DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022402 **NDA APPROVAL**

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 acknowledge receipt of your submissions dated July 23 and 30, August 11 and 18, September 29, October 20, and December 4, 2008, and January 29, February 20, March 2, 12, and 25, April 22, and July 2, 8 and 10, 2009.

This new drug application provides for the use of codeine sulfate tablets for the relief of mild to moderately severe pain when the use of an opioid analgesic is appropriate.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical to the enclosed labeling text for the package insert. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 022402**."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).*

Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022402**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the products with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROPRIETARY NAME

If you choose to use a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

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 are waiving the pediatric study requirement for ages birth to one month because there is evidence strongly suggesting that codeine would be ineffective and unsafe in this pediatric group because the metabolic pathways to metabolize codeine are not mature before one month of age.

We are deferring submission of your pediatric studies for ages one month to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1. Deferred efficacy, safety and pharmacokinetic (single and multiple dose) study under PREA for codeine sulfate in pediatric patients with mild to moderately severe pain in pediatric patients 12 - 17 years old.

Final Protocol Submission Date:	November 1, 2009
Study Completion Date:	April 1, 2010
Final Report Submission Date:	October 1, 2011

2. Deferred efficacy, safety and pharmacokinetic (single and multiple dose) study under PREA for codeine sulfate in pediatric patients with mild to moderately severe pain in pediatric patients 2 - 12 years old.

Final Protocol Submission Date	January 1, 2010
Study Completion Date:	June 1, 2010
Final Report Submission Date:	December 1, 2011

3. Deferred efficacy, safety and pharmacokinetic (single and multiple dose) study under PREA for codeine sulfate in pediatric patients with mild to moderately severe pain in pediatric patients 1 month - 2 years old.

Final Protocol Submission Date:	May 1, 2010
Study Completion Date:	October 1, 2010
Final Report Submission Date:	April 1, 2012

Submit the clinical protocols to your IND, with a cross-reference letter to this NDA. Submit final study reports to this NDA. Use the following designator to prominently label all submissions: "**Required Pediatric Assessments**".

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of genotoxicity or histopathological changes associated with exposure to the drug substance impurity codeine methyl ether at the proposed levels.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

4. 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.

   The timetable you submitted via email on July 7, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission Date:	December 1, 2009
Study Completion Date:	July 1, 2010
Final Report Submission:	December 31, 2010

5. 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.

   The timetable you submitted via email on July 7, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission Date:	December 1, 2009
Study Completion Date:	July 1, 2010
Final Report Submission:	December 31, 2010

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

   The timetable you submitted via email on July 7, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission Date:	December 1, 2009
Study Completion Date:	July 1, 2010
Final Report Submission:	December 31, 2010

Submit the protocols and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and i 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS OF SECTION 506B OF THE FD&C ACT

We remind you of your postmarketing study commitment agreed to in your email dated July 9, 2009. This commitment is listed below.

7. Submit a prior approval supplement with the final, data-reflecting regulatory specifications for dissolution, hardness and friability. The supplement will include data as outlined below.

    a. 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.

    b. 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.

    Study Completion: by June 1, 2012
    Final Report Submission: by July 1, 2012

Submit chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**", "**Postmarketing Commitment Final Report**", or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

EXPIRATION DATING PERIOD

The currently approved expiry period for the drug product is 18 months, starting from the first use of drug substance in the drug product manufacturing process. The drug product expiry period may be extended to 24 months based on acceptable stability data collected according to the approved stability protocol, in accord with 21 CFR 314.70. We remind you of your July 8, 2009, agreement that any extension of drug product expiry period beyond 24 months may be accomplished only via a prior approval supplement with adequate supporting data.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Sincerely,

{See appended electronic signature page}

Sharon Hertz, M.D.
Deputy Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures
Package Insert
Carton and Container Labeling

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

/s/

Sharon Hertz
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