen
Cc: elizabeth.ernst@boehringer-ingelheim.com
Subject: NDA 202-245 Codeine OS - Request for concurrence by the CMC reviewer on one of the questions

Dear Kathy,

RLI has been actively working on the CMC deficiency that we received for our NDA. ☺ There is one point of contention that we have regarding the CMC reviewers request. For question 2c the FDA would like that we (b) (4) the proposed acceptance criteria for individual and total impurities to reflect the release and stability data.

The challenge and confusion that we are struggling with is that RLI currently has an approved NDA for the codeine tablet with limits that are wider for the (b) (4) and (b) (4) then what is being asked for the oral solution. Therefore we would like to obtain concurrence with the FDA that the limits for the OS could be identical to what is currently approved for our codeine tablets. Below is a table for your convenience.

(b) (4)

In order to (b) (4) our release spec for the OS product it would mean that the spec for the API and the drug product are the same. For now our API supplier is not willing to (b) (4) their limit so in order to provide RLI some room for variability it only makes sense that the limits for the tablet and OS be the same.

In addition, the ICH limit for these products would be (b) (4) based on the TDD. Is there a particular issue and/or concern that the CMC reviewer has with our OS product and thus is requesting (b) (4) limits?

If you could please discuss our request with the CMC reviewer and if he/she would like to discuss further I would suggest that we have a teleconference. Hopefully the FDA will agree that our limits for both drug products (oral solution and tablets) can be the same.

Please advise.

Regards

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

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/s/

KATHLEEN M DAVIES
04/26/2011

From:	Davies, Kathleen
To:	"elizabeth.ernst@boehringer-ingelheim.com";
Subject:	NDA 202245/CMC IR
Date:	Thursday, April 07, 2011 4:36:00 PM
Attachments:	CMC IR Apr 7.pdf

Hi Liz,

Please refer to your pending NDA 202245 for codeine. The CMC team has an additional information request (attached). If you have any questions, please let me know.

Kind Regards,
Kathleen

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/s/

KATHLEEN M DAVIES
04/07/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Tuesday, March 15, 2011 12:28 PM
To: 'elizabeth.ernst@boehringer-ingelheim.com'
Subject: RE: NDA 202-245 Information request

Dear Ms. Ernst,

Your amendment dated 10 March 2011 is inadequate to demonstrate that your product is free of the objectionable microorganism *Burkholderia cepacia*. While *B. cepacia* used to be classified as a *Pseudomonad,* it is not a member of this genus and as such the USP<62> test for the absence of *Pseudomonas* is not adequate. We refer you to *Envir. Microbiol*. 13(1):1-12, 2011 for more information on the *B. cepacia* complex of organisms. If your internal work instruction 046-(b) (4) S2005 Isolation, Characterization, and Identification of Microorganisms contains a validated screen specific for *B. cepacia,* provide this work instruction and the method validation studies. USP<62> does not describe validated studies which demonstrate the absence of this objectionable organism.

Your risk assessment is inadequate to determine the likelihood of *B. cepacia* contamination of your final drug product. Your reliance on the preservative system and the capacity of a test for *Pseudomonas* to provide assurance of absence of this objectionable organism is insufficient. *B. cepacia* complex are highly adaptable organisms which are capable of growth in preserved drug products and water used in industrial applications. Additionally, organisms isolated in pharmaceutical plants have been shown to be more resistant to preservatives than strains grown under traditional laboratory conditions. We refer you to *J. Appl. Microbiol.* 1997 Sep;83(3):322-6 for more information. Please identify potential sources for introduction of *B. cepacia* during the manufacturing process and describe the steps to minimize the risk of *B. cepacia* complex organisms in the final drug product.

As there are currently no compendial methods for detection of *B. cepacia* complex we have provided a suggestion for a potential validation scheme. However, any validated method capable of detecting *B. cepacia* complex organisms would be adequate. At this point in time it would be sufficient to precondition representative strain(s) of *B. cepacia* in water and/or your drug product without (b) (4) and demonstrate that the proposed method in USP<62> is capable of detecting small numbers of this microorganism. Your validation studies should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning (minimum 48 hours) of the organisms occurs during these method validation studies.

Please acknowledge the receipt, and prove tentative timeline for your response.

Reference ID: 2918481

Thank you

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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SWATI A PATWARDHAN
03/15/2011

From: Davies, Kathleen
To: "elizabeth.ernst@boehringer-ingelheim.com";
Subject: NDA 202245/codeine - request for information
Date: Tuesday, March 08, 2011 4:04:00 PM

Hi Liz,

Please refer to your pending NDA 202245 for codeine. The review team has the follow request for information (below). Let me know if you have any questions.

Kind Regards,

Kathleen

You have referenced DMF (b) (4) *for data pertaining to the the composition and safety of the Orange Flavor, XBF-709818 in your drug product formulation. However, this DMF is no longer active and therefore, the information can not be accessed. You must submit the quantitative chemical composition and CAS numbers for the components of the Orange Flavor and include references to appropriate food additive regulations or other data to support the safety of this novel excipient. Refer to the following guidance document for further information on the safety qualification of novel excipients: 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm****.*

From: Davies, Kathleen
To: "elizabeth.ernst@boehringer-ingelheim.com";
Subject: NDA 202245/codeine - follow up cmc question
Date: Friday, February 04, 2011 4:21:00 PM

Hi Liz,

The Division has an additional follow up comment regarding NDA 202245 (see below). If you have any questions, please let me know.

Kathleen

Include a calibrated dosing device for administering the drug product to the patient, e.g., calibrated oral syringe. Also, include a measuring device for the Pharmacy dispensing as applicable. Provide revised Container Closure section of the NDA application and update labeling and other sections as needed. In addition, provide the following.

a. Submit complete CMC information on the container closure change, including letters of authorization (LOA) as applicable, to support the new dosing syringe, as soon as possible.

b. Submit a justification of the selected dosing device and provide brief data (e.g., assay/volume of the measured dose) demonstrating adequate accuracy of the dose to be administered to patient with the proposed dosing device in comparison to the dosing device used during the comparative bioavailability studies.

c. Submit a sample of the new packaging configuration for the drug product, i.e., carton, empty bottle and dosing device.

From: elizabeth.ernst@boehringer-ingelheim.com [mailto:elizabeth.ernst@boehringer-ingelheim.com]
Sent: Wednesday, February 02, 2011 4:22 PM
To: Davies, Kathleen

Cc: elizabeth.ernst@boehringer-ingelheim.com
Subject: RE: NDA 202245/codeine - follow up on stability question

Dear Kathleen,

I just received confirmation that the 9 month samples were pulled and are in testing. I am trying to get a date from the team as to when we will have a final report to send you.

On another note has the FDA reviewed our request that was outlined in our 75 day response? Below is a summary of the question and our proposal.

Request for Information #4

Propose an in-use period (shelf-life) for your drug product, and provide in-use stability data to support the in-use period.

Response #4

We have not yet conducted in-use stability studies to support an in-use shelf life. We are however, submitting a DRAFT stability protocol ST-PRO-1674-10-04, Stability Protocol for Codeine Sulfate Oral Suspension,30mg/5mL, (batch 40000XXA), which simulates the use of the product in practice and which will support a proposed in-use shelf life. We commit to providing the results of this study and the proposed in-use shelf life prior to final approval.

We want to implement this study but was hoping for some feedback from the reviewer. If she/he is ok with our protocol we will initiate. Any feedback is helpful.

Regards

Liz

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Wednesday, February 02, 2011 3:08 PM
To: Ernst,Elizabeth ROX-US-C
Subject: NDA 202245/codeine - follow up on stability question

HI Elizabeth,

Please refer to your NDA 202245 for codeine and to my request for a status update on the stability data (in-use) and to whether we will be receiving more stability data since the NDA was submitted with 6-months stability.

This information, if you would like it considered for this NDA, must be submitted in the next few weeks, no later than the end of February. Otherwise, we cannot guarantee it will be reviewed for this review cycle. Please provide me an update on the status of these items.

Kind Regards,

Kathleen

From: Davies, Kathleen
To: "elizabeth.ernst@boehringer-ingelheim.com";
Subject: NDA 202245/codeine - follow up on stability question
Date: Wednesday, February 02, 2011 3:08:00 PM

HI Elizabeth,

Please refer to your NDA 202245 for codeine and to my request for a status update on the stability data (in-use) and to whether we will be receiving more stability data since the NDA was submitted with 6-months stability.

This information, if you would like it considered for this NDA, must be submitted in the next few weeks, no later than the end of February. Otherwise, we cannot guarantee it will be reviewed for this review cycle. Please provide me an update on the status of these items.

Kind Regards,

Kathleen

From:	Davies, Kathleen
To:	"elizabeth.ernst@boehringer-ingelheim.com";
Subject:	NDA 202245/codeine - stability data
Date:	Tuesday, January 25, 2011 3:09:00 PM

Hi Elizabeth,

We note in your NDA that there is 6-months accelerated stability data. Are you planning to submit additional stability data for this NDA?

Kind Regards,

Kathleen

From:	Davies, Kathleen
To:	"elizabeth.ernst@boehringer-ingelheim.com";
Subject:	NDA 202245/codeine -
Date:	Thursday, December 16, 2010 2:54:00 PM

Hi Elizabeth,

I received your message requesting clarification on the in-use stability comment in the 74-day letter. I spoke to the chemistry review and was provided the following comment:

The in-use period could be defined from the time when the patient/facility start using the drug to the time when it is finished or disposed. Frequent opening of the container closure and dosing the drug can lead to additional decomposition of the drug product, and normally it is not covered by the regular ICH storage conditions. The in-use stability data storage conditions should mimic the conditions of the drug product use, i.e., frequent bottle opening and repeated dosing of the drug product. Based on the submitted data the label will have a statement (b) (4)

If you have additional questions, please let me know.

Kind Regards,

Kathleen Davies, MS
Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301) 796 2205 *Office*
(301) 796 9713 *Fax*

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/s/

KATHLEEN M DAVIES
04/08/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Wednesday, March 02, 2011 3:01 PM
To: 'elizabeth.ernst@boehringer-ingelheim.com'
Subject: RE: NDA 202-245

Hello Ms. Ernst,
We are reviewing the microbiology section of your NDA 202-245 for Codeine Sulfate Oral Solution and have additional information request to evaluate your application

1. **Provide a justification for the total yeast and mold limit of (b) (4) We refer you to USP<1111> which recommends a limit of 10 CFU/mL for oral solutions.**
2. **Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganism *Burkholderia cepacia*. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.**

Please acknowledge the receipt, and prove tentative timeline for your response.

Thank you

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
03/02/2011

From:	Davies, Kathleen
To:	"elizabeth.ernst@boehringer-ingelheim.com";
Subject:	NDA 202245/codeine - pediatric plan
Date:	Tuesday, March 01, 2011 4:02:00 PM

Hi Liz,

Please refer to your pending NDA 202245 for codeine solution. We have the following comment regarding your PREA request:

We acknowledge your submission of the pediatric plan and timeline for codeine sulfate oral solution. This plan will be reviewed by the Pediatric Research Committee, and they now require a protocol synopsis for each planned study. Please submit protocol synopses to the NDA for each planned study by April 1, 2011.

If you have any questions, let me know.

Kathleen

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/s/

KATHLEEN M DAVIES
04/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **OPS, New Drug Microbiology** **David Hussong, Ph.D., Director**			FROM: **Eugenia Nashed, CMC Reviewer, ONDQA** **Swati Patwardhan, PM, ONDQA**	
DATE Feb 1, 2011	IND NO.	NDA NO. **202245** (New NDA)	TYPE OF DOCUMENT	DATE OF DOCUMENT Sep 27, 2010
NAME OF DRUG **Codeine Sulfate Oral Solution, 30 mg/mL** (500 mL multi-dose PET bottle)		PRIORITY CONSIDERATION **Standard**	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE **Mar 3, 2011 (Mid-cycle meeting)**
NAME OF FIRM: **Roxane Laboratories**				

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ PRE--NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT
☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☐ OTHER *(SPECIFY BELOW)*: **New NDA**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOAVAILABILTY STUDIES
☐ PHASE IV STUDIES
☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please evaluate proposed microbiological controls and preservative effectiveness studies.
This is a new NDA submitted electronically to HFD-170. Kathleen Davis is the PM.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

EUGENIA M NASHED
02/01/2011

PRASAD PERI
02/02/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Mail: OSE	

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 7, 2011		202245	MG only REMS	January 6, 2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Codeine sulfate oral solution	standard		June 1, 2011

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

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- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
DAAP has a pending NDA 202245 and a REMS notification letter was sent requiring a medication guide only REMS. Sponsor submitted the medication guide and REMS assessment to the NDA on January 6, 2011. DAAP requests that OSE review the REMS and provide comments on the medication guide for labeling negotiations with the sponsor.

PDUFA date: July 27, 2011
PM: Kathleen Davies
MO: Ellen Fields
Link to submission:
EDR Location: \\CDSESUB1\EVSPROD\NDA202245\202245.enx

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Kathleen Davies, RPM	☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

KATHLEEN M DAVIES
01/07/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO: **CDER-DDMAC-RPM**	FROM: (Name/Title, Office/Division/Phone number of requestor) Kathleen Davies, RPM OND/DAAP/6-2205

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
January 4, 2011		202245	PI

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Codeine sulfate oral solution	Standard		May 20, 2011

NAME OF FIRM:	
Roxane	PDUFA Date: July 27, 2011

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☐ CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☒ ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☒ INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission:
\\CDSESUB1\EVSPROD\NDA202245\202245.enx

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: March 3, 2011

Labeling Meetings: June 14 and 28, 2011

Wrap-Up Meeting: June 2, 2011

SIGNATURE OF REQUESTER
Kathleen Davies

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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/s/

KATHLEEN M DAVIES
01/04/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 202245 **PRE-APPROVAL REMS NOTIFICATION**

Roxane Laboratories
1809 Wilson Road
Columbus, Ohio 43228

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

Dear Ms. Ernst:

Please refer to your September 27, 2010 New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Codeine Sulfate Oral Solution 30mg/5mL.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Codeine Sulfate Oral Solution to ensure that the benefits of the drug outweigh the risk of medication errors, which may result in life-threatening overdoses.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide, as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Codeine Sulfate Oral Solution poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Codeine Sulfate Oral Solution. FDA has determined that Codeine Sulfate Oral Solution is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Codeine Sulfate Oral Solution.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Codeine Sulfate Oral Solution.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information pertinent to Codeine Sulfate Oral Solution (see Appendix A). Once FDA finds the content of the REMS acceptable and determines that the application can be approved, we will include this document and the Medication Guide as attachments to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Before we can continue our evaluation of this NDA, you will need to submit the proposed REMS.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend that you use one of the following two statements depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- "Dispense the enclosed Medication Guide to each patient." or
- "Dispense the accompanying Medication Guide to each patient."

For administrative purposes, designate the proposed REMS submission as "**PROPOSED REMS for NDA 202245**" and all subsequent submissions related to the proposed REMS as "**PROPOSED REMS-AMENDMENT for NDA 202245**."

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, call Kathleen Davies, Senior Regulatory Project Manager, at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Deputy Director
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SHARON H HERTZ
12/06/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202245

FILING COMMUNICATION

Roxane Laboratories
1809 Wilson Road
Columbus, Ohio 43228

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

Dear Ms. Ernst:

Please refer to your New Drug Application (NDA) dated and received September 27, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Codeine Sulfate Oral Solution 30mg/5mL.

We also refer to your submission dated October 21, 2010.

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 July 27, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 27, 2011.

During our filing review of your application, we identified the following potential review issues:

1. Your drug product stability specification for (b) (4) of not more than (NMT) (b) (4) exceeds the safety qualification threshold of NMT 0.2%. Although there are adequate genetic toxicology data available to support the safety of this specification, you have not submitted adequate justification regarding the general toxicity of this impurity. To address this issue, you may (b) (4) the specification to NMT (b) (4), or, in order support

your proposed specification, either conduct a repeat-dose toxicology study of at least 90 days duration, or provide a scientific justification based on quantitative data.

2. You have not provided adequate safety justification for the novel excipient, Orange Flavor, XBF-709818. You must provide the quantitative formulation, including CAS numbers, for all components of the flavor and provide justification for the safety of up to 174 mg/day of this flavoring agent in your drug product. We refer you to the following guidance document: 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. Provide a DMF reference for the Orange Flavor.

2. Provide photostability data as per ICH Q1B.

3. Provide an extractables/leachables evaluation of the container/closure system with the oral solution with adequate justification of any findings. Alternatively, provide data describing compliance of the components to indirect food additive regulations to support compatibility of the container/closure with the aqueous oral solution.

4. Propose an in-use period (shelf-life) for your drug product, and provide in-use stability data to support the in-use period.

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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests 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.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Kathleen Davies, Senior Regulatory Project Manager, at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BOB A RAPPAPORT
11/26/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Controlled Substance Staff, HFD007

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Kathleen Davies, Division of Anesthesia and Analgesia Products, HFD170

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 16, 2010		202245	Original Submission	September 27, 2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Codeine	Standard		May 1, 2011

NAME OF FIRM: Roxane

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☒ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

DAAP received an NDA for codeine sulfate. There are no specific questions for CSS; however, because Codeine is scheduled, the Division wanted to notify CSS of the submission. If CSS has any questions or comment, please contact either the PM or Team Leader for this NDA.

PDUFA date: July 27, 2011
PM: Kathleen Davies, 62205
TL: Ellen Fields, 61209
EDR Location: \\CDSESUB1\EVSPROD\NDA202245\202245.enx

SIGNATURE OF REQUESTOR
Kathleen Davies

METHOD OF DELIVERY (Check one)
☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

KATHLEEN M DAVIES
11/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Mail: OSE	Kathleen Davies, Division of Anesthesia and Analgesia Products, HFD170

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 16, 2010		202245	Original Submission	September 27, 2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Codeine	Standard		June 1, 2011

NAME OF FIRM: Roxane

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
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- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

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☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

DAAP received an NDA for codeine oral solution. This NDA references the previously approved codeine tablet (NDA 22-402), approved 7/16/2009. The Sponsor is using the approved package insert as a basis for this NDA's label. There is no proprietary name for this NDA.

DAAP requests that OSE review the PI and carton/container labeling and provide comments for labeling negotiations with the sponsor.

EDR Location: \\CDSESUB1\EVSPROD\NDA202245\202245.enx

PDUFA: July 27, 2011
TL: Ellen Fields
PM: Kathleen Davies

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Kathleen Davies	X EMAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

KATHLEEN M DAVIES
11/22/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202245 **NDA ACKNOWLEDGMENT**

Roxane Laboratories
1809 Wilson Road
Columbus, Ohio 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 (FDCA) for the following:

Name of Drug Product: Codeine Sulfate Oral Solution 30mg/5mL

Date of Application: September 27, 2010

Date of Receipt: September 27, 2010

Our Reference Number: NDA 202245

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 November 26, 2010 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(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. 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 should 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 and Analgesia 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/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm

If you have any questions, call me at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

Kathleen Davies, M.S.
Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

KATHLEEN M DAVIES
10/05/2010