

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203856Orig1s000**

**CHEMISTRY REVIEW(S)**

**NDA 203856**

**Cyclophosphamide Capsule  
25mg and 50 mg**

**Roxane Laboratories, Inc.**

**Josephine Jee**

**Office of New Drug Quality Assessment**

**For the Division of Drug Oncology Products 1**

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# Chemistry Review Data Sheet

1. NDA 203856 (Resubmission No. 2)

2. REVIEW # 2

3. REVIEW DATE: 30-AUG-2013

Date Assigned: 17-JUL-2013

4. REVIEWER: Josephine Jee

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	21-DEC-2011
Amendment – Pediatric Waiver	11-JAN-2012
Amendment (Responsibility of each Facility)	19-JAN-2012
Amendment – Update of Facilities	23-JAN-2012
Amendment – Inspection Site Ready to Inspect	02-FEB-2012
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Amendment - Response to IR (b) (4) Res. Solv.)	16 JAN-2013
Amendment – Clarification of CBE-30 Plan for HCO Site Changes	22-FEB-2013
Amendment - IND reference to application	12-MAR-2013
Amendment – Submission of Final Printed Labeling (Container Labels)	14-MAR-2013
Amendment – IR Responses	19-MAR-2013
Amendment - Teleconference Response (21-MAR-2013 T-con)	25-MAR-2013

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original (CMC) – Resubmission to respond to C/R dated 03-MAY-2013	17-JUL-2013
Amendment – Revised Labeling & Inspection Status	30-JUL-2013
Amendment – Revised Labeling	08-AUG-2013
Amendment – Revised Labeling	19-AUG-2013
Amendment - Revised Labeling	26-AUG-2013
Amendment - Revised Labeling	30-AUG-2013

## Chemistry Review Data Sheet

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Roxane Laboratories, Inc. (Boehringer Ingelheim)  
Address: 1809 Wilson Rd  
Columbus, OH 43228  
Representative: Randall Wilson  
Vice President, Scientific, Medical and Regulatory Affairs  
Telephone: 614-272-4799

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A  
b) Non-Proprietary Name (USAN): Cyclophosphamide  
Code Name/# (ONDC only):  
c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3,5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2), Cytosan® Tablets, 25 mg and 50 mg, NDA 12-141.

10. PHARMACOL. CATEGORY: Alkylating Agent (nitrogen mustard) with antineoplastic and immunosuppressant properties

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 25 mg, and 50 mg

13. ROUTE OF ADMINISTRATION: Orally

14. Rx/OTC DISPENSED:  Rx  OTC

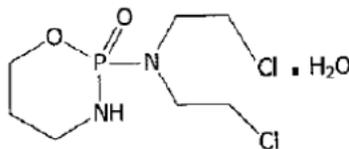
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(+)-2-[Bis (2-chloroethyl) amino] tetrahydro-2H-1,3,2,-oxazaphosphorine 2-oxide, monohydrate



Empirical formula is:  $C_7H_{15}Cl_2N_2O_2P \cdot H_2O$

Molecular weight: 279.1

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

**A. Supporting DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS <sup>3</sup>
(b) (4)	II		(b) (4)	3	Adequate	28-FEB-2013	J.Jee
	III		3	Adequate	07-MAR-2003	J. Salemme	
	III		3	Adequate	20-MAR-2013	J.Jee	
	III		3	Adequate	10-SEP-2012	Nina Ni	
	III		3	Adequate	14-MAY-2012	Z. Dong	
	III		3	Adequate	14-FEB-2012	G. Holbert	
			3	Adequate	16-FEB-2012	G. Holbert	
			3	Adequate	21-MAR-2012	G. Holbert	

Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

<sup>3</sup> Include reference to location in most recent CMC review

**B. Other Supporting Documents:**

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
ANDA	Boehringer/Roxane	ANDA 040032	Approved	17-AUG-1999	This ANDA is approved for Cyclophosphamide Tablets, 25 mg and 50 mg
IND		IND 112446	Approved	15-MAR-2013	Cyclophosphamide Capsules

**C. Related Documents:**

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
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## Chemistry Review Data Sheet

NDA	12141	Bristol-Myers Squibb	This application served as the RLD for Cyclophosphamide Tablets, 25 mg and 50 mg, this application was approved on 16-NOV-1959.
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## 18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				No statistical analysis of drug product stability data deemed necessary.
EES	Site inspections	25-JUL-2013	M. RAMANADHAM	Acceptable. Overall OC recommendation dated 08-JAN-2013
Pharm/Tox	Drug substance, drug product impurity qualification (organic and inorganic)	19-MAR-2013 & 23-AUG-2013	G. Chang/T. Palmby	Acceptable. Acceptance criteria for (b) (4) and unspecified impurity.
Biopharm	<i>In-vivo</i> Bioequivalence Waiver	14-MAR-2013 & 20-AUG-2013	Z. Dong	The <i>in-vivo</i> bioequivalence is granted and the recommendation is approval.
OSE/DMEPA	Labeling consult	14-AUG-2013	J. Abdus-Samad	Review dated 14-AUG-2013; Refer to this Review for DMEPA comments.
Methods Validation	N/A			Method validation is not requested as per ONDQA criteria.
EA	Environmental Assessment	19-MAR-2013	J.Jee	Acceptable
Microbiology				No microbiology evaluation deemed necessary, since the drug product is a solid dosage form.

# The Chemistry Review for NDA 203-856

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The NDA is recommended for approval from Chemistry, Manufacturing, and Controls perspective.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

### II. Summary of Chemistry Assessment

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### 1. Drug Substance

The active ingredient is cyclophosphamide. It is manufactured by (b) (4).  
(b) (4) Detailed information on the drug substance is referenced to (b) (4). This DMF was reviewed on 28-FEB-2013 and found to be adequate. Note that (b) (4).

Cyclophosphamide is included in the current USP. Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. Cyclophosphamide is a white crystalline powder that is soluble in water, freely soluble in alcohol and slightly soluble in ether.

The drug substance specification proposed in this NDA meet all the specifications in the current USP Monograph for Cyclophosphamide. These tests include: (1) Description, (2) Identification (Raman Spectroscopy (alternate ID test), Infrared, HPLC), (3) Water, (4) pH, (5) Heavy Metals, (6) Limit of (b) (4), (7) Limit of Degradation Products (Related compounds (b) (4), and Any specified Impurity), (8) Limit of (b) (4), (9) Limit of (b) (4), (11) Residual Solvents (b) (4), (b) (4), (b) (4), (12) Assay, and (13) Related Substances (b) (4), Any Unspecified Impurity and Total Impurity).

In addition to the impurities identified in the current USP under "Limit of Degradation Products", the Applicant has identified two additional known impurities and one unknown impurity under the category "Related Substances". The proposed acceptance criteria for the related substances meet ICHQ3B. The acceptance criteria for Related Substances and Residual Organic Solvents (not listed in ICH Q3C) were consulted with T. Palmby, Ph.D, and G. Chang, Ph.D., Pharm/Tox Reviewers who recommended that the proposed specifications are acceptable.

## Executive Summary Section

Based on the stability data for drug substance, (b) (4) retest period is granted when cyclophosphamide API is stored in the proposed packaging conditions at (b) (4)

***There are no changes in the Cyclophosphamide Drug Substance submitted in the 17-JUL-2013 Submission.***

**2. Drug Product**

The drug product is an immediate release capsule dosage form. The capsules are formulated in two different strengths: 25 mg and 50 mg.

Cyclophosphamide Capsule, 25 mg is described as blue/blue opaque capsule with "54 006" printed in black ink on the capsule body, containing white to off-white powder.

Cyclophosphamide Capsule, 50 mg is described as blue/blue opaque capsule with "54 881" printed in black ink on the capsule body, containing white to off-white powder. They are packaged in HDPE bottles.

The inactive ingredients are USP/NF materials, Pregelatinized Starch, NF, and Sodium Steryl Fumarate, NF, with the exception of hard gelatin capsules, (b) (4)

The critical formulation development efforts were focused in the selection of suitable (b) (4) (b) (4). The capsules are manufactured as a (b) (4)

The critical parameters (b) (4)

all these parameters directly affect the dissolution, content uniformity, and the amount of degradants in DP.

One specified degradant/impurity (identified in USP Monograph for Cyclophosphamide Drug Substance) is identified in the drug product. Since, there is no compendial monograph for Cyclophosphamide Capsule and there is no approved cyclophosphamide capsule, the recommendation for acceptable levels of known and unknown impurities in cyclophosphamide capsule would be based on ICHQ3B qualifications limits. The acceptance criteria of degradants and residual organic solvents were consulted with Drs. T. Palmby and G. Chang, Pharm/Tox Reviewers. Please refer to the Pharmacology/Toxicology review for additional information regarding impurity qualification.

The tests for the drug product include: (1) Description, (2) Identification (HPLC), (3) Dissolution, (4) Uniformity of Dosage Forms, (5) Assay, (6) Degradation Products (b) (4), and Single Largest Degradant, and Total Degradants), and (7) Residual Solvents.

Primary stability results were submitted on 03-JUL-2012 for the proposed strengths, 25 mg capsules (3 lots) and 50 mg capsules (3 lots), at 25°C/60% RH (12 months) and 40°C/75% RH (6 months) storage conditions.

## Executive Summary Section

The reported stability results of one lot of 25 mg and one lot of 50 mg capsules (b) (4) (b) (4) did not meet acceptance criteria for dissolution and degradation products (unspecified degradation products) testing. Based on the preliminary studies, BIRLI stated on 25-MAR-2013 Submission that these results were observed in only two batches out of a total of six batches tested and the root cause appears to be specific Lot #10040039 of API used (b) (4). Further results of this study were provided as an amendment to the NDA on April 29, 2013. This Amendment was reviewed and it was concluded that the applicant did not adequately address the issues discussed on 25-MAR-2013; see Memorandum dated 30-APR-2013. Therefore, based on the above unresolved issues a Complete Response Letter was issued dated 03-MAY-2013.

On 14-MAY-2013, Roxane requested to obtain agreement of filing strategy taking into consideration the potential drug shortage issues due to the closure of Oak street manufacturing facility. DOP1 met on 14-JUN-2013 and recommended that Roxane should submit the appropriate stability data at long term and accelerated storage conditions for batches manufactured at the Wilson Road HCO facility.

On June 18, 2013, Teleconference (Post Action – Complete Response) between RLI and FDA (A. Al Hakim, J. Jee, and L. Skarupa) discussed RLI's concern of the acceptability of less than 12 months stability data for batches manufactured at HCO. FDA indicated that this is an exception due to the potential of "Drug Shortage" issues. However, the conditions are that RLI must submit the remaining data at the intervals of (0, 3, 6, 9, 12, and 24 M) in the Annual Reports. It was also decided 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 at that time.

On 17-JUL-2013, Roxane submitted two batches for each of the strengths (25 mg and 50 mg capsules) manufactured at the Wilson Road (HCO) facility at 25°C/60% RH, 3M; 30°C/65% RH, 3 months; and 40°C/75% RH, 3 months, storage conditions. In addition to the new batches manufactured at HCO, the applicant submitted updated stability for up to 24 months for batches that were submitted on 03-JUL-2012 Submission. These submitted dissolution data were consulted with Z. Dong, Ph.D., BioPharm Reviewer, on 13-AUG-2013. On 13-AUG-2013, Dr. Dong recommended "The dissolution results for the new stability data are within DP specification, even though some are stage 2 testing for 12 units." Refer to Biopharm Review.

Based on the stability studies provided and related data, an expiration period of **24 months** is granted.

**B. Description of How the Drug Product is Intended to be Used**

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.

## Executive Summary Section

**C. Basis for Approvability or Not-Approval Recommendation**

A detailed pharmaceutical development report and manufacturing process descriptions were provided in the NDA for the drug substance (DMF (b)(4)) and drug product. Adequate data have been provided to ensure the quality of the drug substance and drug product in the 17-JUL-2013 Submission.

The CMC revisions of the package insert have been incorporated into the revised labeling during the labeling negotiations of the NDA. The revised container labels and labeling, as were amended by the applicant on 30-JUL-2013, and modified on 08-AUG-2013, 19-AUG-2013, 26-AUG-2013, and 30-AUG-2013. The 26-AUG-2013 labeling version needed to add "Manufactured by" before the name of the manufacturer. On 30-AUG-2013, Roxane submitted acceptable labels and labeling. An overall acceptable recommendation from the Office of Compliance was issued dated 25-JUL-2013.

**Background Information**

The CMC information of the drug substance was referenced to DMF (b)(4). This DMF was reviewed on 28-FEB-2013 and found to be adequate.

A detailed pharmaceutical development report was submitted to the NDA. The drug product was developed as an immediate release capsule dosage form. The capsules were formulated in two different strengths: 25 mg and 50 mg. Critical parameters and critical attributes were identified.

On 04-JAN-2013, Roxane agreed to change the acceptance criteria for the Dissolution to Q of (b)(4) in 15 min. In this same communication, Roxane stated, in part, "During the course of testing, analysts observed that the (b)(4) for two lots (4000592B and 4000591) (b)(4). As assessment was made that the (b)(4) (b)(4). A closer examination of the root cause behind the (b)(4) is currently on going."

On 21-MAR-2013, a Teleconference between the Agency and BIRLI to discuss out of specifications dissolution and degradation products results in the lots cited above. BIRLI responded on 25-MAR-2013 Amendment and stated in part "The investigation of the two additional lots suggested the API is the most probable root cause." A commitment was made by BIRLI to continue to identify the critical attribute(s) of the drug substance and ensure suitable controls are in place. BIRLI expects the results of this study by April 30, 2013.

The primary stability batches submitted were manufactured at the proposed commercial manufacturing located at 330 Oak Street, Columbus, Ohio. The applicant proposed to close this site and move to the new commercial facility located at 1809 Wilson Road, Columbus, Ohio. The Agency did not agree to have 1809 Wilson Road facility submitted in this current NDA submission (03-JUL-2012), since the registration batches were manufactured at 330 Oak Street facility; refer to communications dated 08-NOV-2012 (clarification of facilities). On 12-DEC-2012, BIRLI proposed to remove 1809 Wilson Road facility from the current NDA submission. On 22-FEB-2013, BIRLI proposed to submit a CBE-30 Supplemental NDA for the 1809 Wilson Road facility; the acceptability of the CBE-30 will be recommended by the Post-Marketing Branch.

## Executive Summary Section

The Office of Compliance has issued an overall “acceptable” recommendation for each facility used for manufacturing and control of drug substance and drug product on 25-JUL-2013.

The CMC revisions of the package insert have been incorporated into the revised labeling during the labeling negotiations of the NDA. The revised container labels and carton labeling, as amended by the applicant on 30-JUL-2013, and modified on 08-AUG-2013, 19-AUG-2013, 26-AUG-2013 and on 26-AUG-2013. On 30-AUG-2013, the applicant submitted acceptable container labels and package insert labeling from CMC perspective.

The following CMC/DMEPA recommendations were made and sent to RLI:

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.”

On 26-AUG-2013, RLI submitted the recommended changes and they are found acceptable. However, RLI did not have the phrase: “Manufactured by or Distributed by” to identify the responsibility of Roxane Laboratories, Inc. Roxane further revised the labels and labeling and submitted acceptable labels and labeling on 30-AUG-2013.

### III. Administrative

This NDA was submitted in electronic (labeling section only) as a 505(b)(2) application. A Quality Overall Summary is included in the application.

A. Reviewer’s Signature

See electronic signatures in DARRTS.

B. Endorsement Block

See electronic signatures in DARRTS

C. CC Block

See electronic signatures in DARRTS

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/s/  
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JOSEPHINE M JEE  
09/04/2013

ALI H AL HAKIM  
09/04/2013

## CHEMISTRY REVIEWER MEMORANDUM

**To:** NDA 203856  
**From:** Josephine Jee., CMC Reviewer, ONDQA  
**Thru:** Ali Al Hakim, Ph.D., Chief, Branch II  
**Date:** 30-APR-2013  
**Drug:** Cyclophosphamide Capsules  
**NDA Applicant:** Roxane Laboratories, Inc.  
**Route of administration:** Capsules  
**Strength:** 25 mg and 50 mg  
**Subject:** Amendment erroneously dated 26-MAR-2013  
(Received by FDA Document Room on 29-APR-2013)

The above submission did not adequately address the CMC outstanding issues discussed with the sponsor on 25-MAR-2013. These issues are related to one NDA batch that did not pass the proposed specifications. Therefore, the CMC conclusion remains the same (NDA is not recommended for approval). For additional details, refer to NDA 203856 Review dated 26-MAR-2013 for further information.

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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.**  
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/s/  
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JOSEPHINE M JEE  
04/30/2013

ALI H AL HAKIM  
04/30/2013

**NDA 203856**

**Cyclophosphamide Capsule  
25mg and 50 mg**

**Roxane Laboratories, Inc.**

**Josephine Jee**

**Office of New Drug Quality Assessment**

**For the Division of Drug Oncology Products 1**

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## Chemistry Review Data Sheet

# Chemistry Review Data Sheet

## 1. NDA 203856 (Resubmission)

## 2. REVIEW #1

3. REVIEW DATE: 26-MAR-2013

Date Assigned: 06-JUL-2012

4. REVIEWERS: Josephine Jee

## 5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	21-DEC-2011
Amendment – Pediatric Waiver	11-JAN-2012
Amendment (Responsibility of each Facility)	19-JAN-2012
Amendment – Update of Facilities	23-JAN-2012
Amendment – Inspection Site Ready to Inspect	02-FEB-2012
Amendment Request for Mtg. (RTF) – Type B	16-MAR-2012
Amendment – Briefing Package for RTF TCON	02-MAY-2012

## 6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original (CMC) – Resubmission after RTF	03-JUL-2012
Amendment – Patent Certification and Revised Labeling	17-JUL-2012
Amendment – Patent	16-AUG-2012
Amendment – Response to IR (Clarification of Man. Sites)	08-NOV-2012
Amendment – Response for Filing Communication (BCS based Biowaver request)	30-NOV-2012
Amendment – Removal of the HCO facility as DP facility	12-DEC-2012
Amendment – Proposed CBE-30 for HCO Facility	20-DEC-2012
Amendment - Response to IR (Update Dissoln. Spec.)	04-JAN-2013
Amendment - Response to IR (b)(4) & Res. Solv.)	16 JAN-2013
Amendment – Clarification of CBE-30 Plan for HCO Site Changes	22-FEB-2013
Amendment - IND reference to application	12-MAR-2013
Amendment – Submission of Final Printed Labeling (Container Labels)	14-MAR-2013
Amendment – IR Responses	19-MAR-2013
Amendment – Teleconference Response (21-MAR-2013 T-con)	25-MAR-2013

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Roxane Laboratories, Inc. (Boehringer Ingelheim)

Address: 1809 Wilson Rd  
Columbus, OH 43228

Representative: Randall Wilson  
Vice President, Scientific, Medical and Regulatory Affairs

Telephone: 614-272-4799

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A  
 b) Non-Proprietary Name (USAN): Cyclophosphamide  
 Code Name/# (ONDC only):  
 c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3,5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2), Cytoxan® Tablets 25 mg and 50 mg, NDA 12-141 (This application is no longer listed in the Orange Book; however, it is still active in DARRTS).

10. PHARMACOL. CATEGORY: Alkylating Agent (nitrogen mustard) with antineoplastic and immunosuppressant properties

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 25 mg, and 50 mg

13. ROUTE OF ADMINISTRATION: Orally

14. Rx/OTC DISPENSED:  Rx  OTC

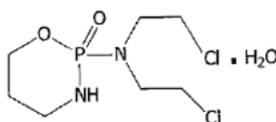
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(+)-2-[Bis (2-chloroethyl) amino] tetrahydro-2H-1,3,2,-oxazaphosphorine 2-oxide, monohydrate



Empirical formula is:  $C_7H_{15}Cl_2N_2O_2P \cdot H_2O$

Molecular weight: 279.1

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS <sup>3</sup>

Chemistry Review Data Sheet

(b) (4)	II	(b) (4)	3	Adequate	28-FEB-2013	J.Jee
	III		3	Adequate	07-MAR-2003	J. Salemme
	III		3	Adequate	20-MAR-2013	J.Jee
	III		3	Adequate	10-SEP-2012	Nina Ni
	III		3	Adequate	14-MAY-2012	Z. Dong
	III		3	Adequate	14-FEB-2012	G. Holbert
			3	Adequate	16-FEB-2012	G. Holbert
			3	Adequate	21-MAR-2012	G. Holbert

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

<sup>3</sup> Include reference to location in most recent CMC review

**B. Other Supporting Documents:**

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
ANDA	Boehringer/Roxane	ANDA 040032	Approved	17-AUG-1999	This ANDA is approved for Cyclophosphamide Tablets, 25 mg and 50 mg
IND		IND 112446	Approved	15-MAR-2013	Cyclophosphamide Capsules

**C. Related Documents:**

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
NDA	12145	Bristol-Myers Squibb	This application should have served as the RLD for Cyclophosphamide Tablets, 25 mg and 50 mg, was withdrawn on 07-DEC-2007, leaving ANDA 040032 as the RLD.

Chemistry Review Data Sheet

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				No statistical analysis of drug product stability data deemed necessary.
EES	Site inspections	08-JAN-2013	T.Sharp	Acceptable. Overall OC recommendation dated 08-JAN-2013
Pharm/Tox	Drug substance, drug product impurity qualification (organic and inorganic)	19-MAR-2013	G. Chang/T. Palmby	Acceptable. Acceptance criteria for (b) (4) and unspecified impurity.
Biopharm	<i>In-vivo</i> Bioequivalence Waiver	14-MAR-2013	Z. Dong	The in-vivo bioequivalence is granted and the recommendation is approval.
OSE/DMEPA	Labeling consult		J. Abdus-Samad	Labeling Meeting is scheduled for 09-APR-2013. Dr. J. Abdus-Samad will be submitting his review on or about 30-MAR-2013.
Methods Validation	N/A			Method validation is not requested as per ONDQA criteria.
EA	Environmental Assessment	19-MAR-2013	J.Jee	Acceptable
Microbiology				No microbiology evaluation deemed necessary, since the drug product is a solid dosage form.

# The Chemistry Review for NDA 203-856

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The recommendation for the application is Complete Response (CR) from a Chemistry, Manufacturing, and Controls (CMC) perspective until the following issues are addressed adequately:

- Acceptable stability results for Dissolution and Largest Unspecified Degradant that meet the proposed drug product specification for Lots 4000591 (25 mg) and Lot 4000592 (50 mg). The Applicant has committed to provide justifications and corrective measures for out of specification (OOS) results of Dissolution and degradants at the end of April 2013, as per their 25-MAR-2013 Communication.
- Revise the storage statements as they appeared in the containers and package insert labeling to "Store at 20°C - 25°C (68°F to 77°F). [See USP controlled room temperature]." Remove the statement (b) (4)

The Labeling Meeting is scheduled for 09-APR-2013; final Labeling comments will need to be conveyed to the sponsor.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

### II. Summary of Chemistry Assessment

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### 1. Drug Substance

The active ingredient is cyclophosphamide. It is manufactured by (b) (4). Detailed information on the drug substance is referenced to DMF (b) (4); which was reviewed on 28-FEB-2013 and found to be adequate. Note that (b) (4)

Cyclophosphamide is included in the current USP. Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. Cyclophosphamide is a

## Executive Summary Section

white crystalline powder that is soluble in water, freely soluble in alcohol and slightly soluble in ether.

The drug substance specification proposed in this NDA meet all the specifications in the proposed USP Monograph for cyclophosphamide. These tests include: (1) Description, (2) Identification (Raman Spectroscopy (alternate ID test), Infrared, HPLC), (3) Water, (4) pH, (5) Heavy Metals, (6) Limit of <sup>(b) (4)</sup>, (7) Limit of Degradation Products (Related compounds <sup>(b) (4)</sup> and Any specified Impurity), (8) Limit of <sup>(b) (4)</sup>, (9) Limit of <sup>(b) (4)</sup>, (11) Residual Solvents <sup>(b) (4)</sup>, (12) Assay, and (13) Related Substances <sup>(b) (4)</sup> Any Unspecified Impurity and Total Impurity).

In addition to the impurities identified in the current USP under “Limit of Degradation Products”, the Applicant has identified two additional known impurities and one unknown impurity under the category “Related Substances”. The proposed acceptance criteria for the related substances meet ICHQ3B. The acceptance criteria for Related Substances and Residual Organic Solvents (not listed in ICH Q3C) were consulted with T. Palmby, Ph.D, and G. Chang, Ph.D., Pharm/Tox Reviewers who recommended that the proposed specifications are acceptable.

Based on the stability data for drug substance, <sup>(b) (4)</sup> retest period is granted when cyclophosphamide API is stored in the proposed packaging conditions at <sup>(b) (4)</sup>

## 2. Drug Product

The drug product is an immediate release capsule dosage form. The capsules are formulated in two different strengths: 25 mg and 50 mg.

Cyclophosphamide Capsule, 25 mg is described as blue/blue opaque capsule with “54 006” printed in black ink on the capsule body, containing white to off-white powder.

Cyclophosphamide Capsule, 50 mg is described as blue/blue opaque capsule with “54 881” printed in black ink on the capsule body, containing white to off-white powder. They are packaged in HDPE bottles.

The inactive ingredients are USP/NF materials, Pregelatinized Starch, NF, and Sodium Steryl Fumarate, NF, with the exception of hard gelatin capsules, <sup>(b) (4)</sup>

The critical formulation development efforts were focused in the selection of suitable <sup>(b) (4)</sup>

<sup>(b) (4)</sup>; all these parameters directly affect the dissolution, content uniformity, and the amount of degradants in DP.

## Executive Summary Section

One specified degradant/ impurity (identified in USP Monograph for Cyclophosphamide Drug Substance) is identified in the drug product. Since, there is no compendial monograph for Cyclophosphamide Capsule and there is no approved cyclophosphamide capsule, the recommendation for acceptable levels of known and unknown impurities in cyclophosphamide capsule would be based on ICHQ3B qualifications limits. The acceptance criteria of degradants and residual organic solvents were consulted with Drs. T. Palmby and G. Chang, Pharm/Tox Reviewers. Please refer to the Pharmacology/Toxicology review for additional information regarding impurity qualification.

The tests for the drug product include: (1) Description, (2) Identification (HPLC), (3) Dissolution, (4) Uniformity of Dosage Forms, (5) Assay, (6) Degradation Products (b) (4) and Single Largest Degradant, and Total Degradants, and (7) Residual Solvents.

Primary stability results were submitted for the proposed strengths, 25 mg capsules (3 lots) and 50 mg capsules (3 lots), at 25°C/60%RH (12 months) and 40°C/75% RH (6 months) storage conditions.

The reported stability results of one lot of 25 mg and one lot of 50 mg capsules (b) (4) did not meet acceptance criteria for dissolution and degradation products (unspecified degradation products) testing. Based on the preliminary studies, BIRLI stated on 25-MAR-2013 that these results were observed in only two batches out of a total of six batches tested and the root cause appears to be the lot of API used. Further results of this study will be provided as an amendment to the NDA at the end of April 2013. Regarding expiry dating, this issue is pending result of the above study and subsequent NDA amendment.

**B. Description of How the Drug Product is Intended to be Used**

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.

**C. Basis for Approvability or Not-Approval Recommendation**

The NDA is not recommended for approval from CMC point of view for the following reasons:

- Two sublots of drug product batches (out of six sublots) failed to meet the proposed specifications for the two critical test parameters; dissolution and unspecified degradation products.

**Background Information**

The CMC information of the drug substance was referenced to DMF (b) (4), which was reviewed on 28-FEB-2013 and found to be adequate.

A detailed pharmaceutical development report was submitted to the NDA. The drug

## Executive Summary Section

product was developed as an immediate release capsule dosage form. The capsules were formulated in two different strengths: 25 mg and 50 mg. Critical parameters and critical attributes were identified.

On 04-JAN-2013, Roxane agreed to change the acceptance criteria for the Dissolution to Q of (b) (4) in 15 min. In this same communication, Roxane stated, in part, "During the course of testing, analysts observed that the (b) (4)

(b) (4) A closer examination of the root cause behind the (b) (4) is currently on going."

On 21-MAR-2013, a Teleconference between the Agency and BIRLI to discuss out of specifications dissolution and degradation products results in the lots cited above. BIRLI responded on 25-MAR-2013 and stated in part "The investigation of the two additional lots suggested the API is the most probable root cause." A commitment was made by BIRLI to continue to identify the critical attribute(s) of the drug substance and ensure suitable controls are in place. BIRLI expects the results of this study by the end of April 2013.

The primary stability batches submitted were manufactured at the proposed commercial manufacturing located at 330 Oak Street, Columbus, Ohio proposed to close and move to the new commercial facility located at 1809 Wilson Road, Columbus, Ohio. The Agency did not agree to have 1809 Wilson Road facility submitted in this current NDA submission, since the registration batches were manufactured at 330 Oak Street facility; refer to communications dated 08-NOV-2012 (clarification of facilities). On 12-DEC-2012, BIRLI proposed to remove 1809 Wilson Road facility from the current NDA submission. On 22-FEB-2013, BIRLI proposed to submit a CBE-30 Supplemental NDA for the 1809 Wilson Road facility; the acceptability of the CBE-30 will be recommended by the Post-Marketing Branch.

The Office of Compliance has issued an overall "acceptable" recommendation for each facility used for manufacturing and control of drug substance and drug product.

Revise the storage statements as they appeared in the container and package insert labeling "Storage at or below 25°C (77°F) is recommended; (b) (4)

Add the statement "Keep out of reach of children" to the container labels."

The content of the labeling appear to be the same as the approved labels; however, the proposed (b) (4) were not confirmed (b) (4)  
The labeling meeting is scheduled on 09-APR-2013.

### III. Administrative

This NDA was submitted in electronic (labeling section only) as a 505(b)(2) application. A Quality Overall Summary is included in the application.

## Executive Summary Section

**A. Reviewer's Signature**

See electronic signatures in DARRTS.

**B. Endorsement Block**

See electronic signatures in DARRTS

**C. CC Block**

See electronic signatures in DARRTS

60 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

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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.**  
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/s/  
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JOSEPHINE M JEE  
04/02/2013

ALI H AL HAKIM  
04/02/2013

**PRODUCT QUALITY (Small Molecule)**  
**FILING REVIEW FOR NDA or Supplement (ONDQA)**

**NDA Number: 203-856**      **Supplement Number and Type:**      **Established/Proper Name:**  
**Applicant: Roxane**                      **Letter Date: 7-3-12**                      **Cyclophosphamide**  
**Laboratories, Inc.**                      **Stamp Date: 7-3-12**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On initial overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	√		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	√		
3.	Are all the pages in the CMC section legible?	√		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			N/A

**PRODUCT QUALITY (Small Molecule)**  
**FILING REVIEW FOR NDA or Supplement (ONDQA)**

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	√		Resubmitted
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	√		Resubmitted

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	√		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	√		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	<p>Has an environmental assessment report or categorical exclusion been provided?</p>	√		

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	√		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	√		
14.	Does the section contain information regarding the characterization of the DS?	√		
15.	Does the section contain controls for the DS?	√		
16.	Has stability data and analysis been provided for the drug substance?	√		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	√		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	√		
21.	Is there a batch production record and a proposed master batch record?	√		Executed Batch Record
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?			
23.	Have any biowaivers been requested?	√		
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		Review issue. The NDA was RTF due to lack of insufficient DP stability data. In this resubmission, applicant provided additional DP stability data for a commercially viable shelf-life.
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>F. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
29.	Is there a methods validation package?	√		

<b>G. MICROBIOLOGY</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		√	Capsule formulation.

<b>H. MASTER FILES (DMF/MAF)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	√		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	Type II		(b) (4)	October 20, 2011	Yes
	Type III		January 21, 2010	Yes	
	Type III		July 27, 2010.	Yes	

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

		(b) (4)		
(b) (4)	Type III		April 12, 2010	Yes
	Type III		May 25, 2009	Yes
	Type III		May 11, 2010	Yes
	Type III		August 2, 2010	Yes
	Type III		May 15, 2009	Yes

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	√		

**PRODUCT QUALITY (Small Molecule)**  
**FILING REVIEW FOR NDA or Supplement (ONDQA)**

33.	Have the immediate container and carton labels been provided?	√		
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**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	√		Applicant provided additional DP stability data for a commercially viable shelf-life
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Describe filing issues here or on additional sheets
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		√	Describe potential review issues here or on additional sheets

*{Haripada Sarker}*

8-28-2012

Name of  
Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer  
Division of Pre-Marketing Assessment #  
Office of New Drug Quality Assessment

Date

*{Nallaperum Chidambaram}*

8-28-2012

Name of  
Branch Chief  
Division of Pre-Marketing Assessment #  
Office of New Drug Quality Assessment

Date

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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.**  
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/s/  
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HARIPADA SARKER  
08/28/2012

NALLAPERUM CHIDAMBARAM  
08/28/2012  
I concur

**Initial Quality Assessment  
Branch II  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment**

**OND Division:** DOP1, OHOP  
**NDA:** 203-856  
**Applicant:** Roxane Laboratories, Inc.  
**Stamp Date:** 21 December, 2011  
**PDUFA Goal Date:** 21 October, 2012 (standard)  
**Established Name:** Cyclophosphamide  
**Trade Name:** Not available  
**Chemical Class:** Type-1 (change in formulation)  
**Dosage Form and Strength:** Capsule – 25 mg and 50 mg  
**Route of Administration:** Oral  
**Indication:** Cyclophosphamide is more frequently used concurrently or sequentially with other antineoplastic drugs, etc., and is useful in carefully selected cases of biopsy proven "minimal change" nephritic syndrome in children but should not be used as primary therapy.

**eCTD Reference for CMC** eCTD.

**Regulatory Filing** For 505 (b) (2)  
**Related IND** IND 112446  
**Reference DMFs** DMFs: (b) (4) ;  
(b) (4) .

**Assessed by:** Haripada Sarker

No Yes

**ONDQA Fileability:** x

**Comments for 74-Day Letter:** x

## Background Summary

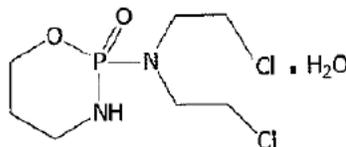
The application, Roxane Laboratories, Inc. (RLI) introduces the drug product, Cyclophosphamide, which is supplied as 25 mg and 50 mg capsules for oral administration. RLI changes the previously approved dosage form from (tablet) to a capsule product in the current NDA. In late 2008, the brand manufacturer of Cytoxan (under NDA 12141, Baxter Healthcare) discontinued production and distribution of their cyclophosphamide product and RLI's ANDA 040032 became the RLD (reference listed drug). There are currently no other approved ANDAs for Cyclophosphamide Tablets and therefore RLI are the sole source and manufacturer for this product. The Cytoxan Injection is available in the market under NDA 12142 with same applicant, Baxter Healthcare.

In pre-IND/pre-NDA meeting dated July 27, 2011 under IND 112446, the only CMC issue was related to DP stability batches. RLI proposed three stability batches with six months of long term and accelerated stability data. In response, Agency made appropriate comment (see pre-IND/pre-NDA meeting response dated July 27, 2011). The CMC information of this NDA is submitted in eCTDQ format.

## Drug Substance (DS)

Applicant refers to (b) (4) Type II DMF (Drug Master File) (b) (4) for CMC information of the Cyclophosphamide drug substance. Following are the brief DS information included in this NDA. The DS is a white to off-white crystalline powder. All synthesis process information is contained in (b) (4) DMF (b) (4). The DMF letter of authorization is provided. Applicant indicated that Cyclophosphamide has USP monograph, and controlled as per USP. Open Parts of (b) (4) DMF are included in this NDA

The drug substance manufacturer performs all characterization of the drug substance and impurities. The DS is controlled by in-house test specifications, and is described in Boehringer Ingelheim Roxane Inc. (BIRI) specification for the Drug Substance, Internal No. (b) (4). Test methods are provided with Validation report. No reference standards or materials are note in addition to those described for testing. The container closure system for the drug substance is described in (b) (4) (b) (4) DMF. The structure of Cyclophosphamide is identified as following.



DS is manufactured by (b) (4) RLI provided the list of List of all establishments involved in the manufacture of the finished product and the active pharmaceutical ingredient for cyclophosphamide capsules, 25 mg and 50 mg. However, one of the sites, BIRI, (b) (4)

(b) (4) A Tcon is scheduled on February 1, 2012 to clarify the status of this site. In Tcon, applicant stated that the site is currently ready for inspection for this application, and official amendment will be submitted soon.

The stability of the drug substance is described in DMF (b)(4) and is included in this submission. Base on the stability study, the retest date for Cyclophosphamide USP is set as (b)(4).

*DS Critical Issues*

- Type II DMF (b)(4) needs to be review for DS, and identify the critical issue to resolve as early as possible. Verify the Cyclophosphamide USP standard to current control of DS in this NDA.
- New degradants in DS, when compared with Cyclophosphamide USP specification.
- EER information for DS needs to be re-examined for accuracy.
- If new site, BIRI, (b)(4) is included for this NDA, verify the site specific comparability protocol.
- Verify DS retest period.

**Drug Product (DP)**

Two strengths, 25 mg and 50 mg, are proposed for Cyclophosphamide Capsules. Applicant indicated that these strengths are identical to the currently approved Cyclophosphamide Tablets, 25 mg and 50 mg. The approved DP (tablet) was developed as (b)(4)

(b)(4)

Following Table provides the component and composition for the DP.

Table. Component and Composition for Cyclophosphamide Capsules

<u>Ingredients</u>	<u>Purpose</u>	<u>Quality Standard</u>	<u>Amount (mg/capsule)</u>		<u>Amount (%/capsule)</u>
			<u>25 mg capsule</u>	<u>50 mg capsule</u>	<u>25 and 50 mg capsules</u>
Cyclophosphamide, USP	Active Ingredient	(b)(4)			(b)(4)
Pregelatinized Starch, NF		(b)(4)			(b)(4)
Sodium Steryl Fumarate, NF		(b)(4)			(b)(4)
		(b)(4)			(b)(4)
		(b)(4)			(b)(4)

<sup>1</sup> Equivalent to 25 mg of Cyclophosphamide (Anhydrous). <sup>2</sup> Equivalent to 50 mg of Cyclophosphamide (Anhydrous)

All excipients used in the formulation of Cyclophosphamide Capsules, 25 mg and 50 mg are tested per USP/NF requirements, with the exception of the capsules used. The Capsules are tested as per their specifications provided in the same specifications as the supplier.

The drug product will be manufactured, tested, labeled, packaged and released by Boehringer Ingelheim Roxane, Inc. (BIRI). The proposed DP manufacturing site is listed below:

Boehringer Ingelheim Roxane, Inc. (BIRI)  
1809 Wilson Road  
Columbus, Ohio 43228

The address of other new facility is as following,  
Boehringer Ingelheim Roxane, Inc.  
OAK STREET FACILITY  
1809 Wilson Road  
Columbus, Ohio  
43228  
FDA Reg # 15 10690

Applicant intended to transfer the DP manufacturing and control to new site, and is located in the same campus of BIRI under same address of the current site.

This new site, BIRI, (b) (4) is also listed as future site for DP commercial production; however, this site was not ready for inspection in original NDA submission. In Tcon dated February 1, 2012 applicant confirmed that the site is currently ready for inspection for this application, and official amendment will be submitted soon.

DP is manufactured as (b) (4) capsule manufacturing process. Information provided on steps of the manufacturing process identified as critical and the in-process tests performed to control these steps along with the acceptance criteria for the drug product registration and the proposed commercial batch manufacturing. The drug product specifications, determined from current release and stability data on the three lots from each strength (25 and 50 mg) are provided. No additional reference standards or materials were used for testing.

The proposed commercial packaging configurations for Cyclophosphamide Capsules, 25 mg and 50 mg, are as follows:

Cyclophosphamide Capsules, 25 mg - Bottles of 100 capsules:

(b) (4)

Cyclophosphamide Capsules, 50 mg - Bottles of 100 capsules:

(b) (4)

DP stability studies are included for three registration batches over the period of six months at long term and at accelerated conditions. Stability Summary is provided as following.

Cyclophosphamide Capsules, 25 mg

Batch Numbers	(b) (4) Stored At 40°C/75% RH*	(b) (4) Stored At 25°C/60% RH*
4000507A	6 Months	6 Months

4000591A	6 Months	6 Months
4000594A	6 Months	6 Months

Cyclophosphamide Capsules, 50 mg

Batch Numbers	(b) (4) Bottles Stored At 40°C/75% RH*	(b) (4) Bottles Stored At 25°C/60% RH*
4000508A	6 Months	6 Months
4000592A	6 Months	6 Months
4000592B	6 Months	6 Months

\* RH = Relative Humidity

Stability of DP was monitored by Description, dissolution, assay and degradation product. All the batches apparently meet the proposed specification within the test period of six months. The DP stability specification is found to be similar to corresponding DP release specification.

No statistical analysis of DP stability is included to support the proposed DP expiration dating. The Applicant proposes a 24-month expiration dating period for the Cyclophosphamide Capsules, when stored at 25°C (77°F).

*Drug Product Critical Issues*

- New degradants in DP, when compared with RLD specification.
- Dissolution test data needs to be evaluated by Biopharm reviewer for change in dosage form from Tablet to Capsule.
- Check EES of DP sites for accuracy.
- DMFs for container/closure systems need to be reviewed for adequacy of the NDA.
- Check stability test data on drug product over the period of intended storage time.
- Justification of 24-months expiration based on 6-months stability data in the submission. Whether ICH Q1E can be applied for this extrapolation to justify the proposed expiration.
- Harmonize release and stability specifications for impurities.

**Fileability Template**

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		

9	Has stability data and analysis been provided to support the requested expiration date?		√	Pending review of stability update.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		Review issue.
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√ √  √ √		<b>Microbiology</b> <b>Biopharm</b> Statistics (stability) OCP/CDRH/CBER LNC DMEPA <b>EER</b>

**Have all DMF References been identified? Yes (√) No ( )**

DMF Number	Holder	Description	LOA Included
		(b) (4)	Yes
			Yes
			Yes

(b) (4)	
	Yes

**Comments and Recommendations**

The application is not fileable; following fileability issue regarding drug product stability has been identified at this point. Facilities have been entered into EES for inspection. A single reviewer is recommended for this NDA, since the manufacturing process is not particularly complex.

1. 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.

Haripada Sarker, Ph.D.  
CMC Lead

February 17, 2012  
Date

Sarah Pope Miksinski, Ph.D.  
Branch Chief

February 17, 2012  
Date

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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.**  
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/s/  
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HARIPADA SARKER  
02/17/2012

SARAH P MIKSINSKI  
02/17/2012