

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203856Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 203856

SUPPL #

HFD # 150

Trade Name None

Generic Name Cyclophosphamide Capsules, 25 mg and 50 mg

Applicant Name Roxane Laboratories, Inc.

Approval Date, If Known

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.

Roxane requested waiver to do the BA/BE studies; Roxane Laboratories owns ANDA 40032 (the generic cyclophosphamide tablets). On November 2007, Baxter (NDA 12141) removes Cytosan tablets from marketing not for safety reasons. The ANDA 40032 became the RLD in the Orange Book.

Biopharm Review (March 4, 2013) granted the BA/BE waiver. The waiver was granted under the following: **“REGULATORY APPLICATIONS OF THE BCS A. INDs/NDAs**
Evidence demonstrating in vivo BA or information to permit FDA to waive this evidence must be included in NDAs (21 CFR 320.21(a)). A specific objective is to establish in vivo performance of the dosage form used in the clinical studies that provided primary evidence of efficacy and safety. The sponsor may wish to determine the relative BA of an IR solid oral dosage form by comparison with an oral solution, suspension,

or intravenous injection (21 CFR 320.25 (d)(2) and 320.25 (d)(3)). The BA of the clinical trial dosage form should be optimized during the IND period.

Once the in vivo BA of a formulation is established during the IND period, waivers of subsequent in vivo BE studies, following major changes in components, composition, and/or method of manufacture (e.g., similar to SUPAC-IR Level 3 changes⁶) may be possible using the BCS. BCS-based biowaivers are applicable to the to-be-marketed formulation when changes in components, composition, and/or method of manufacture occur to the clinical trial formulation, as long as the dosage forms have rapid and similar in vitro dissolution profiles (see sections II and III). This approach is useful only when the drug substance is highly soluble and highly permeable (BCS Class 1), and the formulations pre- and postchange are pharmaceutical equivalents (under the definition at 21 CFR 320.1 (c)). BCS-based biowaivers are intended only for BE studies. They do not apply to food effect BA studies or other pharmacokinetic studies.

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#	012141	cyclophosphamide tablets (Discontinued)
NDA#	012142	cyclophosphamide for injection, USP (Discontinued)
ANDA#	040032	Cyclophosphamide Tablets, USP, 25 mg and 50 mg (Reference Listed Drug)

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 7:

(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.

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:
Frank Cross, Jr.
Senior Regulatory Health Project Manager
Date: September 10, 2013

Name of Office/Division Director signing form:
Amna Ibrahim, M.D.
Deputy Director
Division of Oncology Products 1
Office of Hematology and Oncology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

FRANK H CROSS
09/16/2013

AMNA IBRAHIM
09/16/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 203856 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: not applicable Established/Proper Name: cyclophosphamide Dosage Form: Capsule, 25 mg and 50 mg		Applicant: Roxane Laboratories Agent for Applicant (if applicable):
RPM: Frank Cross Jr.		Division: DOP1
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>NDA 012141 cyclophosphamide tablets.</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>NDA 203856 is a capsule.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of Last Check: Last checked on 9/16/13</p> <p><u>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.</u></p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>September 17, 2013</u> 	<input checked="" type="checkbox"/> AP September 16, 2013 <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	<input type="checkbox"/> None Complete Response(May 3, 2013); Refuse to File (February 17, 2012)	

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.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ 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 _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 5</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<p> <input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other </p>

³ 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	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified (No relevant patents per August 16, 2012, submission) <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) (Paragraph II certification - no unexpired patents per July 3, 2012 submission) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

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

Answer the following questions for **each** paragraph IV certification:

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	Yes
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Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Actions and date: Approval (September 16, 2013); Complete Response(May 3, 2013); Refuse to File(February 17,2012)
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Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	September 5, 2013
<ul style="list-style-type: none"> Original applicant-proposed labeling 	July 29, 2013; July 3, 2012; December 21, 2011
<ul style="list-style-type: none"> Example of class labeling, if applicable 	N/A

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. • Original applicant-proposed labeling • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	August 30, 2013
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	None – no proprietary name
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM September 9, 2012; August 21, 2013 (2) <input checked="" type="checkbox"/> DMEPA April 2, 2013; August 14, 2013; September 5, 2013 <input type="checkbox"/> DMPP/PLT (DRISK) <input type="checkbox"/> ODPD (DDMAC) <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> February 17, 2012; September 13, 2012 <input checked="" type="checkbox"/> April 23, 2013; August 19, 2013 <input checked="" type="checkbox"/> August 23, 2013
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC April 3, 2013 • “It was determined cyclophosphamide is a DESI drug and is not subject to PREA.” • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	Not applicable
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	Yes
❖ Internal memoranda, telecons, etc.	No
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	February 1, 2012 – CMC Tcon May 31, 2012, Post RTF Meeting - Reviewer Comments (May 31, 2012 meeting cancelled); December 4, 2012 - CMC Tcon March 21, 2013 - CMC Tcon June 18, 2013, Post CR Meeting
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None May 3, 2013
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None April 30, 2013; September 6, 2013
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	Cosigned-September 16, 2013
• Clinical review(s) (<i>indicate date for each review</i>)	September 16, 2013
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	No clinical studies

⁶ Filing reviews should be filed with the discipline reviews.

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Cosigned February 8, 2012
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None February 8, 2012; August 28, 2012; March 4, 2013; August 26, 2013
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> Cosigned February 3, 2012; April 26, 2013; August 23, 2013;
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None February 3, 2012; April 26, 2013; August 23, 2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
<ul style="list-style-type: none"> • ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i> 		<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i> 		<input type="checkbox"/> None <u>Branch Chief:</u> April 30, 2013; September 6, 2013; Cosigned reviews: February 17, 2012; August 28, 2012; April 2, 2013; April 30, 2013; September 4, 2013 <u>Team Leader:</u> February 17, 2012; August 28, 2012
<ul style="list-style-type: none"> • Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i> 		<input type="checkbox"/> <u>None</u> <u>CMC:</u> April 2, 2013; April 30, 2013; September 4, 2013 <u>Biopharmaceutics</u> February 9, 2012; August 28, 2012; March 14, 2013; August 20, 2013
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		(per April 2, 2013, CMC review page 69)
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(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 sites⁷)</i>		Date completed: July 25, 2013, per page 26 of CMC review dated September 4, 2013 EER printout included printed September 11, 2013 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per April 2, 2013, review page 67)

⁷ 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.

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

/s/

FRANK H CROSS
09/23/2013

From: jean-yves.maziere@boehringer-ingelheim.com
Sent: Friday, August 30, 2013 10:56 AM
To: Cross Jr, Frank H
Cc: marissa.craddock@boehringer-ingelheim.com; GregoryGreg.Hicks@boehringer-ingelheim.com; megan.stojic@boehringer-ingelheim.com; jean-yves.maziere@boehringer-ingelheim.com
Subject: RE: 8/28/13 FDA Information Request: NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg - 8/26/13 Revised PI and Container labeling

Hello,

Thank you for reaching out to us yesterday about our proposed labeling.

In wanted to follow up on the necessity to advise patients/caregivers to wear gloves in sections 2.3 and 17 of our proposed labeling.

After more research about OSHA and other occupational health guidelines, it is pretty clear to me that the recommendation to wear gloves for personnel have to appear in 2.3. As stated now, it does not specifically target personnel but it includes a general statement that can be interpreted as applicable to patients and caregivers too. It could be potentially retargeted toward personnel only with minor text modifications.

The need for patients to wear gloves does not exist in my opinion. There is only a need to advise against contact with broken capsules (section 17).

Then finally for the caregivers, the situation is of course the most difficult to arbitrate on. It seems reasonable to advise them to wear glove as a principle of precaution, but:

- A capsule is theoretically considered safe to handle compared to tablets, unless there are significant outside surface contaminants.
- In practice, wearing gloves to transfer from a bottle to the patient is burdensome for the caregiver and theoretically implies further disposal of the gloves as potential biohazard material, which is a problem in a home setting.
- A review of several labels for other oral cytotoxic drugs (e.g., topotecan, methotrexate, mercaptopurine, chlorambucil, thalidomide) does not show any mention of advice targeted to caregivers.

Of course, it does not preclude the insertion of such a warning in any way in section 17.

Please do not hesitate contacting us if any additional question arises.

Best regards,

Jean-Yves Maziere, M.D., M.S.
Analyst, Risk Evaluation and Mitigation Strategies (REMS) and Labeling
Roxane Laboratories, Inc.
1900 Arlingate Lane

Columbus, OH 43228

Office: (614) 241-4103 Mobile: (b) (6)

jean-yves.maziere@boehringer-ingenelheim.com

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/s/

FRANK H CROSS
09/05/2013

Cross Jr, Frank H

From: Cross Jr, Frank H
Sent: Tuesday, August 27, 2013 9:06 AM
To: 'marissa.craddock@boehringer-ingelheim.com'
Subject: 8/28/13 FDA Information Request: NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg - 8/26/13 Revised PI and Container labeling

Importance: High

Follow Up Flag: Follow up
Due By: Wednesday, August 28, 2013 4:00 PM
Flag Status: Flagged

Good Morning, Ms. Craddock,

Please indicate the audience you are targeting with the warning statement "Wear gloves when handling container and capsules."

Is this and other similar warnings in the insert labeling aimed at preventing healthcare provider and caregiver exposure to cyclophosphamide? If so, then these warnings do not apply to patients taking cyclophosphamide capsules?

Please respond by COB, Wednesday, 8/28/13

Sincerely,

Frank

Frank H. Cross, Jr., MA, MT (ASCP)
Senior Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration

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(301) 796-9845 (fax)
(301) 796-2330 (Division Main #)
frank.crossjr@fda.hhs.gov

From: Cross Jr, Frank H
Sent: Monday, August 26, 2013 3:24 PM

To: 'marissa.craddock@boehringer-ingelheim.com'

Subject: RE: FDA Information Request for NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg - Insert Labeling and Container Label

Hi Ms. Craddock,

We did receive the submission through the Gateway.

Will be in touch.

Thank you,

Frank

From: marissa.craddock@boehringer-ingelheim.com [<mailto:marissa.craddock@boehringer-ingelheim.com>]

Sent: Monday, August 26, 2013 3:13 PM

To: Cross Jr, Frank H

Subject: RE: FDA Information Request for NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg - Insert Labeling and Container Label

Hello Mr. Cross,

I just wanted to circle back with you and let you know that our response to the below request was submitted through the Gateway this afternoon. Please let me know if you have any problems receiving it.

Thanks so much,
Marissa

From: Cross Jr, Frank H [<mailto:Frank.CrossJr@fda.hhs.gov>]

Sent: Friday, August 23, 2013 3:18 PM

To: Craddock, Marissa ROX-US-C

Subject: RE: FDA Information Request for NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg - Insert Labeling and Container Label

Good Afternoon, Ms. Craddock,

Thank you for your e-mail. We look forward to receiving your submission.

Please also submit the documents in tracked changes.

Have a good weekend.

Frank

From: marissa.craddock@boehringer-ingelheim.com [<mailto:marissa.craddock@boehringer-ingelheim.com>]

Sent: Friday, August 23, 2013 3:15 PM

To: Cross Jr, Frank H

Subject: RE: FDA Information Request for NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg - Insert Labeling and Container Label

Good Afternoon Mr. Cross,

I have received your email with the changes requested to the PI and container labels. We commit to submitting these changes through the Gateway before COB on Tuesday, August 27th. I will email you when they have been submitted.

Thanks so much and have a nice weekend.

Marissa

From: Cross Jr, Frank H [<mailto:Frank.CrossJr@fda.hhs.gov>]

Sent: Friday, August 23, 2013 3:10 PM

To: 'marissa.craddock@boehringer-ingelheim.com'

Subject: FDA Information Request for NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg - Insert Labeling and Container Label

Good Afternoon, Ms. Craddock,

We reviewed your August 19, 2013 submission and your August 22, 2013 email. Please revise the Insert Labeling and Container Label accordingly.

A. Insert Labeling

Section 16 - How Supplied/Storage and Handling

1. Revise the storage statement to be consistent with USP:

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (between 59°F and 86°F).

B. Container Labels, 25 mg and 50 mg

1. Revise the storage statement on the left side panel to read as follows:

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (between 59°F and 86°F).

2. Bold the statement that appears on the left side panel, "Swallow capsules whole. Do not open, chew, or crush capsules."

Please review and respond by COB, Tuesday, 8/27/13 – official and e-mail submission.

Sincerely,
Frank Cross, Jr.

Frank H. Cross, Jr., MA, MT (ASCP)
Senior Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Office of New Drugs

Center for Drug Evaluation and Research
US Food and Drug Administration

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frank.crossjr@fda.hhs.gov

From: Cross Jr, Frank H
Sent: Friday, August 23, 2013 10:58 AM
To: 'marissa.craddock@boehringer-ingenelheim.com'
Subject: FDA Review of Roxane Labs 8/21/13 email - Storage statement for PI and 8/19/13 Carton/Container - NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg

Good Morning, Ms. Craddock,

The team is still reviewing these items.

Hoping to get back to you today.

Sincerely,

Frank

From: marissa.craddock@boehringer-ingenelheim.com
[<mailto:marissa.craddock@boehringer-ingenelheim.com>]
Sent: Friday, August 23, 2013 10:20 AM
To: Cross Jr, Frank H
Subject: RE: Roxane response to 8/21/13 FDA labeling (PI and PPI) -NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg

Good Morning Mr. Cross,

Has the team had a chance to decide on the removal of "between" from the last part of the storage statement? We'd like to get this submission to you as soon as possible.

Kindest Regards,
Marissa

From: Cross Jr, Frank H [<mailto:Frank.CrossJr@fda.hhs.gov>]
Sent: Thursday, August 22, 2013 1:33 PM
To: Craddock, Marissa ROX-US-C
Subject: Roxane response to 8/21/13 FDA labeling (PI and PPI) -NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg

Good Afternoon, Ms. Craddock,

Thank you for your e-mail and response.

I have forwarded your response to the team.

Will be in touch with you later today or tomorrow.

Sincerely,

Frank

From: marissa.craddock@boehringer-ingelheim.com
[<mailto:marissa.craddock@boehringer-ingelheim.com>]

Sent: Thursday, August 22, 2013 9:13 AM

To: Cross Jr, Frank H

Subject: RE: 8/21/13 FDA Labeling IR - FDA revised labeling (PI and PPI) -NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg

Good Morning Mr. Cross,

We received your voicemail and email regarding our NDA 203856 and comments to the PI. The PI that was included in the 8/19 official submission was the same as the PI emailed to Lisa last Friday, but also included the storage statement change that was requested by Lisa via email on the morning of 8/19.

We are amenable to all of the changes you are requesting in the email we received last evening. However, one concern is the addition of "between" in the second part of the storage statement. This is not consistent with the verbiage that was provided on Monday morning (that was also used in the revision of our container labels), or in other statements that we have seen to date. We would prefer to leave the statement as it was submitted on 8/19 with the verbiage we received from Lisa on Monday morning.

I will be making the changes to the PI and, once I hear from you regarding the storage statement, I will finalize the PI and submit the Word versions of the Baxter copy with all of the comments that have been made and a cleaned up copy. Please let me know if you require any additional versions at this time (SPL, pdf).

I look forward to hearing from you!

Kindest Regards,
Marissa

Marissa L. Craddock | Manager, Labeling and OPDP Communications | Roxane
Laboratories, Inc.

T: (614) 241-4177 | F: (614) 276-2470 | Marissa.Craddock@boehringer-ingelheim.com

From: Hicks, Greg ROX-US-C
Sent: Wednesday, August 21, 2013 5:03 PM
To: Hoane, Krysty ROX-US-C; Craddock, Marissa ROX-US-C
Cc: Maziere, Jean-Yves ROX-US-C; Stojic, Megan ROX-US-C
Subject: FW: 8/21/13 FDA Labeling IR - FDA revised labeling (PI and PPI) -NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg

Please see attached! Thanks,
Greg

From: Cross Jr, Frank H [<mailto:Frank.CrossJr@fda.hhs.gov>]
Sent: Wednesday, August 21, 2013 4:46 PM
To: Hicks, Greg ROX-US-C
Cc: Amann, Tony ROX-US-C; Smith, Sarah (SLS) BIP-US-R
Subject: 8/21/13 FDA Labeling IR - FDA revised labeling (PI and PPI) -NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg

Good Afternoon, Mr. Hicks,

Per my voice mail a few minutes ago:

We have revised your PI/PPI documents (to include some questions) as shown in the attached.

Please review and respond by noon Friday, 8/23. – official and e-mail submission.

Sincerely,

Frank Cross, Jr.

Frank H. Cross, Jr., MA, MT (ASCP)
Senior Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration

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(301) 796-2330 (Division Main #)
frank.crossjr@fda.hhs.gov

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/s/

FRANK H CROSS
08/28/2013

From: Cross Jr, Frank H
Sent: Tuesday, August 27, 2013 11:53 AM
To: 'marissa.craddock@boehringer-ingenelheim.com'
Subject: RE: 8/28/13 FDA Information Request: NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg - 8/26/13 Revised PI and Container labeling
Attachments: baxter-spl-with-roxane-mark-ups-130823.pdf

Ms. Craddock,

Thank you for your e-mail.

With regards to the warning in sections 2.3 and 17 of your insert labeling regarding the use of gloves, are these warnings in the insert labeling aimed at preventing healthcare provider and caregiver exposure to cyclophosphamide? If so, then is it your position that these warnings do not apply to patients taking cyclophosphamide capsules?

Please provide answers to both questions.

Sincerely,
Frank Cross, Jr.

Frank H. Cross, Jr., MA, MT (ASCP)
Senior Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
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(301) 796-2330 (Division Main #)
frank.crossjr@fda.hhs.gov

From: Cross Jr, Frank H
Sent: Tuesday, August 27, 2013 11:19 AM
To: 'marissa.craddock@boehringer-ingenelheim.com'
Subject: RE: 8/28/13 FDA Information Request: NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg - 8/26/13 Revised PI and Container labeling

Dear Ms. Craddock,

I will get back to you.

Thank you,

Frank

From: marissa.craddock@boehringer-ingenelheim.com [<mailto:marissa.craddock@boehringer-ingenelheim.com>]

Sent: Tuesday, August 27, 2013 9:14 AM

To: Cross Jr, Frank H

Subject: RE: 8/28/13 FDA Information Request: NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg - 8/26/13 Revised PI and Container labeling

Good Morning Mr. Cross,

We were requested to add the statement on the principal display panel in the 8/16/13 request from Lisa Skarupa. Please see comment #5 in the attached email.

Kindest Regards,
Marissa

From: Cross Jr, Frank H [<mailto:Frank.CrossJr@fda.hhs.gov>]

Sent: Tuesday, August 27, 2013 9:06 AM

To: Craddock, Marissa ROX-US-C

Subject: 8/28/13 FDA Information Request: NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg - 8/26/13 Revised PI and Container labeling

Importance: High

Good Morning, Ms. Craddock,

Please indicate the audience you are targeting with the warning statement "Wear gloves when handling container and capsules."

Is this and other similar warnings in the insert labeling aimed at preventing healthcare provider and caregiver exposure to cyclophosphamide? If so, then these warnings do not apply to patients taking cyclophosphamide capsules?

Please respond by COB, Wednesday, 8/28/13

Sincerely,

Frank

Frank H. Cross, Jr., MA, MT (ASCP)
Senior Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration

(b)
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10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0876 (office)
(301) 796-9845 (fax)
(301) 796-2330 (Division Main #)
frank.crossjr@fda.hhs.gov

From: Cross Jr, Frank H
Sent: Monday, August 26, 2013 3:24 PM
To: 'marissa.craddock@boehringer-ingenelheim.com'
Subject: RE: FDA Information Request for NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg - Insert Labeling and Container Label

Hi Ms. Craddock,

We did receive the submission through the Gateway.

Will be in touch.

Thank you,

Frank

From: marissa.craddock@boehringer-ingenelheim.com
[<mailto:marissa.craddock@boehringer-ingenelheim.com>]
Sent: Monday, August 26, 2013 3:13 PM
To: Cross Jr, Frank H
Subject: RE: FDA Information Request for NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg - Insert Labeling and Container Label

Hello Mr. Cross,

I just wanted to circle back with you and let you know that our response to the below request was submitted through the Gateway this afternoon. Please let me know if you have any problems receiving it.

Thanks so much,
Marissa

From: Cross Jr, Frank H [<mailto:Frank.CrossJr@fda.hhs.gov>]
Sent: Friday, August 23, 2013 3:18 PM
To: Craddock, Marissa ROX-US-C
Subject: RE: FDA Information Request for NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg - Insert Labeling and Container Label

Good Afternoon, Ms. Craddock,

Thank you for your e-mail. We look forward to receiving your submission.

Please also submit the documents in tracked changes.

Have a good weekend.

Frank

From: marissa.craddock@boehringer-ingelheim.com
[<mailto:marissa.craddock@boehringer-ingelheim.com>]
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To: Cross Jr, Frank H
Subject: RE: FDA Information Request for NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg - Insert Labeling and Container Label

Good Afternoon Mr. Cross,

I have received your email with the changes requested to the PI and container labels. We commit to submitting these changes through the Gateway before COB on Tuesday, August 27th. I will email you when they have been submitted.

Thanks so much and have a nice weekend.

Marissa

From: Cross Jr, Frank H [<mailto:Frank.CrossJr@fda.hhs.gov>]
Sent: Friday, August 23, 2013 3:10 PM
To: 'marissa.craddock@boehringer-ingelheim.com'
Subject: FDA Information Request for NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg - Insert Labeling and Container Label

Good Afternoon, Ms. Craddock,

We reviewed your August 19, 2013 submission and your August 22, 2013 email. Please revise the Insert Labeling and Container Label accordingly.

A. Insert Labeling

Section 16 - How Supplied/Storage and Handling

1. Revise the storage statement to be consistent with USP:

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (between 59°F and 86°F).

B. Container Labels, 25 mg and 50 mg

1. Revise the storage statement on the left side panel to read as follows:

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (between 59°F and 86°F).

2. Bold the statement that appears on the left side panel, "Swallow capsules whole. Do not open, chew, or crush capsules."

Please review and respond by COB, Tuesday, 8/27/13 – official and e-mail submission.

Sincerely,
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Sent: Friday, August 23, 2013 10:58 AM
To: 'marissa.craddock@boehringer-ingelheim.com'
Subject: FDA Review of Roxane Labs 8/21/13 email - Storage statement for PI and 8/19/13 Carton/Container - NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg

Good Morning, Ms. Craddock,

The team is still reviewing these items.

Hoping to get back to you today.

Sincerely,

Frank

From: marissa.craddock@boehringer-ingelheim.com
[<mailto:marissa.craddock@boehringer-ingelheim.com>]
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To: Cross Jr, Frank H
Subject: RE: Roxane response to 8/21/13 FDA labeling (PI and PPI) -NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg

Good Morning Mr. Cross,

Has the team had a chance to decide on the removal of “between” from the last part of the storage statement? We’d like to get this submission to you as soon as possible.

Kindest Regards,
Marissa

From: Cross Jr, Frank H [<mailto:Frank.CrossJr@fda.hhs.gov>]
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To: Craddock, Marissa ROX-US-C
Subject: Roxane response to 8/21/13 FDA labeling (PI and PPI) -NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg

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I have forwarded your response to the team.

Will be in touch with you later today or tomorrow.

Sincerely,

Frank

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We are amenable to all of the changes you are requesting in the email we received last evening. However, one concern is the addition of “between” in the second part of the storage statement. This is not consistent with the verbiage that was provided on Monday morning (that was also used in the revision of our container labels), or in other statements that we have seen to date. We would prefer to leave the statement as it was submitted on 8/19 with the verbiage we received from Lisa on Monday morning.

I will be making the changes to the PI and, once I hear from you regarding the storage statement, I will finalize the PI and submit the Word versions of the

Baxter copy with all of the comments that have been made and a cleaned up copy. Please let me know if you require any additional versions at this time (SPL, pdf).

I look forward to hearing from you!

Kindest Regards,
Marissa

Marissa L. Craddock | Manager, Labeling and OPDP Communications | Roxane Laboratories, Inc.
T: (614) 241-4177 | F: (614) 276-2470 | Marissa.Craddock@boehringer-ingenheim.com



From: Hicks, Greg ROX-US-C
Sent: Wednesday, August 21, 2013 5:03 PM
To: Hoane, Krysty ROX-US-C; Craddock, Marissa ROX-US-C
Cc: Maziere, Jean-Yves ROX-US-C; Stojic, Megan ROX-US-C
Subject: FW: 8/21/13 FDA Labeling IR - FDA revised labeling (PI and PPI) -NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg

Please see attached! Thanks,
Greg

From: Cross Jr, Frank H [<mailto:Frank.CrossJr@fda.hhs.gov>]
Sent: Wednesday, August 21, 2013 4:46 PM
To: Hicks, Greg ROX-US-C
Cc: Amann, Tony ROX-US-C; Smith, Sarah (SLS) BIP-US-R
Subject: 8/21/13 FDA Labeling IR - FDA revised labeling (PI and PPI) -NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg

Good Afternoon, Mr. Hicks,

Per my voice mail a few minutes ago:

We have revised your PI/PPI documents (to include some questions) as shown in the attached.

Please review and respond by noon Friday, 8/23. – official and e-mail submission.

Sincerely,
Frank Cross, Jr.

Frank H. Cross, Jr., MA, MT (ASCP)
Senior Regulatory Health Project Manager
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Office of New Drugs
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frank.crossjr@fda.hhs.gov

26 Pages Of Draft Labeling Have Been Withheld In Full As b4 (CCi/TS) Immediately
Following This Page

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

/s/

FRANK H CROSS
08/28/2013

From: Cross Jr, Frank H
Sent: Wednesday, August 28, 2013 11:59 AM
To: 'marissa.craddock@boehringer-ingelheim.com'
Subject: New 8/28/13 FDA Information Request: NDA 203856, Cyclophosphamide Capsules, 25 mg and 50 mg - 8/26/13 Revised PI and Container labeling

Good Afternoon, Ms. Craddock,

Please respond to the following CMC Information request:

Manufactured by OR Distributed by
Roxane Laboratories, Inc.
Columbus, Ohio 43216
10008219/01
Revised XX 2013
©RLI, 2013

The new labeling submitted on 8/26/13 by Roxane should add the phrase “Manufactured by” or “Distributed by” as indicated in RED, and either provide justification to the highlighted numbers “10008219/01” or strikeout.

Sincerely,

Frank Cross, Jr.

Frank H. Cross, Jr., MA, MT (ASCP)
Senior Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
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frank.crossjr@fda.hhs.gov

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/s/

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08/28/2013

Cross Jr, Frank H

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Sent: Friday, August 23, 2013 3:18 PM
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Have a good weekend.

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

/s/

FRANK H CROSS
08/23/2013

505(b)(2) ASSESSMENT

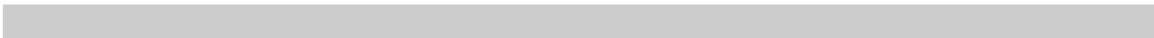
Application Information		
NDA # 203856	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: none Established/Proper Name: cyclophosphamide Dosage Form: capsules Strengths: 25 mg and 50 mg		
Applicant: Roxane Laboratories, Inc.		
Date of Receipt: July 17, 2013		
PDUFA Goal Date: Sept 17, 2013		Action Goal Date (if different): August 30, 2013
Proposed Indication(s): Cyclophosphamide is an alkylating agent indicated for the treatment of malignant diseases such as certain types of lymphomas and leukemias, neuroblastoma and carcinoma of the breast and is often used in combination with other neoplastic drugs. It is also indicated for carefully selected cases of biopsy proven "minimal change" nephrotic syndrome in children.		

GENERAL INFORMATION

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

YES NO

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



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

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

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Baxter's Cytosoxan Tablets NDA 12141	All sections of the label: clinical data, pharmacokinetic data, clinical pharmacology data, CMC data, nonclinical data.

*each source of information should be listed on separate rows

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

Roxane requested waiver to do the BA/BE studies; Roxane Laboratories owns ANDA 40032 (the generic cyclophosphamide tablets). On November 2007, Baxter (NDA 12141) removes Cytosoxan tablets from marketing not for safety reasons. The ANDA 40032 became the RLD in the Orange Book.

Update: Biopharm Review (March 4, 2013) granted the BA/BE waiver. The waiver was granted under the following: **REGULATORY APPLICATIONS OF THE BCS A. INDs/NDAs**

Evidence demonstrating in vivo BA or information to permit FDA to waive this evidence must be included in NDAs (21 CFR 320.21(a)). A specific objective is to establish in vivo performance of the dosage form used in the clinical studies that provided primary evidence of efficacy and safety. The sponsor may wish to determine the relative BA of an IR solid oral dosage form by comparison with an oral solution, suspension, or intravenous injection (21 CFR 320.25 (d)(2) and 320.25 (d)(3)). The BA of the clinical trial dosage form should be optimized during the IND period.

Once the in vivo BA of a formulation is established during the IND period, waivers of subsequent in vivo BE studies, following major changes in components, composition, and/or method of manufacture (e.g., similar to SUPAC-IR Level 3 changes⁶) may be possible using the BCS. BCS-based biowaivers are applicable to the to-be-marketed formulation when changes in components, composition, and/or method of manufacture occur to the clinical trial formulation, as long as the dosage forms have rapid and similar in vitro dissolution profiles (see sections II and III). This approach is useful only when the drug substance is highly soluble and highly permeable (BCS Class 1), and the formulations pre- and postchange are pharmaceutical equivalents (under the definition at 21 CFR 320.1 (c)). BCS-based biowaivers are intended only for BE studies. They do not apply to food effect BA studies or other pharmacokinetic studies.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the

approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If "NO," proceed to question #5.

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

YES NO

If "NO," proceed to question #5.

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

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

YES NO



RELIANCE ON LISTED DRUG(S)

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

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

YES NO

If "NO," proceed to question #10.

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

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Cytosan tablets	NDA 12141	Yes

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

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

N/A YES NO

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

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

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

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

YES NO

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

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

- b) Approved by the DESI process?

YES NO

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

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

- c) Described in a monograph?

YES NO

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

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

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

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

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

YES NO

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

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

A change in formulation/dosage form from tablet to IR capsule.

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

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

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

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

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

YES NO

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

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

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

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

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

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

Pharmaceutical equivalent(s):

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

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

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

YES NO
If “**NO**”, proceed to question #12.

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

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

NDA 12141 is considered a pharmaceutical alternative even though it came off the market and listed in the discontinued section of the Orange Book. Also there is a generic pharmaceutical alternative, Roxane’s generic ANDA 40032.

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

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

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

Listed drug/Patent number(s):

No patents listed proceed to question #14

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

YES NO

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

Listed drug/Patent number(s):

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

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

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

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

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

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

Patent number(s):

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

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

(a) Patent number(s):

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

YES NO

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

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

YES NO

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

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

Date(s):

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

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

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

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/s/

LISA M SKARUPA
08/23/2013

From: sarah-a.smith@boehringer-ingenelheim.com
To: [Skarupa, Lisa](#)
Cc: tony.amann@boehringer-ingenelheim.com
Subject: RE: Additional recommendations: CONTAINER labels I.R./ NDA 203856 for Cyclophosphamide
Date: Monday, August 19, 2013 9:06:16 AM

Thanks Lisa! We will respond today.

Sarah

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Monday, August 19, 2013 8:56 AM
To: Smith,Sarah-A ROX-US-C
Cc: Amann,Tony ROX-US-C
Subject: Additional recommendations: CONTAINER labels I.R./ NDA 203856 for Cyclophosphamide

Dear Sarah,

The following are CMC recommendations to your labeling.

Container Labels: Comment: Revise the storage to reflect “Store at 20°C to 25°C (68°F to 77°F), excursion permitted between 15°C and 30°C (59°F and 86°F).”

Please provide **responses to container labels by Tuesday 12noon August 20th**

Please acknowledge, and if the timeline is acceptable.

Also the following CMC recommendation is for **the Package Insert:**

Comment to Section 16 How Supplied/Storage and Handling :

Revise the storage to reflect “Store at 20°C to 25°C (68°F to 77°F),
excursion permitted between 15°C and 30°C (59°F and 86°F).”

Sincerely,

Lisa

Regulatory Project Manager | Division of Oncology Products 1
Office of Hematology & Oncology Products (OHOP) | CDER | FDA
10903 New Hampshire Avenue | (b) (6) | Silver Spring, MD 20993
301.796.2219 (phone) | 301.796.9845 (FAX) | lisa.skarupa@fda.hhs.gov

From: sarah-a.smith@boehringer-ingenelheim.com [mailto:sarah-a.smith@boehringer-ingenelheim.com]
Sent: Friday, August 16, 2013 4:56 PM
To: Skarupa, Lisa
Cc: tony.amann@boehringer-ingenelheim.com
Subject: Re: CONTAINER labels I.R./ NDA 203856 for Cyclophosphamide

Timeline looks doable!

Will let you know if anything changes.

Thanks Lisa,

Sarah

From: Skarupa, Lisa [<mailto:Lisa.Skarupa@fda.hhs.gov>]
Sent: Friday, August 16, 2013 04:52 PM
To: Smith,Sarah-A ROX-US-C
Cc: Amann,Tony ROX-US-C
Subject: CONTAINER labels I.R./ NDA 203856 for Cyclophosphamide

Dear Sarah,

DMEPA recommends to the Container Labels, 25 mg and 50 mg the following revisions:

1. Revise the statement, Usual Dosage: See package insert for complete prescribing information, to read as follows:

Usual Dosage: See package insert.

This will create space for additional information to appear on the left side panel.

2. Delete the following statement from the left side panel:

 (b) (4)

This will create space for additional information to appear on the left side panel.

3. Relocate the statement, *Each capsules contains xx mg cyclophosphamide USP (calculated as anhydrous)*, to the left side panel.

This will create space for additional information to appear on the principal display panel.

4. Add the following statements to the left side panel.

Swallow capsules whole. Do not open, chew, or crush capsules.

5. Add the following statement to the principal display panel under the boxed statement "Cytotoxic Agent".

Wear gloves when handling container and capsules.

Please provide **responses by Tuesday 12noon August 20th**

Please acknowledge, and if the timeline is acceptable.

Sincerely,
Lisa

Regulatory Project Manager | Division of Oncology Products 1
Office of Hematology & Oncology Products (OHOP) | CDER | FDA
10903 New Hampshire Avenue | [REDACTED] (b) (6) | Silver Spring, MD 20993
301.796.2219 (phone) | 301.796.9845 (FAX) | lisa.skarupa@fda.hhs.gov

From: sarah-a.smith@boehringer-ingelheim.com [<mailto:sarah-a.smith@boehringer-ingelheim.com>]
Sent: Friday, August 16, 2013 3:20 PM
To: Skarupa, Lisa
Cc: tony.amann@boehringer-ingelheim.com
Subject: RE: NDA 203856 for Cyclophosphamide

Thanks Lisa! We have all hands on deck on our end. ☺

From: Skarupa, Lisa [<mailto:Lisa.Skarupa@fda.hhs.gov>]
Sent: Friday, August 16, 2013 3:06 PM
To: Smith,Sarah-A ROX-US-C
Cc: Amann,Tony ROX-US-C
Subject: NDA 203856 for Cyclophosphamide

Dear Sarah,

Please see the attached Acknowledgement letter regarding your re-submission dated July 17, 2013.

Due to the PDUFA goal date of early September, please be aware that labeling negotiations will be very late next week or early August 26, 2013.

Please have your labeling team ready so you can respond quickly. Thank you.

Sincerely,
Lisa

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/s/

LISA M SKARUPA
08/19/2013



NDA 203856

MEETING MINUTES

Roxane Laboratories, Inc.
Attention: Anton Amann, Ph.D.
Executive Director, Drug Regulatory Affairs and Medical Affairs
1809 Wilson Road
Columbus, Ohio 43228

Dear Dr. Amann:

Please refer to your New Drug Application (NDA) dated May 14, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cyclophosphamide capsules 25 mg and 50 mg.

We also refer to the telecon between representatives of your firm and the FDA on June 18, 2013. The purpose of the meeting was to discuss proposed plan to submit cyclophosphamide capsule CMC data to support approval of the NDA.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, Regulatory Project Manager at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Lisa Skarupa
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Post Action (Complete Response) Meeting

Meeting Date and Time: **new meeting date: June 18, 2013 from 10:10am to 11am**
cancelled meeting scheduled June 21, 2013 from 10 am to 11 am

Meeting Location: Teleconference

Application Number: NDA 203856
Product Name: cyclophosphamide capsules, 25 mg and 50 mg
Indication: **Malignant Diseases:** Malignant lymphomas, Hodgkin's disease, Lymphocytic lymphoma, Mixed-cell type lymphoma, Histiocytic lymphoma, Burkitt's lymphoma, Multiple myeloma, leukemias, Mycosis fungoides, Neuroblastoma, Adenocarcinoma of ovary, Retinoblastoma, Breast carcinoma
Nonmalignant Diseases: Biopsy proven "minimal change" nephrotic syndrome in children

Sponsor/Applicant Name: Roxane Laboratories, Inc.

Meeting Chair: Ali Al Hakim, Ph.D., Branch Chief, ONDQA, DNDQAI/BRII
Meeting Recorder: Lisa Skarupa, RPM, DOP1

FDA ATTENDEES

Ali Al Hakim, Ph.D., Branch Chief, ONDQA, DNDQAI/BRII
Josephine Jee, Ph.D., Reviewer, ONDQA, DNDQAI/BRII
Lisa Skarupa, RPM, DOP1

SPONSOR ATTENDEES

Tony Amann, Ph.D., Executive Director, Regulatory and Medical Affairs, Roxane Laboratories, Inc.
Sarah Smith, Associate Director, Drug Regulatory Affairs and Medical Affairs, Roxane Laboratories, Inc.

BACKGROUND

The Applicant Roxane Laboratories Inc. (RLI) of 505b2-NDA 203856, Cyclophosphamide Capsules, originally submitted on December 21, 2011. On February 17, 2012, FDA issues a Refuse-to-File letter because of incomplete stability data. On May 30, 2012, FDA responded to the Applicant's questions recommending that they submit 12 months long-term and 6 months accelerated stability data for 3 primary batches of drug substance and drug product. On July 3, 2012, the Applicant resubmitted their application. On May 3, 2013, FDA issued a Complete Response letter whereby CMC recommended that at the time of resubmission of this NDA the Applicant submit data from three registration batches (for each dosage strength) that conforms to the NDA-proposed specifications for dissolution and impurity levels. On May 17, 2013, the Applicant requested for a post-action meeting.

Conversion of a Tablet product to a Capsule

The currently approved RLI Cyclophosphamide product (ANDA 040032) is a tablet dosage form (b) (4). RLI developed a new capsule formulation (b) (4). This new capsule formulation will enable RLI to utilize the new HCO (b) (4) in order to continue to manufacture this medically necessary oral solid dosage form.

The Applicant planned to close the Oak Street facility (b) (4) and due to a potential drug shortage, the Applicant requested a teleconference to discuss the acceptance of their plan (see table under Discussion) to submit the data summarized earlier on our Cyclophosphamide Capsules to support the approval of their NDA.

2. DISCUSSION

CMC

Question: *As we previously communicated, the current facility that is manufacturing our Cyclophosphamide Tablets (Oak St) is closing (b) (4). The closing of this facility will have a drug shortage impact as RLI is sole source manufacturer for our Cyclophosphamide Tablets. As a result, it is important that we obtain agreement with the FDA on our proposed strategy for submitting data to support our NDA approval at the HCO facility.*

RLI respectfully requests a t-con to discuss the following plan for submission of our Cyclophosphamide Capsule data:

Strength	(b) (4) lot	Capsule lot number	Site of manufacture	Stability
	number			
25 mg	4000506	4000507	Oak Street	24 month data
50 mg	4000506	4000508	Oak Street	24 month data
25 mg	4000593	4000594	Oak Street	24 month data
50 mg	4000593	4000595	Oak Street	24 month data
25 mg	4001238	4001238	HCO	6 months data
50 mg	4001237	4001237	HCO	6 months data

All of these lots were produced using similar equipment (both utilize a (b) (4) (b) (4)) and the same manufacturing process at both the Oak Street Facility and the Wilson Road HCO facility. The difference in size of these lots between HCO and Oak Street was a result of difference in the (b) (4). The stability data for the above lots will be available for submission at the end of June 2013.

Does the Agency agree?

FDA response:

Before we make any recommendation, the new site (the Wilson Road HCO facility) has to have acceptable recommendation from the Office of Compliance. Additionally, you need to submit the stability test data conducted at long term and accelerated storage conditions (0, 3, and 6 month time points) for the batch manufactured at the Wilson Road HCO facility. We urge you to submit the data for our review as soon as possible due to the potential shortage issue.

Roxane Laboratories, Inc. emailed the following question June 17, 2013:

Is the FDA amenable to RLI submitting 0, 3, and 6 month long term and accelerated data on the batch's made from HCO?

Teleconference Discussions: Yes. FDA is will allow the submission of the long term and accelerated storage conditions (0, 3, and 6 month time points) stability data for the Wilson Road HCO when Roxane Laboratories will resubmit the NDA, with the condition that the remaining data be officially submitted to include the 9 mo, 12 mo, 18 mo, and 24 mo stability data as soon as they are available. The Applicant agreed to submit the requested details (see table under ACTION ITEMS). The Applicant stated that they will not have issues with the Office of Compliance and will submit the EIR report. The Applicant also requested an expedited review at the time of the planned July 17, 2013 submission. FDA stated that the data that is planned to be submitted in July has to be reviewed, and therefore an agreement for an expedited review cannot be made.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

Per our discussion this morning this is a summary table of the Cyclophosphamide Capsules data that the Applicant will have available for submission. Please also note that the Applicant will include a copy of the EIR report from our June 2012 inspection of our Wilson Road HCO facility. The

Applicant is prepared to submit their data (along with the other information requested in our 5/3/2013 Complete Response letter) on July 17, 2013.

The table containing our data is provided below.

Strength	(b) (4) lot number	Capsule lot number	Site of manufacture	Stability Start date	40°C/75% RH	25°C/60% RH	30°C/65% RH
25 mg	4000506	4000507	Oak Street	(b) (4)	0,1,2,3,6	0,3,6,9,12,18,24	Not available
50 mg	4000506	4000508	Oak Street		0,1,2,3,6	0,3,6,9,12,18,24	Not available
25 mg	4000593	4000594	Oak Street		0,1,2,3,6	0,3,6,9,12,18,24	Not available
50 mg	4000593	4000595	Oak Street		0,1,2,3,6	0,3,6,9,12,18,24	Not available
25 mg	4001238	4001238	HCO		0,1,2,3,6	0,3,6	Not available
50 mg	4001237	4001237	HCO		0,1,2,3,6	0,3,6	Not available
25 mg	4001431	4001431	HCO		0,1,2,3	0,3	0,3
25 mg	4001432	4001432	HCO		0,1,2,3	0,3	0,3
50 mg	4001433	4001433	HCO		0,1,2,3	0,3	0,3
50 mg	4001434	4001434	HCO		0,1,2,3	0,3	0,3

6.0 ATTACHMENTS AND HANDOUTS

None

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/s/

LISA M SKARUPA
08/18/2013

ALI H AL HAKIM
08/18/2013



NDA 203856

**ACKNOWLEDGE --
CLASS 1 COMPLETE RESPONSE**

Roxane Laboratories, Inc.
Attention: Anton Amann, Ph.D.
Executive Director, Drug Regulatory Affairs and Medical Affairs
1809 Wilson Road
Columbus, OH 43228

Dear Dr. Amann:

We acknowledge receipt on July 17, 2013, of your July 17, 2013, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cyclophosphamide Capsules, 25 mg and 50 mg.

We consider this a complete, class 1 response to our May 3, 2013, action letter. Therefore, the user fee goal date is September 17, 2013.

If you have any questions, call Lisa Skarupa, Regulatory Project Manager, at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Christy Cottrell
Chief, Project Management Staff
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

CHRISTY L COTTRELL
08/16/2013

From: sarah-a.smith@boehringer-ingenelheim.com [mailto:sarah-a.smith@boehringer-ingenelheim.com]
Sent: Friday, August 16, 2013 4:56 PM
To: Skarupa, Lisa
Cc: tony.amann@boehringer-ingenelheim.com
Subject: Re: CONTAINER labels I.R./ NDA 203856 for Cyclophosphamide

Timeline looks doable!

Will let you know if anything changes.

Thanks Lisa,

Sarah

From: Skarupa, Lisa
Sent: Friday, August 16, 2013 4:53 PM
To: 'sarah-a.smith@boehringer-ingenelheim.com'
Cc: tony.amann@boehringer-ingenelheim.com
Subject: CONTAINER labels I.R./ NDA 203856 for Cyclophosphamide
Importance: High

Dear Sarah,

DMEPA recommends to the Container Labels, 25 mg and 50 mg the following revisions:

1. Revise the statement, Usual Dosage: See package insert for complete prescribing information, to read as follows:

Usual Dosage: See package insert.

This will create space for additional information to appear on the left side panel.

2. Delete the following statement from the left side panel:

 (b) (4)

This will create space for additional information to appear on the left side panel.

3. Relocate the statement, *Each capsules contains xx mg cyclophosphamide USP (calculated as anhydrous)*, to the left side panel.

This will create space for additional information to appear on the principal display panel.

4. Add the following statements to the left side panel.

Swallow capsules whole. Do not open, chew, or crush capsules.

5. Add the following statement to the principal display panel under the boxed statement “Cytotoxic Agent”.

(b) (4)

Please provide **responses by Tuesday 12noon August 20th**
Please acknowledge, and if the timeline is acceptable.

Sincerely,

Lisa

Regulatory Project Manager | Division of Oncology Products 1
Office of Hematology & Oncology Products (OHOP) | CDER | FDA
10903 New Hampshire Avenue | (b) (6) | Silver Spring, MD 20993
☐ 301.796.2219 (phone) | ☐ 301.796.9845 (FAX) | ☐ lisa.skarupa@fda.hhs.gov

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/s/

LISA M SKARUPA
08/16/2013

Question : *As we previously communicated, the current facility that is manufacturing our Cyclophosphamide Tablets (Oak St) is closing (b) (4). The closing of this facility will have a drug shortage impact as RLI is sole source manufacturer for our Cyclophosphamide Tablets. As a result, it is important that we obtain agreement with the FDA on our proposed strategy for submitting data to support our NDA approval at the HCO facility.*

RLI respectfully requests a t-con to discuss the following plan for submission of our Cyclophosphamide Capsule data:

Strength	(b) (4) number	Capsule lot number	Site of manufacture	Stability
25 mg	4000506	4000507	Oak Street	24 month data
50 mg	4000506	4000508	Oak Street	24 month data
25 mg	4000593	4000594	Oak Street	24 month data
50 mg	4000593	4000595	Oak Street	24 month data
25 mg	4001238	4001238	HCO	6 months data
50 mg	4001237	4001237	HCO	6 months data

All of these lots were produced using similar equipment (both utilize a (b) (4) (b) (4)) and the same manufacturing process at both the Oak Street Facility and the Wilson Road HCO facility. The difference in size of these lots between HCO and Oak Street was a result of difference in the (b) (4). The stability data for the above lots will be available for submission at the end of June 2013.

Does the Agency agree?

FDA response:

Before we make any recommendation, the new site (the Wilson Road HCO facility) has to have acceptable recommendation from the Office of Compliance. Additionally, you need to submit the stability test data conducted at long term and accelerated storage conditions (0, 3, and 6 month time points) for the batch manufactured at the Wilson Road HCO facility. We urge you to submit the data for our review as soon as possible due to the potential shortage issue.

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/s/

LISA M SKARUPA
06/14/2013



NDA 203856

MEETING REQUEST GRANTED

Roxane Laboratories, Inc.
Attention: Anton Amann, Ph.D.
Executive Director, Drug Regulatory Affairs and Medical Affairs
1809 Wilson Road
Columbus, Ohio 43228

Dear Dr. Amann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cyclophosphamide Capsules, 25 mg and 50 mg.

We also refer to your May 14, 2013, correspondence requesting a Post Action meeting to discuss the following plan for submission of Applicant's Cyclophosphamide Capsule data:

All of the referenced lots were produced using similar equipment (both utilize a (b) (4) (b) (4)) and the same manufacturing process at both the Oak Street Facility and the Wilson Road HCO facility. The difference in size of the referenced lots between HCO and Oak Street was a result of difference in the (b) (4). The stability data for these lots will be available for submission at the end of June 2013. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type A meeting.

The teleconference is scheduled as follows:

Date: June 21, 2013

Time: 10:00 am to 11:00 am

Phone Arrangements: Phone number (b) (4)

CDER Participants, disciplines include Clinical, CMC, Drug Shortage team, NonClinical, and Clinical Pharmacology: Robert Justice, Anna Ibrahim, Ali Al Hakim, Hasmukh Patel, Haripada Sarker, Josephine Jee, Norman Schmuff, Valerie Jensen, Jouhayna Saliba, Jin Ahn, Patricia Cortazar, Laleh Amiri-Kordestani, Zedong Dong, Todd Palmby, George Chang, Qi Liu, Sarah Schrieber

Your meeting request was considered as your meeting package for the teleconference.

Please be advised that if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions

on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Include in your meeting package your proposals for 1) the content of a complete application and 2) any minor components to be submitted within 30 days after your original submission. You should also include, as part of your meeting questions, a request for our agreement with your proposals.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

If you have any questions, call me, Regulatory Project Manager at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Lisa Skarupa
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

LISA M SKARUPA
06/05/2013

MEMORANDUM OF TCON MINUTES

MEETING DATE: 3/21/13
TIME: 2:30 – 3:00 p.m.
LOCATION: TCON- Applicant's dial-in information
APPLICATION: NDA 203856
DRUG NAME: Cyclophosphamide Capsules
APPLICANT: Roxane Laboratories, Inc.
TYPE OF MEETING: FDA requested TCON
MEETING CHAIR: Ali H. Al-Hakim, Ph.D., Branch Chief
MEETING RECORDER: Deborah Mesmer, M.S., Regulatory Health Project Manager for Quality

FDA ATTENDEES:

Ali H. Al-Hakim, Ph.D., Branch Chief
Haripada Sarker, Ph.D., CMC Lead
Josephine Jee, Review Chemist
Zedong Dong, Ph.D., Review Chemist
Sandra Suarez-Sharp, PhD, Biopharmaceutics Team Leader (acting)
Deborah Mesmer, M.S., Regulatory Health Project Manager for Quality, ONDQA
Lisa Skarupa, RN, MSN, Regulatory Health Project Manager, Division of Drug Oncology Products, DOP1

EXTERNAL CONSTITUENT ATTENDEES- Roxanne Laboratories:

Tony Amann, PhD-Executive Director, Drug Regulatory Affairs and Medical Affairs
Sarah Smith, MS-Associate Director, Drug Regulatory Affairs and Medical Affairs
Matt Annibaldi-Manager, Drug Regulatory Affairs and Medical Affairs
Barbara Galbiati, PhD, Technical API
Todd Lewis, Associate Director, Analytical Development
Tom Mahon, Director, Product Development

BACKGROUND:

Two drug product lots failed long term stability based on dissolution (acceptance criterion: Q = (b) (4) at 15 minutes) and impurities. The application does not include a bioequivalence study. The Applicant requests a biowaiver based on the Agency's determination of BCS Class I for the drug substance and drug product.

FDA issued an information request dated March 12, 2013. The Applicant responded on March 18, 2013.

On March 20, 2013, FDA requested a TCON with the Applicant to be held on March 21, 2013. The teleconference was preceded by an FDA internal meeting starting at 2:00 p.m.

MEETING OBJECTIVES:

The objective of the TCON was to discuss dissolution and impurities in the failing batches and to determine if there is adequate stability data (three registration batches) to support the proposed shelf-life of the drug product.

DISCUSSION POINTS:

FDA requested a discussion of the dissolution results and the failure of two batches of drug product at Tier 2. The Applicant was requested to provide justification regarding these issues.

The Applicant responded that the problem is isolated to two lots of drug product and they suspect that the API is the root cause of failure for dissolution at 15 minutes on stability. The same batches also have high degradation products. The applicant is working with [REDACTED] (b) (4) [REDACTED] (b) (4) the API supplier, to identify the problem. The Applicant committed to provide definitive information on the root cause of the problem and assurance that future lots will meet the 15 minute dissolution acceptance criterion. Studies are underway which may take up to six weeks to complete.

FDA acknowledged the Applicant's understanding that all batches need to meet the specifications at release and under stability testing and that the Applicant is working on the problem. FDA requested that the applicant provide information on the root cause of the failures and supporting data by Monday, March 25, 2013.

DECISIONS (AGREEMENTS) REACHED:

The Applicant committed to provide justification/data for the root cause of dissolution failure and to exclude the failing batches. FDA reminded the Applicant of the need for stability data for a minimum of 3 batches of drug product with adequate specifications including adequate dissolution performance.

The applicant committed to provide their response by Monday, March 25, 2013.

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/s/

DEBORAH M MESMER
03/22/2013

ALI H AL HAKIM
03/23/2013



NDA 203856

INFORMATION REQUEST

Roxanne Laboratories, Inc.
Attention: Randall Wilson
Vice President, Scientific, Regulatory and Medical Affairs
1809 Wilson Rd.
Columbus, Ohio 43228

Dear Mr. Wilson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cyclophosphamide Capsules, 25 mg and 50 mg.

We also refer to your amendments dated July 17, and January 4, 2013.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a written response no later than **March 18, 2013**, in order to continue our evaluation of your NDA.

1. Provide only one set of specifications for drug product.
2. Establish acceptance criteria for degradation products based on ICHQ3B qualification limits.
3. Provide appropriate study and data to support the elimination of test and acceptance criteria in the drug product specification for related substances and degradants found in the drug substance but not included in the DP specification.
4. Revise the justification of the acceptance criteria for (b) (4) (NMT (b) (4)); it should be consistent with the proposed acceptance criteria of (b) (4) proposed in the Cyclophosphamide drug substance specification.
5. The proposed shelf-life of 24 months cannot be granted since the registration batches submitted for stability failed the acceptance criteria for dissolution (Q of (b) (4) in 15 minutes). Additionally, the degradants, (b) (4) e and/or Single Largest Unspecified Degradant failed the specifications at shelf life as per ICHQ3B.
6. Provide the study of the (b) (4) as outlined in your communication dated January 4, 2013.
7. Provide the estimated concentration of cyclophosphamide at the point of entry into the aquatic environment.

If you have any questions, call Deborah Mesmer, Regulatory Project Manager, at (301) 796-4023.

Sincerely,

{See appended electronic signature page}

Ali Al-Hakim, Ph.D.
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
03/12/2013



IND 112446

ADVICE/INFORMATION REQUEST

Roxanne Laboratories
Attention: Randall Wilson
Vice President, Scientific, Regulatory and Medical Affairs
1809 Wilson Rd.
Columbus, Ohio

Dear Mr. Wilson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Cyclophosphamide Capsules 25 mg and 50 mg.

We also refer to your amendment dated March 12, 2012, containing information needed to support a BCS Class I designation for cyclophosphamide drug substance.

We have the following comment:

The BCS Committee at CDER has approved your request for a BCS Class-1 classification for cyclophosphamide capsules.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]. If your IND is in eCTD format, submit 7-day reports electronically in eCTD format. If your IND is not in eCTD format, you may submit 7-day reports by telephone or fax;
- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

If you have any questions, contact Deborah Mesmer, Regulatory Project Manager, at (301) 796-4023.

Sincerely,

{See appended electronic signature page}

Ali Al-Hakim, Ph.D.
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
03/12/2013

From: [Mesmer, Deborah](#)
To: ["randy.wilson@boehringer-ingenheim.com"](mailto:randy.wilson@boehringer-ingenheim.com)
Cc: [Skarupa, Lisa](#)
Subject: NDA 203856 IR 03/11/13
Date: Monday, March 11, 2013 3:10:00 PM

Dear Mr. Wilson,
Please refer to NDA 203856 for cyclophosphamide capsules.

Your November 30, 2012, submission provided stability data over a physiologic pH range for the evaluation of your request for a BCS Class I designation for the cyclophosphamide drug substance. You have not cross- referenced your NDA to IND 112446. Please provide this cross reference via a revised Form 356h so that we may continue our review.

Please provide this information by **March 13, 2013**.

Please acknowledge receipt of this message.

Sincerely,

Deborah Mesmer

Deborah Mesmer

Regulatory Project Manager for Quality

Office of New Drug Quality Assessment (ONDQA)

Division of New Drug Quality Assessment (DNDQA1)

Food and Drug Administration

(b) (6)

10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

(301) 796-4023

deborah.mesmer@fda.hhs.gov

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/s/

DEBORAH M MESMER
03/11/2013

MEMORANDUM OF TCON MINUTES

MEETING DATE: 12/4/12
TIME: 2:00 p.m.
LOCATION: TCON- Applicant's dial-in information
Call in number:
(b) (4)
APPLICATION: NDA 203856
DRUG NAME: Cyclophosphamide Capsules
APPLICANT: Roxane Laboratories, Inc.
TYPE OF MEETING: FDA requested TCON
MEETING CHAIR: Nallaperumal Chidambaram, PhD, Acting Branch Chief
MEETING RECORDER: Deborah Mesmer, M.S., Regulatory Health Project Manager for Quality

FDA ATTENDEES:

Haripada Sarker, Ph.D., CMC Lead, ONDQA
Deborah Mesmer, M.S., Regulatory Health Project Manager for Quality, ONDQA
Josephine Jee, Review Chemist, ONDQA
Nallaperumal Chidambaram, PhD, Acting Branch Chief, ONDQA

EXTERNAL CONSTITUENT ATTENDEES:

Sarah Smith-Associate Director, Drug Regulatory Affairs and Medical Affairs
Tom Mahon-Director, Product Development
Matt Annibaldi-Manager, Drug Regulatory Affairs and Medical Affairs
Kerri Finnegan-Executive Director, Regulatory Compliance
Robert Mcelheny-Senior Compliance Professional, Compliance Services

BACKGROUND:

The Applicant submitted two Boehringer Ingelheim Roxane Inc sites for drug product manufacturing in the NDA:

330 Oak Street, Columbus Ohio
1809 Wilson Road (HCO), Columbus Ohio

FDA issued an information request dated November 7, 2012, requesting clarification of which exhibit lots were manufactured at each site. The applicant clarified in a submission dated November 8, 2012, that the three stability batches were manufactured at the 330 Oak Street facility.

MEETING OBJECTIVES:

This TCON was requested to discuss the new manufacturing site at 1809 Wilson Road, Columbus, Ohio 43215, to obtain clarification on stability data. There is no stability data from this facility in the application.

DISCUSSION POINTS:

FDA requested clarification of whether there was stability data for DP manufactured at the Wilson Road (HCO) site. The Applicant stated that the 25 and 50 mg strengths have been manufactured from the HCO site, and there is currently 30-day accelerated stability data with 3 months data available at the end of February 2013. The applicant clarified that the Wilson Rd site will be the primary site for manufacture of this product. The Oak Street site will shut down

(b) (4)

FDA responded that 12 months of long term stability data on 3 lots is needed for the primary site, so it would be difficult to approve the Wilson Rd. site with 3 months data.

The applicant clarified that the original intention was to manufacture from the Wilson Rd site, but construction was not complete, so registration lots were manufactured from the Oak Street Facility.

FDA stated that the Wilson Road facility cannot be approved without the stability data. The Applicant inquired if they may remove the Wilson Rd. site from the application and then file a CBE-30 supplement after approval to add the site to the application.

FDA responded that removing the site was an option. FDA inquired if the site manufactured any capsule dosage form, as a CBE-30 would require the site to be cGMP compliant for the proposed manufacturing profile; otherwise a PAS would be needed. The applicant responded that no capsules had been manufactured at this site.

The Applicant argued that the new HCO building was part to the same campus as the building currently manufacturing the product. The applicant mentioned that they are the sole source for the tablet version of the product. FDA recommended that the Applicant contact the District Office and the Drug Shortages team and then submit a correspondence to their application.

DECISIONS (AGREEMENTS) REACHED:

The Applicant agreed to submit a correspondence, including a summary of manufacturing operations, to inquire if CBE-30 would be appropriate for the first capsule manufactured at the Wilson Road site.

The Applicant agreed to submit their response regarding their decision to remove the Wilson Road site from the NDA within a week.

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/s/

DEBORAH M MESMER
02/11/2013

NALLAPERUM CHIDAMBARAM
02/13/2013

From: randy.wilson@boehringer-ingenelheim.com
To: [Skarupa, Lisa](#)
Cc: [Mesmer, Deborah](#); sarah-a.smith@boehringer-ingenelheim.com
Subject: Re: Feb 11 2013 Information request NDA 203856 Roxane Lab
Date: Monday, February 11, 2013 4:57:13 PM

Hello Lisa,

Thank you for the communication. We will respond to your requests shortly.

Best regards,

Randy Wilson
Randall S. Wilson
Vice President Scientific and Regulatory Affairs

Sent from my BlackBerry Wireless Handheld

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Monday, February 11, 2013 03:52 PM
To: Wilson,Randy (AD) ROX-US-C
Cc: Mesmer, Deborah <Deborah.Mesmer@fda.hhs.gov>; Smith,Sarah-A ROX-US-C
Subject: Feb 11 2013 Information request NDA 203856 Roxane Lab

Dear Randy,

Please see the following I.R.

Please acknowledge receipt and if you concur in responding to this I.R. by February 25th (2 weeks).

This Information Request is based on your December 20, 2012 submission to NDA 203856 regarding manufacturing sites.

In your submission, your cover letter stated "**There are currently no other approved ANDAs for Cyclophosphamide Tablets and therefore we are the sole source and manufacturer of this product.**" And further down in the letter you stated, "**supply of our Cyclophosphamide Tablets** (b) (4). Your plans are to close the Oak (b) (4) and transfer to the new High-Containment-Operations-Facility, a modern facility, at Wilson Road.

1. Please provide us your current inventory of the tablets and a current estimate of how long will this inventory last. Are the tablets currently being made at the Oak Street facility and/or other facility (ies)?
2. Please clarify as to when you expect to move manufacturing into the Wilson Road facility.
3. Please clarify if you intend to manufacture tablets and capsules at the new Wilson Road facility.
4. Please clarify if you plan to market both the tablet and capsule formulations.
5. Regarding the request for CBE-30 because this product is medically necessary, will your facility at Wilson Road be ready to start the 6 months stability data collection now?

Sincerely,

Lisa

Lisa Skarupa
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research
(301) 796-2219
Fax (301)796-9845
lisa.skarupa@fda.hhs.gov

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/s/

LISA M SKARUPA
02/11/2013

From: Skarupa, Lisa
Sent: Monday, January 07, 2013 5:07 PM
To: Randy.Wilson@boehringer-ingenelheim.com
Cc: Mesmer, Deborah
Subject: NDA 203856 NonClinical Information Request January 7 2013

Dear Randy,

Please see the following Nonclinical Information Request. Please acknowledge and provide your response to this Information Request by January 21, 2013:

Provide an adequate justification of the specification for (b) (4).
Your current justification in report 1726-009 states that this specification meets USP
Option (b) (4) however, (b) (4) >.

Sincerely,
Lisa

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/s/

LISA M SKARUPA
01/07/2013

From: [Mesmer, Deborah](mailto:Mesmer,Deborah)
To: ["Randy.Wilson@boehringer-ingenheim.com"](mailto:Randy.Wilson@boehringer-ingenheim.com)
Cc: [Skarupa, Lisa](mailto:Skarupa,Lisa)
Subject: NDA 203856 CMC Information Request
Date: Wednesday, November 07, 2012 9:32:57 AM

Dear Mr. Wilson,

Please refer to NDA 203856 for Cyclophosphamide Capsules, 25 mg and 50mg. We are reviewing the CMC portion of your NDA and have the following request:

You have submitted two Boehringer Ingelheim Roxane Inc. sites in Columbus, Ohio for Drug Product Manufacturing. Please refer to the submitted batch records and clearly indicate which of the exhibit lots were manufactured at the Wilson Road site and which were manufactured at the Oak Street site.

Please submit your response to your application by COB on November 8, 2012, and provide a courtesy copy of your response to me.

Please acknowledge receipt of this request, and let me know if you have any questions.

Sincerely,

Deborah Mesmer

Deborah Mesmer
Regulatory Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Division of New Drug Quality Assessment (DNDQA1)
Food and Drug Administration
 (b) (6)
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
(301) 796-4023
deborah.mesmer@fda.hhs.gov

From: Randy.Wilson@boehringer-ingenheim.com [mailto:Randy.Wilson@boehringer-ingenheim.com]
Sent: Wednesday, November 07, 2012 9:27 AM
To: Mesmer, Deborah
Cc: Randy.Wilson@boehringer-ingenheim.com; Sarah-A.Smith@boehringer-ingenheim.com
Subject: NDA 203856 Phone Call today
Importance: High

Dear Deborah,

Thank you for the phone call today. Please forward the correspondence concerning NDA 203856 to my attention today as discussed by phone this morning. Please confirm receipt of this email when you receive it.

Best Regards,

Randy Wilson

VP Scientific, Medical and Regulatory Affairs

Roxane Laboratories.

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/s/

DEBORAH M MESMER
12/19/2012



NDA 203856

FILING COMMUNICATION

Roxane Laboratories, Inc.
Attention: Randall Wilson
Vice President, Scientific, Medical and Regulatory Affairs
1809 Wilson Road
Columbus, OH 43228

Dear Mr. Wilson:

Please refer to your New Drug Application (NDA) dated July 3, 2012, received July 3, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cyclophosphamide Capsules, 25 mg and 50 mg.

We also refer to your amendments dated July 17, and August 16, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is May 3, 2013.

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 April 5, 2013.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. The FDA Biopharmaceutics Classification System (BCS) committee has determined that stability data over the physiologic pH range are needed to complete the evaluation of your request for a BCS Class 1 assignation for cyclophosphamide drug substance.

Once the gastric stability data are generated, please submit this information under both IND 112446 and NDA 203856. In your NDA, please also include a comment stating that FDA requested this information to support your BCS based biowaiver request for Cyclophosphamide Capsules. We request this information be submitted within one month. If this is not feasible, please provide your proposal with justification.

2. Please submit the individual publications cited within the Moore (1991) reference which supports the relevant updated labeling statements (e.g., regarding the absolute bioavailability, Mathias (1984) and Wagner and Feneberg (1984) are cited within Moore (1991)).

Please respond only to the above requests for 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.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Lisa Skarupa, Regulatory Project Manager, at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, M.D.
Deputy Director
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research

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/s/

AMNA IBRAHIM
09/17/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 203856 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: none Established/Proper Name: cyclophosphamide Dosage Form: capsules Strengths: 25 mg and 50 mg		
Applicant: Roxane Laboratories, Inc. Agent for Applicant (if applicable):		
Date of Application: July 3, 2012 Date of Receipt: July 3, 2012 Date clock started after UN:		
PDUFA Goal Date: May 03, 2013		Action Goal Date (if different):
Filing Date: September 15, 2012		Date of Filing Meeting: August 17, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only) not applicable		
Proposed indication(s)/Proposed change(s): Cyclophosphamide is an alkylating agent indicated for the treatment of malignant diseases such as certain types of lymphomas and leukemias, neuroblastoma and carcinoma of the breast and is often used in combination with other neoplastic drugs. It is also indicated for carefully selected cases of biopsy proven "minimal change" nephrotic syndrome in children.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard Not applicable <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input checked="" type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products	

Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
--	--

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): 112446

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>				
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>		<p>This is capsule, different formulation.</p>																
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		<p>No patents.</p>
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

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

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

1

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

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

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	Electronic submission.

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

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

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

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

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

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 17, 2012

NDA: NDA 203856

PROPRIETARY NAME: none submitted

ESTABLISHED/PROPER NAME: cyclophosphamide

DOSAGE FORM/STRENGTH: capsule

APPLICANT: Roxane Laboratories, Inc.

PROPOSED INDICATIONS: Cyclophosphamide is an alkylating agent indicated for the treatment of malignant diseases such as certain types of lymphomas and leukemias, neuroblastoma and carcinoma of the breast and is often used in combination with other neoplastic drugs. It is also indicated for carefully selected cases of biopsy proven “minimal change” nephrotic syndrome in children.

These indications are slightly more general than Baxter’s cyclophosphamide indications.

BACKGROUND:

On July 3, 2012, Roxane Laboratories, Inc. resubmitted their application to answer the CMC deficiencies stated in the February 17, 2012 Refuse to File letter. NDA 203856 was originally submitted December 21, 2011. On February 17, 2012, a Refuse to File letter was issued to Applicant which reflected the CMC deficiencies on the stability data used to support their application.

Please refer to the Filing Review dated February 17, 2012 for details on the history of the referenced listed drug Baxter HealthCare NDA 12141 and original December 21, 2011 deficiencies.

During Filing Meeting on August 17, 2012, ONDQA pre-Marketing reviewer Hari Sarker stated that information in this resubmission was sufficient.

The ONDQA/CMC statement placed into the February 17, 2012 Refuse to File letter was:

Six months of long term and accelerated stability data of the drug product are not sufficient to support a commercially viable shelf-life. Also note that as per Good Review Management Principles and Practices for PDUFA Products, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079748.pdf>, all NDAs are to be complete in the original submission. This includes all stability data and corresponding data summaries necessary to establish a shelf life. Information submitted to an NDA subsequent to the original

submission may or may not be reviewed as resources allow.

The Applicant also subsequently addressed (NDA amendments July 17, and August 16, 2012 and IND 112446 submission dated March 12, 2012) the other outstanding issues regarding this original 505b2 application by RLI are:

Regulatory

Reliance on an approved ANDA is not acceptable to support your proposed 505(b)(2) application. You need to identify the NDA that was the basis for submission for the ANDA you have incorrectly cited as the listed drug relied upon to support your proposed 505(b)(2) application. You must also provide a patent certification or statement with respect to each patent listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) for the listed drug upon which you rely (see 21 CFR 314.54(a)(1)(vi)).

Labeling

Submit draft labeling revised as follows:

1. Avoid the following:
 - vague, misleading, or promotional terms, e.g. "significantly", or "potent".
 - arbitrary categories of "mild", "moderate" and "severe" that do not have established definitions.
2. Under Section 4 CONTRAINDICATIONS, use a bullet for each contraindication.
3. Under Section 12.3 Pharmacokinetics, if clinical significant, include information regarding effect of food, drug/drug and drug/food (e.g. dietary supplements, grapefruit juice) PK interactions (including inhibition, induction, and genetic characteristics).

BCS Biowaiver request (reviewed by ONDQA Biopharmaceutics):

Please provide all the information/data supporting your request for a BCS-Class 1 designation for your drug product to your IND 112446, not to your NDA resubmission. Note that the evaluation of the data supporting this request will be done under your IND application.

The following are recommendations:

1. Please provide the dissolution method development report including the complete dissolution data supporting/justifying the proposed testing conditions for the dissolution method.
2. Based on the dissolution requirement for the drug product of BCS-Class 1 category, the proposed acceptance criterion for dissolution ($Q = \text{(b) (4)}$ at (b) (4) minutes) is not acceptable. Please tighten the acceptance criterion accordingly to support a fast dissolving BCS-Class 1 drug product (i.e., $Q = \text{(b) (4)}$ at 15 minutes).

Conclusion on filability of July 3, 2012 resubmission: The CMC data was provided as requested. The Biowaiver request with supporting data was submitted to IND 112446. We received the PLR label of cyclophosphamide with appropriate revisions. The Information Request from the Biopharmaceutics Classification System Review Committee will be placed in the Filing Letter, there are no filing issues.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Lisa Skarupa	Y
	CPMS/TL:	Alice Kacuba	N
Cross-Discipline Team Leader (CDTL)	None determined		
Clinical	Reviewer:	Gerry Sokol	N
	TL:	Patricia Cortazar	N
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	NA	
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	NA	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	NA	
	TL:		
Clinical Pharmacology	Reviewer:	Sarah Schrieber	Y
	TL:	Qi Liu	Y
Biostatistics	Reviewer:	No data submitted	
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	George Chang	N
	TL:	Todd Palmby	Y
Statistics (carcinogenicity)	Reviewer:	NA	

	TL:		
Immunogenicity (assay/assay validation) <i>(for BLAs/BLA efficacy supplements)</i>	Reviewer:	NA	
	TL:		
Product Quality (CMC)	Reviewer:	Josephine Jee	Y
	TL:	Haripada Sarker Nallaperum Chidambaram Sarah Pope Miksinski Debbie Mesmer, RPM	Y Y N Y
Product Quality	Reviewer:	Zedong Dong	Y
	TL	Angelica Dorantes	N
Quality Microbiology <i>(for sterile products)</i>	Reviewer:	NA	
	TL:		
CMC Labeling Review	Reviewer:	NA	
	TL:		
Facility Review/Inspection	Reviewer:	NA	
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	NA	
	TL:		
OSE/DRISK (REMS)	Reviewer:	NA	
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NA	
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	NA	
	TL:	NA	
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: No Clinical data submitted for this 505b2, except references are provided for the clinical sections in the package insert.</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: Not necessary for this 505b2.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: No statistical data submitted.</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p>	<input checked="" type="checkbox"/> Not Applicable

<ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments: The Categorical Exclusion was submitted to the December 21, 2011 submission. No EA consult is needed at this time.</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: However, may need at resubmission.</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: Facility Inspection status submitted by Applicant on January 23, 2012.</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Nallaperum Chidambaram, M.D.</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p>	

Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

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

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

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

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

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

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/s/

LISA M SKARUPA
09/13/2012

From: Sarah-A.Smith@boehringer-ingelheim.com
To: [Skarupa, Lisa](mailto:Skarupa_Lisa); Randy.Wilson@boehringer-ingelheim.com
Subject: RE: Roxane Laboratories Post RTF Teleconference
Date: Thursday, May 31, 2012 9:37:03 AM

Dear Lisa-
That is correct. Thank you for your response.

Sarah

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Thursday, May 31, 2012 9:29 AM
To: Smith,Sarah ROX-US-C; Wilson,Randy ROX-US-C
Subject: RE: Roxane Laboratories Post RTF Teleconference

Dear Sarah and Randy,
I am confirming that Roxane Laboratories is canceling the meeting after accepting the responses. Is that correct?
Please note that should you have any further questions, you can submit them as a meeting request.

Sincerely,
Lisa

From: Sarah-A.Smith@boehringer-ingelheim.com [mailto:Sarah-A.Smith@boehringer-ingelheim.com]
Sent: Wednesday, May 30, 2012 6:26 PM
To: Skarupa, Lisa
Cc: Sarah-A.Smith@boehringer-ingelheim.com
Subject: FW: Roxane Laboratories Post RTF Teleconference

Hello Ms. Skarupa-

I am following up on the below email that you sent to Randy Wilson today. Based on the responses and comments from the Division of Oncology Products 1, RLI does not feel that the meeting scheduled for tomorrow is still needed. Please advise if you need any other information from Roxane Laboratories in order to formally cancel this meeting? Roxane will plan on re-filing our NDA when we have obtained 12 months long term and 6 months stability data on the 3 batches that we have manufactured. If you would like, we can let you know when that stability data will be available and when we will plan on filing this information. I anticipate it will be sometime in the July/August timeframe but can let you know a closer date in the next few days.

As always, we appreciate your help with this.

Take care,

Sarah Smith
Associate Director, Drug Regulatory Affairs and Medical Affairs
Roxane Laboratories Inc.
614-241-4122

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Wednesday, May 30, 2012 10:37 AM
To: Wilson,Randy ROX-US-C
Subject: Roxane Laboratories Post RTF Teleconference

Dear Mr. Wilson,

The attached consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 31, 2012 Teleconference from 3pm to 4pm between Roxane Laboratories and the Division of Oncology Products 1. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact me). **If you choose to cancel the meeting, this document will represent the official record.** If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or change the format of the meeting (e.g., from face to face to telecon). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan/the purpose of the meeting/to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact me to discuss the possibility of including these for discussion at the meeting.

Sincerely,

Lisa

Lisa Skarupa, R.N., M.S.N., A.O.C.N.
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-2219
Fax (301)796-9845
lisa.skarupa@fda.hhs.gov

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/s/

LISA M SKARUPA
05/31/2012

1.0 BACKGROUND

The Applicant, Roxane Laboratories, Inc. (RLI), filed an NDA (NDA 203856) on December 21, 2011 for Cyclophosphamide Capsules, 25mg and 50mg. On February 18, 2012, a "Refusal to File" letter was issued for this 505(b)(2) NDA submission on the basis of incomplete stability data. The purpose of this meeting (teleconference) is that the Applicant would like to obtain clarification regarding this action and to discuss an acceptable path forward.

2.0 DISCUSSION

CMC

Question 1: *RLI proposes to submit 12 months of long-term and 6 months of accelerated stability data for one of the three lots RLI has manufactured as well as submitting 9 months of long-term and 6 months of accelerated stability data for the other two of the three drug products lots made to support a commercial shelf-life of 24 months. Is this proposal acceptable to the FDA?*

FDA Response to Question #1:

No. Less than twelve months of long term stability data of the drug product are not generally sufficient to support a commercially viable shelf-life. Per *Good Review Management Principles and Practices for PDUFA Products*, all NDAs should be complete at the time of submission. This includes all stability data and corresponding data summaries necessary to establish a shelf-life. International Conference on Harmonization (ICH) Q1A (R2) states “long-term testing should cover a minimum of 12 months’ duration on at least three primary batches at the time of submission”. Submit in your NDA 12 months long-term and 6 months accelerated stability data for 3 primary batches of drug substance and drug product.

Regulatory

Question 2: *The FDA has suggested that RLI should reference the original NDA as the listed drug relied upon to support our proposed 505(b)(2) NDA. That NDA (012141) for Cytoxan® tablets, 25mg and 50mg, has been discontinued and the RLI tablet formulation (ANDA 040032) is the current RLD in the 'Orange Book'. RLI would like confirmation from the FDA that referencing a discontinued product as the basis of RLI's 505(b)(2) NDA is indeed acceptable?*

RLI would also like to confirm that the comparison of our Cyclophosphamide Capsules to the RLD (RLI's Cyclophosphamide Tablets) for the BCS 1 bio-waiver request is acceptable?

FDA Response to Question #2: **Yes, reliance on a drug that is listed as discontinued in the Orange Book is acceptable. It should be noted that 21 CFR 314.54 requires identification of the “listed drug for which FDA has made a finding of safety and effectiveness,” and thus an applicant may only rely upon a listed drug that is the subject of an NDA approved under section 505(c) of the FD&C Act (in other words, an application approved under section 505(j) of the Act (i.e., ANDA, generic drug) may not be cited as a listed drug relied upon.**

You must also provide a patent certification or statement with respect to each patent listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) for the listed drug upon which you rely (see 21 CFR 314.54(a)(1)(vi)).

Please consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

Regarding the comparison of Cyclophosphamide Capsules to the RLD (Roxane Laboratories' Cyclophosphamide Tablets) for the purpose of BCS 1 bio-waiver, FDA cannot provide a response at this time since the data supporting BCS 1 designation of cyclophosphamide are under review.

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/s/

LISA M SKARUPA
05/30/2012



NDA203856

MEETING REQUEST GRANTED

Roxane Laboratories, Inc.
Attention: Randall Wilson
Vice President, Scientific, Medical and Regulatory Affairs
1809 Wilson Road
Columbus, OH 43228

Dear Mr. Wilson,

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cyclophosphamide capsules, 25 mg and 50 mg.

We also refer to your submission March 16, 2012, requesting a Type B meeting to discuss the Refuse-to-File letter for your NDA submission dated December 21, 2011. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

Date: May 31, 2012
Time: 3:00 pm to 4:00 pm
Location: Teleconference

CDER participants:

Clinical Team: Robert Justice, M.D., Amna Ibrahim, M.D., Yang-Min Ning, M.D., Gerald Sokol, M.D.

CMC Team: Haripada Sarker, Ph.D., Zedong Dong, Ph.D.

NonClinical Team: Anne Pilaro, Ph.D.; Whitney Helms, Ph.D.

ClinPharm Team: Qi Liu, Ph.D., Safaa Burns, Ph.D.

Please e-mail me any updates to your attendees, at least one week prior to the meeting.

Submit background information for the meeting (three paper copies or one electronic copy to the application and 14 desk copies to me), by May 3, 2012 at four weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by May 3, 2012, we may cancel or reschedule the meeting.

Submit the 14 desk copies to the following address:

Lisa Skarupa, RN, MSN, AOCN, Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research

(b) (6)

10903 New Hampshire Avenue
Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS).*

*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

We usually conduct our meetings to center around your questions, i.e., we don't generally have presentations since all the needed information has been presented in your preparation package. The division does not expect you to introduce any new materials that were not originally presented in your meeting package, as the reviewers will not have sufficient time to review new data/materials.

I will fax/email you our draft responses to your questions after our internal pre-meeting (May 29, 2012); you can then decide if a face-to-face meeting with us is still necessary. If we have a meeting, I will have your questions and our responses on the overheads for discussion/revision. They will serve as the basis for the FDA official minutes of the meeting. Let me know your response ASAP. Below is the tentative list of FDA invitees for the meeting.

Due to our expanding White Oak campus, the Center Director has determined that every meeting needs to have a 10 minute transition period for employees to walk to their next meeting. Our goal is to start the meetings on time and end 10 minutes before the scheduled end of the meeting. For example, if a meeting is scheduled to last an hour, then the discussions will last 50 minutes (the meeting can last the full hour if none of the attendees need to go to another meeting). Please prioritize your questions to optimize our discussion in the allotted time.

If you have any questions, call me at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Lisa Skarupa, R.N., M.S.N., A.O.C.N.
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

LISA M SKARUPA
04/18/2012

From: [Skarupa, Lisa](#)
To: ["randy.wilson@boehringer-ingenelheim.com"](mailto:randy.wilson@boehringer-ingenelheim.com)
Subject: NDA 203856 cyclophosphamide
Date: Saturday, February 18, 2012 5:58:49 AM
Attachments: [RefusetoFile \(NDA203856\).pdf](#)

Dear Mr. Wilson,

Please see attached letter regarding your submitted 505b2 application- NDA 203856.

If you have any questions please do not hesitate to contact us.

Sincerely,
Lisa

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/s/

LISA M SKARUPA
02/18/2012



NDA 203856

REFUSAL TO FILE

Roxane Laboratories, Inc.
Attention: Randall Wilson
Vice President, Scientific, Medical and Regulatory Affairs
1809 Wilson Road
Columbus, OH 43228

Dear Mr. Wilson:

Please refer to your New Drug Application (NDA) dated December 21, 2011, received December 21, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cyclophosphamide Capsules, 25 mg and 50 mg.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

CMC:

Six months of long term and accelerated stability data of the drug product are not sufficient to support a commercially viable shelf-life. Also note that as per Good Review Management Principles and Practices for PDUFA Products, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079748.pdf>, all NDAs are to be complete in the original submission. This includes all stability data and corresponding data summaries necessary to establish a shelf life. Information submitted to an NDA subsequent to the original submission may or may not be reviewed as resources allow.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

Additional Comments:

Regulatory

Reliance on an approved ANDA is not acceptable to support your proposed 505(b)(2) application. You need to identify the NDA that was the basis for submission for the ANDA you have incorrectly cited as the listed drug relied upon to support your proposed 505(b)(2) application. You must also provide a patent certification or statement with respect to each patent listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) for the listed drug upon which you rely (see 21 CFR 314.54(a)(1)(vi)).

Labeling

Submit draft labeling revised as follows:

1. Avoid the following:
 - vague, misleading, or promotional terms, e.g. "significantly", or "potent".
 - arbitrary categories of "mild", "moderate" and "severe" that do not have established definitions.
2. Under Section 4 CONTRAINDICATIONS, use a bullet for each contraindication.
3. Under Section 12.3 Pharmacokinetics, if clinically significant, include information regarding effect of food, drug/drug and drug/food (e.g. dietary supplements, grapefruit juice) PK interactions (including inhibition, induction, and genetic characteristics).

Your response must include updated 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>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

Biopharmaceutics

Please provide all the information/data supporting your request for a BCS-Class 1 designation for your drug product to your IND 112446, not to your NDA resubmission. Note that the evaluation of the data supporting this request will be done under your IND application.

The following are recommendations:

1. Please provide the dissolution method development report including the complete dissolution data supporting/justifying the proposed testing conditions for the dissolution method.
2. Based on the dissolution requirement for the drug product of BCS-Class 1 category, the proposed acceptance criterion for dissolution ($Q = \text{[redacted]}^{(b)(4)}$) is not acceptable. Please tighten the acceptance criterion accordingly to support a fast dissolving BCS-Class 1 drug product (i.e., $Q = \text{[redacted]}^{(b)(4)}$ at 15 minutes).

If you have any questions, call Lisa Skarupa, Regulatory Project Manager, at (301) 796-2219.

Sincerely yours,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ROBERT L JUSTICE
02/17/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 203856 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: none Established/Proper Name: cyclophosphamide Dosage Form: capsules Strengths: 25 mg and 50 mg		
Applicant: Roxane Laboratories, Inc. Agent for Applicant (if applicable):		
Date of Application: December 21, 2011 Date of Receipt: December 21, 2011 Date clock started after UN:		
PDUFA Goal Date: Not applicable/RTF.		Action Goal Date (if different):
Filing Date: February 19, 2012		Date of Filing Meeting: February 3, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only) not applicable		
Proposed indication(s)/Proposed change(s): Cyclophosphamide is an alkylating agent indicated for the treatment of malignant diseases such as certain types of lymphomas and leukemias, neuroblastoma and carcinoma of the breast and is often used in combination with other neoplastic drugs. It is also indicated for carefully selected cases of biopsy proven "minimal change" nephrotic syndrome in children.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard Not applicable <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products	

<input type="checkbox"/> Other (drug/device/biological product)

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

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>		<p>This is capsule, different formulation.</p>																
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1444 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		<p>No patents.</p>
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

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

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

1

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

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

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	Electronic submission.

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

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

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

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

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

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 3, 2012

BLA/NDA/Supp #: NDA 203856

PROPRIETARY NAME: none submitted

ESTABLISHED/PROPER NAME: cyclophosphamide

DOSAGE FORM/STRENGTH: capsule

APPLICANT: Roxane Laboratories, Inc.

PROPOSED INDICATIONS: Cyclophosphamide is an alkylating agent indicated for the treatment of malignant diseases such as certain types of lymphomas and leukemias, neuroblastoma and carcinoma of the breast and is often used in combination with other neoplastic drugs. It is also indicated for carefully selected cases of biopsy proven “minimal change” nephrotic syndrome in children. These indications are slightly more general than Baxter’s cyclophosphamide indications.

BACKGROUND:

History of Innovator: Baxter HealthCare is the innovator to the referenced listed drug (RLD) Cyclophosphamide injection (NDAs 12142, Generic cyclophosphamide injectable (040745) and Tablet 50 mg Cytoxan (NDA 12141). Baxter uses one label for both injectable and Tablet formulations. Prior to Baxter’s ownership of NDAs 12141 and 12142, previous owner Bristol Myers Squibb discontinued marketing tablets on November 2007 (NDA 12141); removal from marketing was not for safety reasons.

Roxane Laboratories, Inc. [from now on referred to as “RLI” in this memo] owns oral tablets 25 mg and 50 mg (ANDA40032). RLI’s oral tablets were approved August 17, 1999 as 505(j). In that letter, it stated “The Division of Bioequivalence has determined your Cyclophosphamide Tablets USP, 25 mg and 50 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Cytoxan® Tablets, 25 mg and 50 mg, respectively, of Bristol Myers Squibb Co. Pharmaceutical Research Institute).”

RLI’s refers to a pre-IND meeting placed under preIND# 112446. On June 10, 2011, Roxane requested a pre-IND Meeting to discuss the waiver of In vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification system in lieu of bioequivalence study to support the change in dosage form (from tablets to capsules). FDA responded July 19, 2011 requesting information be submitted to preIND# 112446:

“If your drug substance/drug product is classified as a Biopharmaceutics Classification System (BCS) Class 1, you may request a waiver of the CFR's requirement to provide *in vivo* bioequivalence data to support the proposed change in formulation from a tablet to a capsule. The multi-media dissolution profile comparison and f2 data supporting your biowaiver request should be provided.

Regarding BCS, note that the BCS Committee at CDER will evaluate the supportive solubility, permeability, gastric stability, and dissolution data and will determine if cyclophosphamide Tablets can be classified as BCS Class 1. To provide the BCS information needed to support your BCS Class 1 request, please follow the recommendations given in the guidance.”

On December 21, 2011 RLI submitted their 505b2 application providing for a new dosage form, from tablet formulation to capsule formulation. Because Baxter's NDA for tablets were removed from marketing, ANDA 40032 became the RLD; Orange Book reflects this. RLI submits their 505b2 application, referencing ANDA 40032, and not Baxter's cyclophosphamide NDA. RLI submitted paragraph II patent certification for the listed drug cyclophosphamide tablets 25mg and 50 mg. There was no clinical data or nonclinical data submitted for this 505b2 application hence, no Financial Disclosure provided. RLI does not request for any exclusivity.

During Filing Meeting on February 3rd 2012, ONDQA pre-Marketing reviewer Hari Sarker recommended Refuse to File. This is based on insufficient stability information to support the commercial viable shelf life that is normally required for 505b2 submissions. In addition, there was a batch's failure in drug dissolution. This was a concern for the BCS committee review process. RLI submitted the request for BCS biowaiver in this 505b2 submission (Section 1.12.5) instead of their IND.

Biopharmaceutics Classification System (BCS) is a regulatory mechanism through which generic companies can obtain a waiver of clinical bioequivalence studies, also called a biowaiver. According to the 2000 FDA BCS Guidance, compounds that are classified as Class I (highly soluble, highly permeable) are eligible for BCS biowaivers. For such compounds, the rate and extent of drug absorption is unlikely to be affected by drug dissolution and/or GI residence time, and *in vivo* bioequivalence studies (for new formulations, etc.) may be waived based on *in vitro* permeability and solubility data. It was concluded that RLI still needs to finalize the requirements for BCS Class 1 (highly soluble, highly permeable) under the IND prior to submitting this 505b2.

The ONDQA/CMC statement placed into the Refuse to File letter is:

Six months of long term and accelerated stability data of the drug product are not sufficient to support a commercially viable shelf-life. Also note that as per Good Review Management Principles and Practices for PDUFA Products, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079748.pdf>, all NDAs are to be complete in the original submission. This includes all stability data and corresponding data summaries necessary to

establish a shelf life. Information submitted to an NDA subsequent to the original submission may or may not be reviewed as resources allow.

Other outstanding issues regarding this original 505b2 application by RLI are:

Regulatory

Reliance on an approved ANDA is not acceptable to support your proposed 505(b)(2) application. You need to identify the NDA that was the basis for submission for the ANDA you have incorrectly cited as the listed drug relied upon to support your proposed 505(b)(2) application. You must also provide a patent certification or statement with respect to each patent listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) for the listed drug upon which you rely (see 21 CFR 314.54(a)(1)(vi)).

Labeling

Submit draft labeling revised as follows:

1. Avoid the following:
 - vague, misleading, or promotional terms, e.g. "significantly", or "potent".
 - arbitrary categories of "mild", "moderate" and "severe" that do not have established definitions.
2. Under Section 4 CONTRAINDICATIONS, use a bullet for each contraindication.
3. Under Section 12.3 Pharmacokinetics, if clinically significant, include information regarding effect of food, drug/drug and drug/food (e.g. dietary supplements, grapefruit juice) PK interactions (including inhibition, induction, and genetic characteristics).

Your response must include updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

BCS Biowaiver request (reviewed by ONDQA Biopharmaceutics):

Please provide all the information/data supporting your request for a BCS-Class 1 designation for your drug product to your IND 112446, not to your NDA resubmission. Note that the evaluation of the data supporting this request will be done under your IND application.

The following are recommendations:

1. Please provide the dissolution method development report including the complete dissolution data supporting/justifying the proposed testing conditions for the dissolution method.

2. Based on the dissolution requirement for the drug product of BCS-Class 1 category, the proposed acceptance criterion for dissolution (Q = (b)(4)) is not acceptable. Please tighten the acceptance criterion accordingly to support a fast dissolving BCS-Class 1 drug product (i.e., Q = (b)(4) at 15 minutes).

Conclusion: Refuse to file on the basis of ONDQA finding inadequate stability data for this 505b2 application.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Lisa Skarupa	Y
	CPMS/TL:	Alice Kacuba	N
Cross-Discipline Team Leader (CDTL)	None determined		
Clinical	Reviewer:	Gerry Sokol	N
	TL:	Amy McKee	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	NA	
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	NA	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	NA	
	TL:		

Clinical Pharmacology	Reviewer:	Sarah Schrieber	Y
	TL:	Qi Liu	Y
Biostatistics	Reviewer:	NA	
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Whitney Helms	N
	TL:	Anne Pilaro	Y
Statistics (carcinogenicity)	Reviewer:	NA	
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	NA	
	TL:		
Product Quality (CMC)	Reviewer:	Haripada Sarker	Y
	TL:	Sarah Pope Miksinski	N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	NA	
	TL:		
CMC Labeling Review	Reviewer:	NA	
	TL:		
Facility Review/Inspection	Reviewer:	NA	
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	NA	
	TL:		
OSE/DRISK (REMS)	Reviewer:	NA	
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NA	
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	NA	
	TL:	NA	
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers: ONDQA Biopharmaceutics	Reviewer: Zedong Dong TL : Chidambaram Nellaperum		Y Y
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: No Clinical data submitted for this 505b2.</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: Not necessary for this 505b2.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

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

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: Did not meet standard 12-month stability data.</p>	<p><input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input checked="" type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: However, may need at resubmission.</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: Facility Inspection status submitted by Applicant on January 23, 2012.</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Amna Ibrahim, M.D.</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input checked="" type="checkbox"/>	<p>The application is unsuitable for filing. Explain why: stability data was inadequate for standard requirements for 505b2 applications.</p>
<input type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input type="checkbox"/>	<p>Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).</p>
<input checked="" type="checkbox"/>	<p>If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).</p>
<input type="checkbox"/>	<p>If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.</p>

<input type="checkbox"/>	
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

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

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

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

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

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

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

/s/

LISA M SKARUPA
02/17/2012



NDA 203856

REFUSAL TO FILE

Roxane Laboratories, Inc.
Attention: Randall Wilson
Vice President, Scientific, Medical and Regulatory Affairs
1809 Wilson Road
Columbus, OH 43228

Dear Mr. Wilson:

Please refer to your New Drug Application (NDA) dated December 21, 2011, received December 21, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cyclophosphamide Capsules, 25 mg and 50 mg.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

CMC:

Six months of long term and accelerated stability data of the drug product are not sufficient to support a commercially viable shelf-life. Also note that as per Good Review Management Principles and Practices for PDUFA Products, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079748.pdf>, all NDAs are to be complete in the original submission. This includes all stability data and corresponding data summaries necessary to establish a shelf life. Information submitted to an NDA subsequent to the original submission may or may not be reviewed as resources allow.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

Additional Comments:

Regulatory

Reliance on an approved ANDA is not acceptable to support your proposed 505(b)(2) application. You need to identify the NDA that was the basis for submission for the ANDA you have incorrectly cited as the listed drug relied upon to support your proposed 505(b)(2) application. You must also provide a patent certification or statement with respect to each patent listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) for the listed drug upon which you rely (see 21 CFR 314.54(a)(1)(vi)).

Labeling

Submit draft labeling revised as follows:

1. Avoid the following:
 - vague, misleading, or promotional terms, e.g. "significantly", or "potent".
 - arbitrary categories of "mild", "moderate" and "severe" that do not have established definitions.
2. Under Section 4 CONTRAINDICATIONS, use a bullet for each contraindication.
3. Under Section 12.3 Pharmacokinetics, if clinically significant, include information regarding effect of food, drug/drug and drug/food (e.g. dietary supplements, grapefruit juice) PK interactions (including inhibition, induction, and genetic characteristics).

Your response must include updated 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>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

Biopharmaceutics

Please provide all the information/data supporting your request for a BCS-Class 1 designation for your drug product to your IND 112446, not to your NDA resubmission. Note that the evaluation of the data supporting this request will be done under your IND application.

The following are recommendations:

1. Please provide the dissolution method development report including the complete dissolution data supporting/justifying the proposed testing conditions for the dissolution method.
2. Based on the dissolution requirement for the drug product of BCS-Class 1 category, the proposed acceptance criterion for dissolution ($Q = \text{[redacted]}^{(b)(4)}$) is not acceptable. Please tighten the acceptance criterion accordingly to support a fast dissolving BCS-Class 1 drug product (i.e., $Q = \text{[redacted]}^{(b)(4)}$ at 15 minutes).

If you have any questions, call Lisa Skarupa, Regulatory Project Manager, at (301) 796-2219.

Sincerely yours,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ROBERT L JUSTICE
02/17/2012

From: [Mesmer, Deborah](mailto:Mesmer,Deborah)
To: ["Sarah-A.Smith@boehringer-ingelheim.com"](mailto:Sarah-A.Smith@boehringer-ingelheim.com)
Subject: NDA 203856
Date: Friday, January 20, 2012 3:16:00 PM
Attachments: [establishments example table.doc](#)

Dear Ms. Smith,

As a follow-up to our phone conversation today, and in preparation for the TCON on Tuesday January 31, 2012, from 13:00 -14:00 ET, I am providing you with an example template for providing manufacturing site information for NDA 203856 in table form.

Please find the example attached, and modify to suit your needs. The example is intended to show format only, and does not necessarily cover all manufacturing responsibilities.

Sincerely,

Debbie Mesmer

Deborah Mesmer

Regulatory Project Manager for Quality

Office of New Drug Quality Assessment (ONDQA)

Division of New Drug Quality Assessment (DNDQA1)

Food and Drug Administration

(b) (6)

10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

(301) 796-4023

deborah.mesmer@fda.hhs.gov

List of All Establishments Involved in the Manufacture of the Finished Product and the Active Pharmaceutical Ingredient for XX.

Drug Substance

Establishment Name	Site Address and Registration Number	Contact Person Information	Responsibilities*	Comments	Ready for Inspection
ABC Lab		Name Phone Fax email	Drug Substance manufacture	DMF 1234	Yes
XYZ Lab			Performs stability and release testing for drug substance	Never Inspected by FDA	Yes

Drug Product

Establishment Name	Site Address and Registration Number	Contact Person Information	Responsibilities*	Comments	Ready for Inspection
DEF Lab		Name Phone Fax email	Drug Product manufacture, stability and release testing (except microbiological testing)		Yes
MNO Lab			Performs microbiological testing for drug product		Yes

*Manufacturing Step(s) or Type of Testing (Establishment function)

The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

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/s/

DEBORAH M MESMER
02/03/2012

MEMORANDUM OF TCON

MEETING DATE: February 1, 2012
TIME: 3:30 – 4:00 p.m.
LOCATION: WO 21/1537
APPLICATION: NDA 203856
DRUG NAME: cyclophosphamide capsules
APPLICANT: Roxane Laboratories, Inc.
TYPE OF MEETING: FDA requested TCON
MEETING CHAIR: Sarah Pope Miksinski, PhD
MEETING RECORDER: Deborah Mesmer

FDA ATTENDEES:

ONDQA

Sarah Pope Miksinski
Haripada Sarker
Amit Mitra
Deborah Mesmer
Zedong Dong

OC/OMPQ

Vipul Dholakia

EXTERNAL CONSTITUENT ATTENDEES:

Sarah Smith, Drug Regulatory Affairs
Matthew Annibaldi, Drug Regulatory Affairs
Robert McElheny, Regulatory Compliance
Mukul Agrawal, Medical Affairs
Tom Mahon, Product Development

BACKGROUND:

NDA 203856 was received on December 21, 2011. On January 17, 2011, Deborah Mesmer telephoned Sarah Smith of Roxane Laboratories to request clarification of manufacturing site responsibilities and a statement of readiness for inspection for the sites.

In an amendment dated January 19, 2011, the applicant submitted an amended 356H form with manufacturing site attachment. The form stated, “The following sites listed below are ready for inspection with the exception of the new (b) (4) on the Wilson Road Campus. Boehringer Ingelheim has been working closely with the District office on the expansion of the Wilson Road Campus for the addition of the (b) (4). The new (b) (4) will be ready for inspection in the second quarter of this year.”

The subject site proposed for drug product manufacturing is:

Boehringer Ingelheim Roxane, Inc.
1810 Wilson Road
Columbus, Ohio 43228

On January 20, 2011, Deborah Mesmer telephoned Sarah Smith to request a teleconference to discuss manufacturing sites for the application. Ms. Smith was also asked to re-submit the manufacturing sites in a tabular format (example was provided by FDA by email) to further clarify the manufacturing responsibilities for each site.

On January 23, 2011, the Applicant submitted a revised table for manufacturing sites. The (b) (4) Wilson Road was listed as ready for inspection in "Q2 of 2012".

The TCON was scheduled for January 31, 2012, and then re-scheduled due to technical difficulties for February 1, 2012.

MEETING OBJECTIVES:

To discuss the readiness for inspection of the site at (b) (4) Wilson Road. This is a potential fileability issue.

DISCUSSION POINTS:

FDA referenced the pre-NDA meeting for the application wherein the Applicant was advised that all sites should be ready for inspection upon submission of the application. The Applicant was advised that the (b) (4) Wilson Road not being ready for inspection at the time of NDA submission was a potential filing issue.

The applicant explained their plan to transfer high containment products from the Oak Street (b) (4) Building. The applicant stated while the site had not yet been inspected, they were working with FDA on scheduling the inspection for another product (the first product) that has been manufactured at the facility. FDA emphasized that we were currently determining fileability for NDA 203856. The applicant clarified that the (b) (4) Wilson Road site is ready for inspection.

DECISIONS (AGREEMENTS) REACHED:

FDA requested that the applicant submit to NDA 203856 a confirmation that all sites are ready for inspection and have been since the day of submission. The applicant agreed to make the submission.

POST-MEETING NOTE:

A submission dated February 2, 2011, provided a revised table of manufacturing sites indicating that the (b) (4) Building was ready for inspection.

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/s/

DEBORAH M MESMER
02/03/2012