

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203856Orig1s000**

**OTHER REVIEW(S)**

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

**Label, Labeling and Packaging Review**

Date: September 5, 2013

Reviewer: Jibril Abdus-Samad, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Cyclophosphamide Capsules  
25 mg and 50 mg

Application Type/Number: NDA 203856

Applicant: Roxane Laboratories, Inc.

OSE RCM #: 2013-1745-1

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## Contents

1	INTRODUCTION .....	1
2	METHODS AND MATERIALS REVIEWED .....	1
2.1	Labels and Labeling .....	1
2.2	Previously Completed Reviews .....	1
3	CONCLUSIONS.....	1
	Appendix.....	2

## **1 INTRODUCTION**

This review evaluates the revised container labels and insert labeling for Cyclophosphamide Capsules for NDA 203856 submitted in response to the Division of Medication Error Prevention and Analysis' comments in OSE Reviews 2012-2531 (dated April 2, 2013) and 2013-1745 (dated August 14, 2013).

## **2 METHODS AND MATERIALS REVIEWED**

### **2.1 LABELS AND LABELING**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted August 30, 2013 (Appendix A)
- Insert Labeling submitted September 5, 2013

### **2.2 PREVIOUSLY COMPLETED REVIEWS**

DMEPA previously reviewed Cyclophosphamide Capsules in OSE Reviews 2012-2531 and 2013-1745, and we looked at the reviews to ensure all our recommendations were implemented. All the revisions to the labels and labeling were implemented.

## **3 CONCLUSIONS**

DMEPA finds the Applicant's revisions to the container labels and insert labeling acceptable.

If you have questions, please contact Frances Fahnbulleh, OSE project manager, at 301-796-0942.

---

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

## APPENDIX

### Appendix A: Container Labels, 25 mg and 50 mg

Each capsule contains 25 mg cyclophosphamide USP (calculated as anhydrous).  
Usual Dosage: See package insert.  
**Swallow capsules whole. Do not open, chew, or crush capsules.**

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).

Dispense in a tight container as defined in the USP/NF.

*Manufactured by:*  
Roxane Laboratories, Inc.  
Columbus, Ohio 43216  
10008218/01 © RLI, 2013

NDC 0054-0382-25 100 Capsules

**CYCLOPHOSPHAMIDE Capsules**

**25 mg**

**CYTOTOXIC AGENT**

Wear gloves when handling container and capsules.

R<sub>x</sub> only

Boehringer Ingelheim  
Roxane Laboratories

3 N  
00540 38225  
4

EXP. LOT

Each capsule contains 50 mg cyclophosphamide USP (calculated as anhydrous).  
Usual Dosage: See package insert.  
**Swallow capsules whole. Do not open, chew, or crush capsules.**

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).

Dispense in a tight container as defined in the USP/NF.

*Manufactured by:*  
Roxane Laboratories, Inc.  
Columbus, Ohio 43216  
10008217/01 © RLI, 2013

NDC 0054-0383-25 100 Capsules

**CYCLOPHOSPHAMIDE Capsules**

**50 mg**

**CYTOTOXIC AGENT**

Wear gloves when handling container and capsules.

R<sub>x</sub> only

Boehringer Ingelheim  
Roxane Laboratories

3 N  
00540 38325  
1

EXP. LOT

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

/s/  
-----

JIBRIL ABDUS-SAMAD  
09/05/2013

TODD D BRIDGES  
09/05/2013

# REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements**

**Application:** NDA\_203856

**Application Type:** 505(b)(2)

**Name of Drug:** Cyclophosphamide Capsules

**Applicant:** Roxane Laboratories, Inc.

**Submission Date:** July 17, 2013

**Receipt Date:** July 17, 2013

## **1.0 Regulatory History and Applicant's Main Proposals**

NDA 203856 was originally submitted December 21, 2011.

On July 3, 2012, Roxane Laboratories, Inc. resubmitted their application in response to the February 17, 2012, Refuse to File letter which outlined CMC deficiencies pertaining to stability data.

On July 17, 2013, Roxane Laboratories, Inc. resubmitted their application in response to the May 3, 2013 Complete Response letter which outlined CMC deficiencies pertaining to data from three registration batches. The July 17, 2013, resubmission was classified as a Class 1 Resubmission.

## **2.0 Review of the Prescribing Information (PI)**

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## **3.0 Conclusions/Recommendations**

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

# Selected Requirements of Prescribing Information (SRPI)

## 4.0 Appendix

---

### Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

---

### Highlights (HL)

#### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:**

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:**

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- NO** 4. White space must be present before each major heading in HL.

**Comment:** *Missing White Spaces.*

**YES**

## Selected Requirements of Prescribing Information (SRPI)

5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

**YES**

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

**YES**

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

### HIGHLIGHTS DETAILS

#### Highlights Heading

**YES**

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

#### Highlights Limitation Statement

**YES**

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

#### Product Title

**YES**

10. Product title in HL must be **bolded**.

Comment: *Product title must include the route of administration(e.g., "for oral use").*

## Selected Requirements of Prescribing Information (SRPI)

### Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:** *The date of Initial US Approval should be the date the drug was first introduced to the US market (i.e., date of the innovator's approval - 1959).*

### Boxed Warning

- N/A** 12. All text must be **bolded**.

**Comment:**

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

**Comment:**

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

**Comment:**

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

**Comment:**

### Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

**Comment:**

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

**Comment:**

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

**Comment:**

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

**Comment:**

### Indications and Usage

## Selected Requirements of Prescribing Information (SRPI)

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

### Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

### Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *Month will have to be updated at the time when this 505b2 will be approved.*

---

## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

## Selected Requirements of Prescribing Information (SRPI)

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading **“FULL PRESCRIBING INFORMATION: CONTENTS”** must be followed by an asterisk and the following statement must appear at the end of TOC: **“\*Sections or subsections omitted from the Full Prescribing Information are not listed.”**

Comment:

---

## Full Prescribing Information (FPI)

### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: **“FULL PRESCRIBING INFORMATION”**.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>

## Selected Requirements of Prescribing Information (SRPI)

<b>8 USE IN SPECIFIC POPULATIONS</b>
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
<b>9 DRUG ABUSE AND DEPENDENCE</b>
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

**N/A**

39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

**Comment:**

**YES**

40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

**Comment:**

**N/A**

41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

**N/A**

42. All text is **bolded**.

**Comment:**

**N/A**

43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

## Selected Requirements of Prescribing Information (SRPI)

N/A

44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

**Comment:**

### Contraindications

YES

45. If no Contraindications are known, this section must state “None”.

**Comment:**

### Adverse Reactions

N/A

46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

**Comment:** Information in this section were not from clinical trial, rather from published literature.

YES

47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

**Comment:** The statement was "The following adverse reactions have been identified from clinical trials or post-marketing surveillance. Because they are reported from a population from unknown size, precise estimates of frequency cannot be made. "

### Patient Counseling Information

N/A

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

**Comment:**

---

-----  
**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  
08/16/2013

CHRISTY L COTTRELL  
08/21/2013

**REGULATORY PROJECT MANAGER LABELING REVIEW  
(PHYSICIAN LABELING RULE)  
Division of Oncology Products 1, DOP1**

**Application Number:** NDA 203856

**Name of Drug:** cyclophosphamide capsules 25 mg and 50 mg

**Applicant:** Roxane Laboratories, Inc.

**Material Reviewed:**

**Submission Date:** July 17, 2013

**Receipt Date:** July 17, 2013

**Background and Summary**

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.

On July 3, 2012, Roxane Laboratories, Inc. resubmitted their application to answer the CMC deficiencies. The package insert was revised based on the modifications listed on the February 17, 2012 letter and resubmitted on July 17, 2012. On May 2, 2013, a Complete Response letter was issued to the Applicant which reflected the CMC deficiencies on the NDA registration batches.

On July 17, 2013, the Applicant resubmitted their application in response to the Complete Response; the resubmitted application was considered a Class 1 Resubmission. The following RPM Labeling Review was based on the comparison between the RLD Package Insert (Baxter's NDA 12142/12141 approved in May 7, 2013) and the revised Roxane Laboratories Package Insert.

14 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/  
-----

LISA M SKARUPA  
08/19/2013

CHRISTY L COTTRELL  
08/21/2013

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

**Label, Labeling, and Packaging Review**

Date: August 14, 2013

Reviewer: Jibril Abdus-Samad, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh  
Division of Medication Error Prevention and Analysis

Deputy Director: Kellie Taylor, PharmD, MPH  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Cyclophosphamide Capsules  
25 mg and 50 mg

Application Type/Number: NDA 203856

Applicant: Roxane Laboratories, Inc.

OSE RCM #: 2013-1745

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## Contents

1	INTRODUCTION .....	1
1.1	Regulatory History .....	1
1.2	Product Information .....	1
2	METHODS AND MATERIALS REVIEWED .....	2
2.1	Selection of Medication Error Cases.....	2
2.2	Literature Search .....	2
2.3	Labels and Labeling .....	3
2.4	Previously Completed Reviews .....	3
3	CONCLUSIONS.....	3
3.1	Comments to the Division.....	3
3.2	Comments to the Applicant.....	4
	Appendices.....	5

## 1 INTRODUCTION

This review evaluates the proposed container labels for Cyclophosphamide Capsules, NDA 203856 for areas of vulnerability that could lead to medication errors.

### 1.1 REGULATORY HISTORY

On December 21, 2011, the Applicant submitted this 505(b)2 NDA for Cyclophosphamide Capsules with the identical characteristics (indication, dosage, and strength) as the tablet formulation. Subsequent to receiving a Refuse to File, the Applicant resubmitted the NDA on July 3, 2012, which received a Complete Response due to product quality issues. On July 17, 2013 the Applicant submitted a Class 1 resubmission, which is the focus of this review.

The Applicant is currently the only manufacturer of a solid-oral dosage form of Cyclophosphamide in the U.S. market, (b) (4)

### 1.2 PRODUCT INFORMATION

The following product information is provided in the July 29, 2013 labeling submission.

- Active Ingredient: Cyclophosphamide
- Indication of Use:

Treatment of 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, and Breast Carcinoma.

Treatment of Nonmalignant Disease: Biopsy proven "minimal change" nephrotic syndrome in children

- Route of Administration: Oral
- Dosage Form: Capsules
- Strength: 25 mg and 50 mg
- Dose and Frequency:

Treatment of Malignant Diseases: 1 mg per kg to 5 mg per kg per day for both initial and maintenance dosing.

Treatment of Nonmalignant Disease: (b) (4)

- How Supplied: Bottles of 100 capsules

- Storage: [REDACTED] (b) (4)
- Container and Closure System: High Density Polyethylene Bottles

## 2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Cyclophosphamide medication error reports (See Appendix A for a description of the FAERS database). We also reviewed the container labels and package insert labeling submitted by the Applicant.

### 2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1.

<b>Table 1: FAERS Search Strategy</b>	
Date	March 13, 2013 (date since last DMEPA review) to August 5, 2013
Drug Names	Cyclophosphamide
MedDRA Search Strategy	Medication Errors HLT Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS search identified 14 cases. None of these cases were relevant to this review because they involved adverse drug reactions unrelated to a medication error or medication errors for other drug products.

### 2.2 LITERATURE SEARCH

We searched PubMed with the search terms, Cyclophosphamide medication errors. Additionally, we searched ISMP publications on August 8, 2013 for additional cases and actions concerning Cyclophosphamide. There was one publication retrieved since our last search on March 13, 2013. The ISMP Medication Safety Alert<sup>1</sup> discussed patients that received lower doses of cyclophosphamide and gemcitabine because the hospital and outside pharmacy did not have a common understanding of the amount of overfill in the intravenous bags that contained the chemotherapy. This issue is not relevant to this Cyclophosphamide Capsule review.

<sup>1</sup> ISMP Medication Safety Alert! Nurse Advise-ERR. June 2013, Volume 11 Issue 6

## 2.3 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>2</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted August 8, 2013 (Appendix B)
- Insert Labeling submitted July 30, 2013

## 2.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously reviewed Cyclophosphamide Capsules in OSE Review 2012-2531 and provided container label recommendations. The aforementioned recommendations (Appendix C) have been included in Section 3.2 of this review (Comments to the Applicant) because the Agency did not conduct labeling negotiations with the Applicant in the previous review cycle.

Additionally, in the previous review, we recommended adding handling instructions on the container labels that are consistent with the proposed insert labeling. The proposed insert labeling, which is now updated based on the Listed Drug, includes instructions to prevent inadvertent exposure to Cyclophosphamide. These instructions advise users to wear gloves when handling bottles containing Cyclophosphamide and to avoid (b) (4) chewing, or crushing the capsules.

## 3 CONCLUSIONS

DMEPA concludes that the proposed container labels can be improved to promote the safe use of the product. In Section 3.2 (Comments to the Applicant), we include our recommendation to include handling instructions on the container labels with recommendations from OSE Review 2012-2531 that were not conveyed to the Applicant.

### 3.1 COMMENTS TO THE DIVISION

DMEPA provides the following recommendations for the insert labeling for consideration by the review division prior to approval of this NDA.

A. Preparation, Handling and Administration – section 2.3

Revise the sentence, “To prevent inadvertent exposure to the active substance, the cyclophosphamide capsules should not be (b) (4) chewed, or crushed,” to read:

To prevent inadvertent exposure to the active substance, the cyclophosphamide capsules should be swallowed whole. The capsules should not be opened, chewed, or crushed.

---

<sup>2</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

B. Patient Counseling Information – section 17

Revise the statement “Do not <sup>(b) (4)</sup>, chew, or crush capsules” to read:

Do not open, chew, or crush capsules.

If you have questions or need clarifications, please contact Frances Fahnbulleh, OSE project manager, at 301-796-0942.

**3.2 COMMENTS TO THE APPLICANT**

DMEPA recommends the following comments be implemented prior to approval.

A. Container Labels, 25 mg and 50 mg

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.

## **APPENDICES**

### **Appendix A. Database Descriptions**

#### **FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

**Appendix B:** Container labels, 25 mg and 50 mg capsules



**Appendix C:** Container Label Recommendations from OSE Review 2012-2531 not conveyed to the Applicant

DMEPA recommends the following comments be implemented.

A. Container Labels, 25 mg and 50 mg

1. Delete the following statement from the left side panel.

 (b) (4)

2. 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.

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

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

/s/  
-----

JIBRIL ABDUS-SAMAD  
08/14/2013

TODD D BRIDGES  
08/14/2013

KELLIE A TAYLOR  
08/14/2013

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

**Label Review**

Date: April 2, 2013

Reviewer: Jibril Abdus-Samad, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh  
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Cyclophosphamide Capsules  
25 mg and 50 mg

Application Type/Number: NDA 203856

Applicant: Roxane Laboratories, Inc.

OSE RCM #: 2012-2531

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## Contents

1	Introduction.....	1
1.1	Regulatory History.....	1
1.2	Product Information.....	1
2	Methods and Materials Reviewed.....	2
2.1	Selection of Medication Error Cases.....	2
2.2	Literature Search.....	3
2.3	Labels and Labeling.....	3
2.4	Previously Completed Reviews.....	3
3	Integrated Summary of Medication Error Risk Assessment.....	4
3.1	Handling Instructions on Container Labels.....	4
3.2	Storage Information.....	5
3.3	Usual Dosage Statement.....	6
4	Conclusions and Recommendations.....	6
4.1	Comments to the Division.....	6
4.2	Comments to the Applicant.....	6
	References.....	7
	Appendices.....	7

## 1 INTRODUCTION

This review evaluates the proposed container labels for Cyclophosphamide Capsules, NDA 203856 for areas of vulnerability that could lead to medication errors.

### 1.1 REGULATORY HISTORY

The listed drug for this application, Cytoxan (Cyclophosphamide) Tablets (NDA 012141), was approved November 16, 1959; however, Baxter no longer markets the tablets. The Applicant for this NDA (Roxane) currently markets Cyclophosphamide Tablets (25 mg and 50 mg) under ANDA 040032. On December 21, 2011, the Applicant submitted this 505(b)2 NDA for approval of Cyclophosphamide Capsules with the identical characteristics (indication, dosage, and strength) as the tablet formulation. Subsequent to receiving a Refuse to File, the Applicant resubmitted the NDA on July 3, 2012.

Additionally on December 20, 2012, the Applicant submitted information about the new manufacturing site in response to an information request from the Office of New Drug Quality and Assessment (ONDQA). Within the response, the Applicant provided the following rationale for introduction of the Cyclophosphamide Capsules (b) (4)

- continue to provide exposure protection to end-users.
- provide a more stable product (b) (4)
- closing of the current facility (b) (4)

Furthermore, the Applicant is the only manufacturer of a solid-oral dosage form of Cyclophosphamide for the U.S. market (b) (4)

Moreover, the Listed Drug NDA 012141 (Baxter) is currently under review at the Agency for a labeling supplement for Physician Labeling Rule (PLR) conversion. Upon approval of the supplement, the Agency will request the Applicant for this application (NDA 203856) update their insert labeling to comply with the new PLR format. Thus, DMEPA will not comment on the insert labeling in this review.

### 1.2 PRODUCT INFORMATION

The following product information is provided in the November 30, 2012 submission.

- Active Ingredient: Cyclophosphamide
- Indication of Use:

Treatment of 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, and Breast Carcinoma.

Treatment of Nonmalignant Disease: Biopsy proven “minimal change” nephrotic syndrome in children

- Route of Administration: Oral
- Dosage Form: Capsules
- Strength: 25 mg and 50 mg
- Dose and Frequency:

Treatment of Malignant Diseases: 1 mg per kg to 5 mg per kg per day for both initial and maintenance dosing.

Treatment of Nonmalignant Disease: [REDACTED] (b) (4)

- How Supplied: Bottles of 100 capsules
- Storage: [REDACTED] (b) (4)
- Container and Closure System: High Density Polyethylene Bottles

## 2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS database for Cyclophosphamide medication error reports. We also reviewed the Cyclophosphamide labels submitted by the Applicant.

### 2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 1.

<b>Table 1: FAERS Search Strategy</b>	
Date	January 4, 2013 until March 13, 2013 (date since last DMEPA review to present)
Drug Names	Cyclophosphamide
MedDRA Search Strategy	Medication Errors HLT Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database searches strategy yielded zero cases.

## **2.2 LITERATURE SEARCH**

We searched PubMed with the search terms, Cyclophosphamide medication errors. Additionally, we searched ISMP publications on March 13, 2013 for additional cases and actions concerning Cyclophosphamide. We retrieved a few articles from the ISMP Newsletters that consisted of the following:

- Description of a medication error secondary to the ordering physician's use of a trailing zero when prescribing Cyclophosphamide for a non-oncology indication.
- Discussion of the differences between the lyophilized and sterile powder versions of Cyclophosphamide.
- Discussion of an overdose of Cyclophosphamide from 1994 that helped spark the modern patient safety movement.
- Discussion of wrong drug errors due to container labels and carton labeling of Cyclophosphamide produced by a different manufacturer.
- Discussion of the dangers of investigational drug name abbreviations and acronyms.

## **2.3 LABELS AND LABELING**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted March 14, 2013 (Appendix B)
- Currently marketed Container Labels for Cyclophosphamide Tablets ANDA 040032 (Appendix C)

## **2.4 PREVIOUSLY COMPLETED REVIEWS**

In OSE Review 2012-3020, dated March 7, 2013, DMEPA provided comments for Physician Labeling Rule conversion of the listed drug Cyclophosphamide NDA 012141. Additionally, the review noted a wrong strength medication error that has relevance to this review. The medication error involved a patient that was underdosed for 9 days due to receiving Cytoxan 25 mg tablets instead of 50 mg tablets. The report notes the lack of bar coding contributed to this error. No patient outcomes were reported. This error involved a different manufacturer and the container labels for product under this review contain bar codes and adequate strength differentiation.

---

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

### 3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

Review of the proposed labels identified deficiencies in communicating proper handling and storage instructions.

#### 3.1 HANDLING INSTRUCTIONS ON CONTAINER LABELS

The container labels lacks handling instructions to inform end-users such as healthcare providers (HCP) and caregivers of proper handling to prevent exposure to the contents of the capsules. Similar to the currently marketed Cyclophosphamide Tablets (ANDA 040032), the container labels contain the words, *Cytotoxic Agent*, on the principal display panel and the insert labeling contains handling instructions. However, these methods of communicating proper handling are deficient for the following reasons:

- Some end-users, such as patients, caregivers, and pharmacy technicians, may not know the words *Cytotoxic Agent* are intended to communicate specific handling instructions. This is more of a concern because Cyclophosphamide is indicated for non-oncologic indications (nephrotic syndrome in pediatric patients) and thus, end-users unfamiliar with handling cytotoxic agents may interact with the product incorrectly.
- The handling instructions are located in the insert labeling rather than at the point of interaction (container label) between the end-user and the product.

Table 2: Handling instructions comparison

Product	Cyclophosphamide Capsules	Cyclophosphamide Tablets
NDA	203856 (proposed)	012141 (Listed Drug)
Handling Instructions	Care should be exercised in the handling of Cyclophosphamide Capsules. Cyclophosphamide Capsules should not be opened or crushed. If capsules are accidentally opened or damaged, rigorous precautions should be taken (b) (4)	To minimize the risk of dermal exposure, always wear impervious gloves when handling bottles containing cyclophosphamide tablets. This includes all handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration.

From the perspective of HCPs and caregivers, opening or damaging the capsules increases the likelihood of exposure and absorption of the contents of the capsule via inhalation, contact with the skin, or mucous membranes. Thus, patients should be instructed to swallow capsules whole to limit exposure of the capsule contents to HCP and caregivers. Additionally, HCP and caregivers should be instructed to wear gloves during routine handling to limit exposure. We note the Applicant proposes use of gloves (b) (4) to avoid exposure in case of breakage of capsules. This proposed handling instructions has not been discussed with the team due to the aforementioned reasons of PLR conversion of the Listed Drug. On March 28, 2013, DMEPA emailed the reviewers from Clinical, Office of New Drug Quality Assessment, Clinical Pharmacology, and Non-Clinical for this application requesting their perspective on the following questions:

- Is there evidence to suggest the need for gloves (b) (4) for routine handling of Cyclophosphamide Capsules?
- Who is the targeted audience for the warning to avoid inhalation, contact with the skin, or mucous membranes and to use gloves (b) (4)?

At the time of this review, we await a response from the team. However, at minimum, DMEPA recommends utilizing the handling instructions from the listed drug, Cyclophosphamide tablets, which recommends use of gloves when handling the bottles in general. Moreover, we recommend incorporating handling instructions on the container labels that are consistent with the finalized handling instructions in the Cyclophosphamide capsules insert labeling.

Furthermore, we recognize the handling and administration statements may be covered by pharmacy labels or the capsules may be dispensed in a separate bottle. However, the handling and administration instructions will be reinforced to HCPs through these statements as well as to the patients and caregivers via drug information literature dispensed by the pharmacy.

### **3.2 STORAGE INFORMATION**

The storage information lacks the following:

- a recommended temperature range.
- presentation of the temperature range in the usual format that states the recommended temperature range followed by any temperature excursions permitted.

DMEPA defers to the Office of New Drug Quality Assessment in determination of the appropriate storage conditions.

### 3.3 USUAL DOSAGE STATEMENT

The second sentence following the usual dosage statement, (b) (4)

does not provide useful information for HCPs. This statement applies to all prescription (Rx Only) drug products, and therefore is not necessary for this Cyclophosphamide label. This space on the label can be used for other helpful information necessary to help ensure safe use of Cyclophosphamide.

## 4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed container labels can be improved to promote the safe use of the product.

### 4.1 COMMENTS TO THE DIVISION

DMEPA provides the following comment for consideration by the review division prior to approval of this NDA.

#### A. Handling Instructions

We recommend incorporating handling instructions on the container labels that are consistent with the finalized handling instructions in the Cyclophosphamide capsules insert labeling. This will be discussed during the planned labeling meetings.

#### B. Storage Conditions Statement

ONDQA should determine the proposed storage condition statement and format in the package insert and on the container labels is appropriate.

If you have questions or need clarifications, please contact Francis Fahnbulleh, OSE project manager, at 301-796-0942.

### 4.2 COMMENTS TO THE APPLICANT

DMEPA recommends the following comments be implemented.

#### A. Container Labels, 25 mg and 50 mg

1. Delete the following statement from the left side panel.

(b) (4)

2. 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.

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

## **REFERENCES**

Abdus-Samad, Jibril. OSE Review 2012-3020 Cyclophosphamide Labeling. March 7, 2013.

## **APPENDICES**

### **Appendix A:**

#### **FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

**Appendix B:** Container Labels, 25 mg and 50 mg capsules



**Appendix C:** Currently marketed Container Labels, 25 mg and 50 mg tablets

Usual Dosage: See package insert for complete prescribing information. Must not be prescribed without thorough knowledge of dose, indications and toxicity as contained in accompanying literature.

Storage at or below 25°C (77°F) is recommended; this product will withstand brief exposure to temperatures up to 30°C (86°F), but should be protected from temperatures above 30°C (86°F).

Dispense in a tight container as defined in the USP/NF.

**TABLETS IDENTIFIED 54 630**  
Roxane Laboratories, Inc.  
Columbus, Ohio 43216

NDC 0054-4129-25 100 Tablets  
**CYCLOPHOSPHAMIDE**  
Tablets USP  
**25 mg**  
**CYTOTOXIC AGENT**

Each tablet contains 25 mg cyclophosphamide USP (calculated as anhydrous).  
**R<sub>x</sub> only**

Boehringer Ingelheim  
Roxane Laboratories

3 N  
0054-4129-25  
1

EXP. LOT

4152005/03  
© RLI, 2010

Usual Dosage: See package insert for complete prescribing information. Must not be prescribed without thorough knowledge of dose, indications and toxicity as contained in accompanying literature.

Storage at or below 25°C (77°F) is recommended; this product will withstand brief exposure to temperatures up to 30°C (86°F), but should be protected from temperatures above 30°C (86°F).

Dispense in a tight container as defined in the USP/NF.

**TABLETS IDENTIFIED 54 980**  
Roxane Laboratories, Inc.  
Columbus, Ohio 43216

NDC 0054-4130-25 100 Tablets  
**CYCLOPHOSPHAMIDE**  
Tablets USP  
**50 mg**  
**CYTOTOXIC AGENT**

Each tablet contains cyclophosphamide USP (calculated as anhydrous) 50 mg.  
**R<sub>x</sub> only**

Boehringer Ingelheim  
Roxane Laboratories

3 N  
0054-4130-25  
7

EXP. LOT

4152000/02  
© RLI, 2007

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

/s/  
-----

JIBRIL ABDUS-SAMAD  
04/02/2013

TODD D BRIDGES  
04/02/2013

SCOTT M DALLAS  
04/02/2013

# **REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)**

## **Division of Oncology Products 1, DOP1**

**Application Number:** NDA 203856

**Name of Drug:** cyclophosphamide capsules 25 mg and 50 mg

**Applicant:** Roxane Laboratories, Inc.

### **Material Reviewed:**

**Submission Date:** July 17, 2012

**Receipt Date:** July 17, 2012

### **Background and Summary**

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.

On July 3, 2012, Roxane Laboratories, Inc. resubmitted their application to answer the CMC deficiencies. However, the package insert was not submitted. The package insert was revised based on the modifications listed on the February 17, 2012 letter. The proposed package insert will be reviewed by all disciplines; there are only two RPM comments of this package insert at this time.

14 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/  
-----

LISA M SKARUPA  
09/09/2012