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RESEARCH**

APPLICATION NUMBER:

203856Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA:	203856 Resubmission (SDN 24)
Drug:	Cyclophosphamide capsule
Strengths:	25 and 50 mg
Sponsor:	Roaxane Lab
Submission Date:	7/17/13
Submission Type:	Original NDA, 505(b)(2), Standard Review
Reviewer:	Sarah J. Schrieber, Pharm.D.
Team Leader:	Qi Liu, Ph.D.

BACKGROUND: NDA 203-856 was submitted under FDC 505(b)(2) category for Cyclophosphamide Capsules 25 mg and 50 mg for the treatment of malignant diseases, often used in combination with other neoplastic drugs, or for the treatment of carefully selected cases of biopsy proven “minimal change” nephritic syndrome in children. The reference drug product for this NDA is Cyclophosphamide Tablets (ANDA 40-032), also manufactured by Roxane Laboratories. This application includes a request for a BE waiver in lieu of a human bioequivalence study to support the bridge in formulation from a tablet to a capsule. The biowaiver is based on the data submitted under IND 112,446 on 3/12/12 to support the approval of a Biopharmaceutics Classification System (BCS)-Class 1 classification for cyclophosphamide. In the previous review cycle, a Complete Response action was taken on 05/03/2013 due to a CMC issue. FDA granted a BCS-Class 1 based bioequivalence waiver. Clinical pharmacology review team recommended approval of the NDA from the clinical pharmacology perspective during the first review cycle.

SUBMISSION: The resubmission of NDA 203-856 dated 07/17/2013 addresses the CMC deficiency listed in the Complete Response document dated 05/03/2013. Specifically, the Applicant provided the stability data for five batches of each strength of cyclophosphamide capsules.

REVIEW AND RECOMMENDATION: The clinical pharmacology review was completed during the first review cycle with no pending issues (Sarah Schrieber reviewer). With respect to the resubmission of the NDA 203-856 for Cyclophosphamide Capsules, approval is recommended in this review cycle from the clinical pharmacology perspective.

Sarah J. Schrieber, Pharm.D.

August 26, 2013

Reviewing Clinical Pharmacologist

Date

Qi Liu, Ph.D.

August 26, 2013

Team Leader/Supervisor

Date

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/s/

SARAH J SCHRIEBER
08/26/2013

QI LIU
08/26/2013

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	203-856 Resubmission
Submission Date:	07/17/2013
Brand Name:	N/A
Generic Name:	Cyclophosphamide, USP
Formulation:	Immediate Release Capsule
Strength:	25 mg and 50 mg
Applicant:	Roxane Laboratories, Inc.
Type of submission:	Original NDA, 505(b)(2), Standard Review
Reviewer:	Zedong Dong, Ph.D.

BACKGROUND: NDA 203-856 was submitted under FDC 505(b)(2) category for Cyclophosphamide Capsules 25 mg and 50 mg for the treatment of malignant diseases, often used in combination with other neoplastic drugs, or for the treatment of carefully selected cases of biopsy proven “minimal change” nephritic syndrome in children. The reference drug product for this NDA is Cyclophosphamide Tablets (ANDA 40-032), also manufactured by Roxane Laboratories. This application includes a request for a BE waiver in lieu of a human bioequivalence study to support the bridge in formulation from a tablet to a capsule. The biowaiver is based on the data submitted in IND 112,446 to support the approval of a BCS-Class 1 classification for cyclophosphamide. In the previous review cycle, a Complete Response action was taken on 05/03/2013 due to a CMC issue.

SUBMISSION: The resubmission of NDA 203-856 dated 07/17/2013 addresses the CMC deficiency listed in the Complete Response document dated 05/03/2013. Specifically, the Applicant provided the stability data for five batches of each strength of cyclophosphamide capsules.

REVIEW AND RECOMMENDATION: The Biopharmaceutics review was completed during the first review cycle with no pending issues. The following table presents the approved dissolution method and acceptance criterion for Cyclophosphamide Capsules.

DISSOLUTION METHOD AND ACCEPTANCE CRITERION

Drug Name	Dosage Form	USP Apparatus/Speed	Medium Tier 1	Medium Tier 2	Acceptance Criterion
Cyclophosphamide	IR Capsule	USP Basket at 100 rpm	900 ml of DI water (deareated) at 37°C	900 ml of DI water with pepsin (deareated) at 37°C	Q = (b)(4) at 15 min

It should be noted that Biopharmaceutics granted a BCS-Class 1 based bioequivalence waiver and recommended approval of the NDA during the first review cycle.

With respect to the resubmission of the NDA 203-856 for Cyclophosphamide Capsules, approval is recommended in this review cycle from the Biopharmaceutics perspective.

Zedong Dong, Ph.D.
Reviewer
ONDQA Biopharmaceutics

Date

Angelica Dorantes, Ph.D.
Team Leader
ONDQA Biopharmaceutics

Date

CC: NDA 203-856
Lisa Skarupa

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/s/

ZEDONG DONG
08/20/2013

ANGELICA DORANTES
08/20/2013

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	203-856
Submission Date:	12/21/2011; 07/03/2012; 01/04/2013
Brand Name:	N/A
Generic Name:	Cyclophosphamide, USP
Formulation:	Immediate Release Capsule
Strength:	25 mg and 50 mg
Applicant:	Roxane Laboratories, Inc.
Type of submission:	Original NDA, 505(b)(2), Standard Review
Reviewer:	Zedong Dong, Ph.D.

SUMMARY

Background: NDA 203-856 was submitted under FDC 505(b)(2) category for Cyclophosphamide Capsules 25 mg and 50 mg for the treatment of malignant diseases, often used in combination with other neoplastic drugs, or for the treatment of carefully selected cases of biopsy proven “minimal change” nephritic syndrome in children. The reference drug product for this NDA is Cyclophosphamide Tablets (ANDA 40-032), also manufactured by Roxane Laboratories. This application includes a request for a BE waiver in lieu of a human bioequivalence study to support the bridge in formulation from a tablet to a capsule. The biowaiver is based on the data submitted in IND 112,446 to support the approval of a BCS-Class 1 classification for cyclophosphamide.

Submission: This is a resubmission of NDA 203-856 due to a refusal to file (RTF) action on 02/17/2012 for deficiencies on CMC and Biopharmaceutics issues.

Review: This Biopharmaceutics review is focused on the evaluation and acceptability of the proposed dissolution method and acceptance criterion for cyclophosphamide capsules.

Note that the firm’s requests for a BCS-Class 1 assignment for cyclophosphamide and for a BCS-based biowaiver were reviewed and approved under their IND 112,446 submission. On 3/13/13, FDA notified the sponsor that the BCS Committee at CDER approved their request for a BCS Class-1 classification for cyclophosphamide capsules.

BIOPHARMACEUTICS REVIEW

The dissolution development report was not included in the NDA submission. The Applicant is proposing to use the same compendial dissolution method currently used for Cyclophosphamide Tablets. However, slightly different HPLC conditions (b) (4) are used for the assay of the dissolution samples of the proposed Cyclophosphamide Capsules. The validation of the analytical method is acceptable.

The sponsor's initially proposed a dissolution acceptance criterion of $Q = (b) (4)$ minutes. However, since cyclophosphamide capsules has been classified as BCS Class-1 drug substance/drug product, FDA requested the tightening of the dissolution acceptance criterion to $Q = (b) (4)$ in 15 minutes. On 1/4/13, the Applicant agreed to this recommendation.

RECOMMENDATION

ONDQA-Biopharmaceutics has evaluated the information provided in the Resubmission of Original NDA 203856 for Cyclophosphamide Capsules. Upon the review of the overall dissolution information the following dissolution method and acceptance criterion are acceptable.

Drug Name	Dosage Form	USP Apparatus/Speed	Medium Tier 1	Medium Tier 2	Acceptance Criterion
Cyclophosphamide	IR Capsule	USP Basket at 100 rpm	900 ml of DI water (deareated) at 37°C	900 ml of DI water with pepsin (deareated) at 37°C	$Q = (b) (4)$ at 15 min

Note that under IND 112,446 the BCS Committee at CDER/FDA approved the BCS Class-1 classification for cyclophosphamide capsules. Also the request for a BCS-based biowaiver for cyclophosphamide capsules (25 mg and 50 mg) in reference to cyclophosphamide tablets (25 mg and 50 mg) was granted.

From the Biopharmaceutics perspective, NDA 203-856 for Cyclophosphamide Capsules is recommended for approval.

 Zedong Dong, Ph.D.
 Reviewer
 ONDQA Biopharmaceutics

 Date

 Angelica Dorantes, Ph.D.
 Supervisory Lead
 ONDQA Biopharmaceutics

 Date

CC: NDA 203-856
 Lisa Skarupa, Debbie Mesmer

BIOPHARMACEUTICS EVALUATION - REVIEW NOTES

INTRODUCTION

The resubmission of 505(b)(2) NDA 203-856 for Cyclophosphamide Capsules 25 mg and 50 mg is for the treatment of malignant diseases, often used in combination with other neoplastic drugs, or for the treatment of carefully selected cases of biopsy proven “minimal change” nephritic syndrome in children. The reference drug product for this NDA is Cyclophosphamide Tablets (ANDA 40-032), also manufactured by Roxane Laboratories. This is a resubmission of NDA 203-856 due to a refusal to file (RTF) action on 02/17/2012 due to CMC and Biopharmaceutics issues.

STATUS OF BCS CLASS I DESIGNATION OF CYCLOPHOSPHAMIDE

Note that under IND 112,446 for cyclophosphamide capsules, the firm provided a request for a BCS Class-I designation for cyclophosphamide, as well as a biowaiver request for cyclophosphamide capsules. The overall solubility, permeability, gastric permeability, and dissolution information/data supporting these requests was reviewed by Drs. Sarah Schrieber and Zedong Dong, OCP and ONDQA Reviewers, respectively. A memo with this information was sent to the BCS Committee for their final recommendation of the BCS classification of cyclophosphamide. On January 24, 2013, the BCS Committee agreed to the classification of Cyclophosphamide as BCS Class 1 (*refer to Drs. Schrieber and Dong review in DARRTS dated 3/7/13*). Based on this approval, the BCS based waiver request for the submission of an *in vivo* bioequivalence study was granted as per the FDA guidance “Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System” (*refer to Dr. Zedong Dong Biopharmaceutics review in DARRTS dated 3/8/13*).

PRODUCT FORMULATION

Table 1 summarizes the formulation composition for both dose strengths of the capsules.

Table 1. Formulation Compositions 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)
Pregelatinized Starch, NF					(b) (4)
Sodium Steryl Fumarate, NF					(b) (4)
					(b) (4)

¹ Equivalent to 25 mg of Cyclophosphamide (Anhydrous)

² Equivalent to 50 mg of Cyclophosphamide (Anhydrous)

This review is focused on the evaluation of dissolution acceptance criterion for the Cyclophosphamide capsules.

This application includes a request for a biowaiver in lieu of a human pharmacokinetic study to support the change in formulation from a tablet to a capsule. The biowaiver is based on the data submitted in IND 112,446 to support the approval of a BCS-Class 1 classification for Cyclophosphamide. Note that the requested BCS based biowaiver was granted on 3/6/13 under the IND submission.

DISSOLUTION METHODOLOGY AND SPECIFICATIONS

In the NDA, no dissolution development report is provided. The applicant uses the same dissolution method as the compendial method for Cyclophosphamide tablet. The proposed dissolution method for the Cyclophosphamide Capsules (25 mg and 50 mg) is shown below, with a proposed acceptance criterion of $Q =$ (b) (4). The dissolution method is also used during drug product development to optimize the formulation composition and manufacturing process parameters.

DISSOLUTION CONDITIONS

USP Apparatus:

Speed:

Medium - Tier I:

Medium - Tier II:

Temperature:

Volume:

Sampling Time:

Pull Volume:

Tier I Filter:

Tier II Filter:

(b) (4)

(b) (4)

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Reviewer Comments

1. Since the biowaiver request is based on the BCS I classification of cyclophosphamide, indicating fast dissolving characteristics for the drug product, it was recommended that the dissolution criterion be tighten to $Q = (b)(4)$ at 15 minutes.

The following information request was sent to the applicant:

- Provide the dissolution profiles ($n=12$, mean, range and RSD) for the registration batches (25 mg and 50 mg) for both release testing and stability study.
- Because the bioequivalence waiver request is based on BCS I designation of the drug product, tighten the acceptance criterion to $Q = (b)(4)$ at 15 minutes for both strengths of cyclophosphamide capsules.

On 1/4/2013, the applicant agreed to revise the dissolution criterion to $Q = (b)(4)$ at 15 minutes. The final dissolution specifications for Cyclophosphamide Capsules are summarized below.

Table 3. Dissolution Specification for Cyclophosphamide Capsules (25 mg and 50 mg)

Test	Analytical Procedure	Release Acceptance Criteria	Stability Acceptance Criteria
Dissolution	1726-03	<p>Capsules tested with Tier I media meet USP <711> S1, S2 and S3 criteria:</p> <p>NLT $(b)(4)$(Q) of the labeled amount dissolves in 15 minutes.</p>	<p><u>Tier I</u> 6 capsules tested with Tier I media, meet USP <711> S1 criteria:</p> <p>NLT $(b)(4)$(Q) of the labeled amount dissolves in 15 minutes.</p> <p>If S1 criteria are not met for Tier I, proceed to Tier II</p> <p><u>Tier II</u> Capsules tested with Tier II media (with Pepsin) meet USP <711> S1, S2 and S3 criteria:</p> <p>NLT $(b)(4)$(Q) of the labeled amount dissolves in 15 minutes.</p>

In addition, the applicant provided the dissolution profiles of the Cyclophosphamide Capsules for both release testing and stability studies for the registration batches. Except for Lot 4000508 (50 mg), which does not have a 15-minute time point, all the rest five lots of registration batches meet the $Q = (b)(4)$ at 15 minutes acceptance criteria (see Appendix A). The dissolution results (average = 99%, RSD = $(b)(4)$ range = $(b)(4)$) for 20-minute time point for the release testing for Lot 4000508 were provided, and stability results under long term conditions (25°C/75% RH) for Lot 4000508 show satisfactory dissolution results at 3-, 6-, and 18- month time points (see Appendix B).

2. Failure to meet the dissolution acceptance criteria ($Q = (b)(4)$ at 15 minutes) was observed with some of the stability time points. This finding was communicated to

the CMC reviewer, Josephine Jee. Nevertheless, based on the BCS Class I designation of Cyclophosphamide Capsules as agreed upon by the BCS Committee, the recommended acceptance criteria of $Q = \text{(b) (4)}$ at 15 minutes for the dissolution test for of Cyclophosphamide Capsules is adequate.

RECOMMENDATION

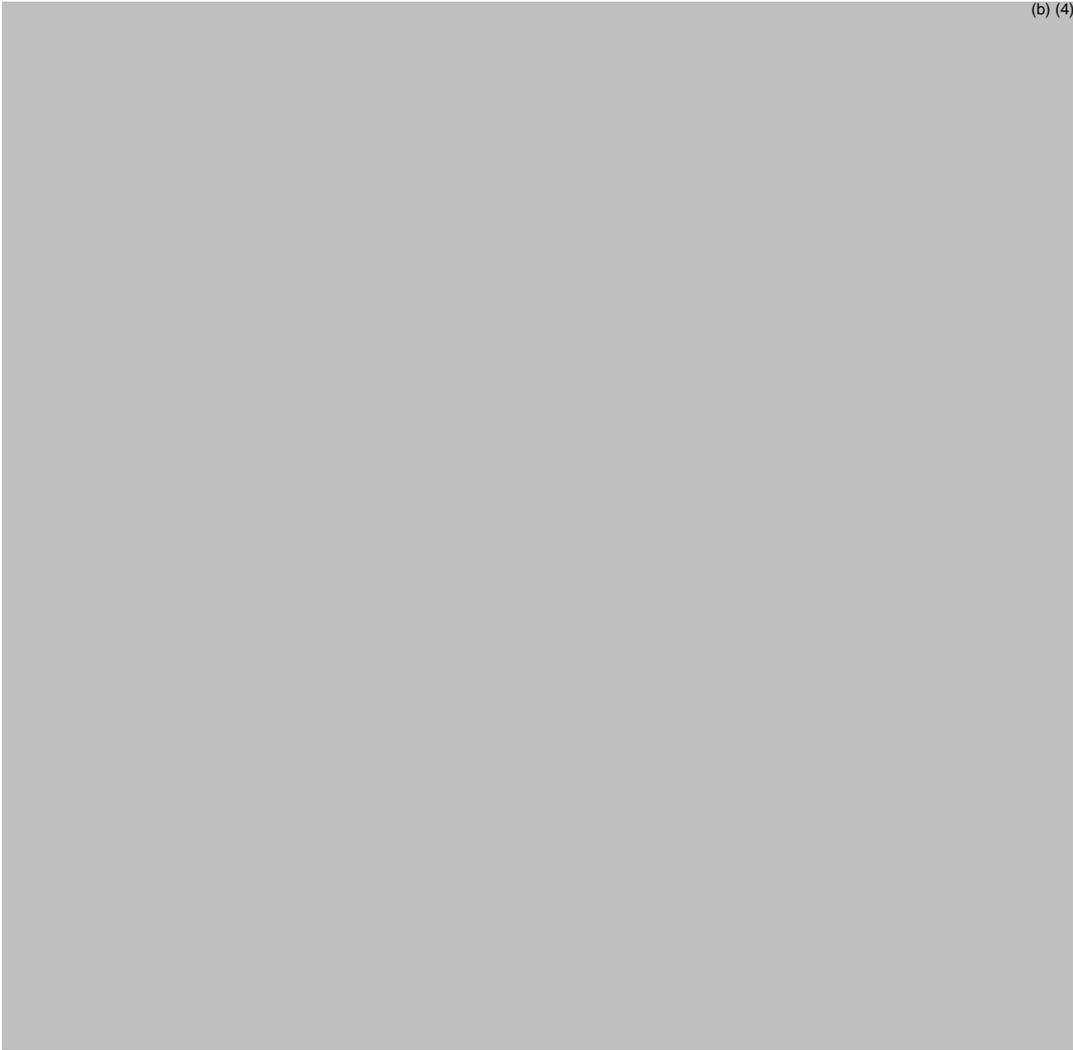
Upon the review of the overall information/data provided in the Original NDA submission and its amendments, the request for a waiver of *in vivo* studies was granted under the NDA based on the BCS I designation of Cyclophosphamide capsules. The validation results of the dissolution method are acceptable. The final dissolution acceptance criteria for Cyclophosphamide Capsules (25 mg and 50 mg) is $Q = \text{(b) (4)}$ at 15 minutes. Therefore, NDA 203-856 is recommended for approval from the Biopharmaceutics perspective.

**APPENDIX A: Dissolution Profiles for the Registration Batches (Release Test)
(25 mg: Lots 4000507, 4000591, 4000594; 50 mg: Lots 4000508, 4000592, 4000595)**



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APPENDIX B: Long Term Dissolution Stability Results for Lot 4000508



(b) (4)

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/s/

ZEDONG DONG
03/14/2013

ANGELICA DORANTES
03/14/2013

Clinical Pharmacology Review

NDA:	203856
Drug:	Cyclophosphamide capsule
Strengths:	25 and 50 mg
Sponsor:	Roaxane Lab
Submission Type:	505(b)(2); General Correspondence- BCS Classification Request
Submission Date:	7/2/12 under NDA 203856; 3/12/12 under IND 112446
Reviewer:	Sarah J. Schrieber, Pharm.D.
Team Leader:	Qi Liu, Ph.D.

Executive Summary:

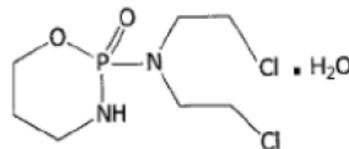
The objective of this NDA submission is to seek approval for the use of Cyclophosphamide capsules, 25 mg and 50 mg, via a 505(b)(2) pathway. The Reference Listed Drug (RLD) is Baxter Healthcare's Cytoxan® (cyclophosphamide tablets, NDA 012141).

A biowaiver was requested by the sponsor for Cyclophosphamide capsules under IND 112446 on 3/12/12 based on the Biopharmaceutics Classification System (BCS). Permeability of cyclophosphamide was evaluated using an *in vitro* monolayer model. Based on the data submitted, the clinical pharmacology reviewer concluded that cyclophosphamide is a highly permeable drug.

2 Question Based Review

2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Molecular Weight 279.1 g/mol
White to off white crystalline powder
Dissociation constant (pKa): 9.91
log octanol-water partition coefficient (log Kow): 0.63



2.2 Does the data submitted support that cyclophosphamide is a highly permeable drug?

The data submitted to describe the permeability of the drug met the threshold recommendations provided by the BCS guidance. The *in vitro* Caco-2 cell method used to determine permeability was adequately validated per the BCS guidance recommendations.

Permeability of cyclophosphamide was evaluated using an *in vitro* monolayer model, the Caco-2 human colon adenocarcinoma-derived cell line. The permeability studies were conducted at (b) (4).

Methods: Dosing solutions of cyclophosphamide were prepared in permeability assay buffer (HBSSg) at concentrations of 7.66, 76.6, and 766 μM . The internal permeability standards, (b) (4) (high-permeability internal standard) and (b) (4) (monolayer integrity marker compound), were included in each dosing solution. For unidirectional (apical-to-basolateral, A-to-B) permeability, samples were analyzed for cyclophosphamide, (b) (4), and (b) (4). For bidirectional permeability (A-to-B and B-to-A), cyclophosphamide was dosed alone and cyclophosphamide was the only analyte quantified. Permeability experiments were conducted with four replicates (n=4) at each concentration. For the apical-to-basolateral (A-to-B) permeability, dosing solutions were applied to the apical side, and for the basolateral-to-apical (B-to-A) permeability, dosing solutions were applied to the basolateral side. The pH was at 7.4 for both the apical and the basolateral side. The apical volume was 0.5 mL, and the basolateral volume was 1.5 mL. During permeability assays and post-experiment (PE) tests, cell monolayers were incubated in a humidified atmosphere at 37°C with 5% CO₂. The plates containing the cell monolayers were shaken using a Lab-Line Instruments Titer Plate Shaker set to a speed of 2.0 (130 rpm). The sampling times were 15, 30, and 45 min for the receivers, and 0 and 45 min for the donors. The sample volumes were 200 μL of the receiver and 50 μL of the donor. The receiver volume was replaced with fresh drug-free buffer after sample collection at 15 and 30 min. After the bidirectional permeability experiment was complete, the basolateral buffer was replaced with fresh drug-free buffer, and the apical buffer was replaced with fresh buffer containing (b) (4) for a post-experiment (PE) test. PE samples were collected at 30 min and analyzed for (b) (4). No PE test was conducted following the unidirectional (A-to-B) permeability assessment: the apparent permeability (P_{app}) of co-dosed (b) (4) and the ratio of (b) (4) P_{app} to (b) (4) P_{app} were used to monitor monolayer integrity.

Summary of Experimental Parameters

Dosing Concentrations:	7.66, 76.6, and 766 μM cyclophosphamide
Internal Controls:	(b) (4) (unidirectional only)
Replicates:	4
Directions:	A-to-B and B-to-A
Pre-incubation:	None
pH:	7.4 (apical and basolateral)
Time Points:	15, 30, and 45 min for receivers; 0 and 45 min for donors

Data Analysis:

Cumulative concentration in the receiver compartment: Since fluid withdrawn and replaced of at each sampling time point, cumulative concentrations were be calculated before the linear permeability curve could be constructed. For A-to-B receiver samples, the cumulative concentration at each time point, C_c, was equal to the sum of the measured concentration at that time point, C_m, and (b) (4) of the measured concentrations at the previous time points, since 200 μL of the 1.5 mL total sample was withdrawn and replaced. Similarly, for B-to-A receiver samples, the cumulative concentration at each time point, C_c, was equal to the sum of the measured concentration at that time point, C_m, and (b) (4) of the measured concentrations at the previous time points, since 200 μL of the 0.5 mL total sample was withdrawn and replaced.

For A-to-B receiver samples,

(b) (4)

For B-to-A receiver samples,

(b) (4)

Concentration in the donor compartment: Donor samples were not replaced with fresh buffer. Therefore, measured donor sample concentrations were used in the calculations.

Apparent permeability and recovery: The apparent permeability (P_{app}) and percent recovery were calculated as follows:

$$P_{app} = \frac{(b) (4)}{(b) (4)}$$
$$\text{Percent Recovery} = \frac{(b) (4)}{(b) (4)}$$

Where,

- (b) (4)
-
-
-
-
-
-

Efflux ratio: The efflux ratio is defined as: $P_{app} \text{ (B-to-A)} / P_{app} \text{ (A-to-B)}$.

Results: According to the BCS Guidance, the permeability study should be performed at concentration equivalent to 0.01, 0.1 and 1 times the highest dose strength dissolved in 250 mL. Based on the proposed highest dose strength of 50 mg of cyclophosphamide and its molecular weight of 261.07 (free base), the three dosing levels selected were 7.66 μM (1% of the proposed highest dose strength in 250 mL), 76.6 μM (10% of the highest proposed dose strength in 250 mL), and 766 μM (100% of the highest proposed dose strength in 250 mL). The internal control compounds, (b) (4) were included in each permeability experiment. The absorption of (b) (4) in humans is reported to be at least 90%. (b) (4), which has a fractional absorption of about 50% in humans, was included because its permeability is a sensitive indicator of Caco-2 membrane integrity (i.e. tightness). The bi-direction permeability of cyclophosphamide was also evaluated in order to explore possible active transport mechanisms. The following table presents the apparent A-to-B permeability values for the test compound, cyclophosphamide, and the internal reference compounds, (b) (4).

As shown in the table, the Caco-2 model discriminated low permeability compounds from high permeability compounds. The permeability of cyclophosphamide does not appear to be concentration-dependent. The permeability rank order of the three compounds was cyclophosphamide > (b) (4) at all three concentrations tested.

The recovery of cyclophosphamide and the two internal reference compounds at all three tested concentrations was high ranging from 87.2% to 105%.

Nominal Cyclophosphamide Dosing Concentration (μM)		7.66	76.6	766
Cyclophosphamide	P_{app}^a	30.1 ± 4.21	25.3 ± 6.51	31.3 ± 6.27
	Recovery (%)	95.0 ± 2.64	93.4 ± 3.57	105 ± 3.68
(b) (4)	P_{app}^a	7.11 ± 0.849	5.28 ± 0.755	6.86 ± 0.643
	Recovery (%)	92.9 ± 3.21	87.2 ± 5.75	103 ± 6.76
	P_{app}^a	0.324 ± 0.0901	0.235 ± 0.0631	0.298 ± 0.0948
	Recovery (%)	96.6 ± 3.82	93.0 ± 3.73	95.0 ± 2.65

^aUnits of P_{app} are 10^{-6} cm/s; e.g., "1.0" represents a value of 1.0×10^{-6} cm/s.

Cyclophosphamide is a passively transported drug. The efflux ratios for cyclophosphamide were between 0.745 and 1.02 at all test concentrations. Similar P_{app} values were obtained using different dosing concentrations and in both the A-to-B and B-to-A directions, indicating a lack of dependency of the measured *in vitro* permeability of cyclophosphamide on initial drug concentration or transport direction. These results which show a lack of directional dependence of permeability and no trend of decreasing A-to-B apparent permeability coefficient (P_{app}) with increasing concentration, are evidence that cyclophosphamide permeates Caco-2 monolayers primarily by passive diffusion.

Bidirectional (B-to-A and A-to-B) Permeability of Cyclophosphamide (mean \pm SD, n=4)

Dosing Conc. (μM)	A-to-B		B-to-A		Efflux Ratio ^a
	P_{app} (10^{-6} cm/s)	Recovery (%)	P_{app} ($\times 10^{-6}$ cm/s)	Recovery (%)	
7.66	29.6 ± 6.48	98.9 ± 5.88	30.2 ± 1.36	100 ± 2.74	1.02
76.6	37.4 ± 14.8	103 ± 7.94	28.1 ± 1.76^b	103 ± 7.18^b	0.752
766	34.9 ± 0.442^c	91.8 ± 3.82^c	26.0 ± 3.28^b	93.4 ± 0.699^b	0.745

^aEfflux ratios were calculated using the mean A-to-B and B-to-A P_{app} values.

^bOne monolayer failed on post-experiment atenolol P_{app} and was excluded from calculations (n=3).

^cOne monolayer failed on linearity and was excluded from calculations (n=3).

The BCS guidance recommends establishing suitability of a permeability method on 20 model drugs, the sponsor provided validation for 23 model drugs. As shown in the table below from the validation report (6ASLPBCSval), the rank order of permeability for the model compounds are consistent with the rank order of fraction absorbed in humans. The permeability of compounds are in three classes, i.e. high (Fraction absorbed in humans >90), medium (50 < Fraction absorbed in humans < 90), low (Fraction absorbed in humans < 50). Compounds with permeability coefficients in the Caco-2 monolayer assay greater than 2×10^{-6} cm/s, had a high fraction absorbed (>90%) in humans, whereas compounds with permeability coefficients less than 1×10^{-6} cm/s had a low fraction absorbed in humans. The sponsor's 23 model compounds cover a wide range of fraction

absorbed values. Based on the Caco-2 cell monolayer permeability method accurately identified all 23 test compounds as either low- or high-permeability, and Caco-2 cell monolayer assay is suitable for BCS study. The permeability coefficients and recovery values of the 23 test compounds used to establish the selectivity of the Caco-2 cell monolayer assay are listed in the table below.

Test Compound	pH 7.4		Permeability Class	Fraction Absorbed in Humans
	Permeability ($\times 10^{-6}$ cm/s)	Recovery (%)		
Antipyrine*	62.54 \pm 15.28	99.95 \pm 7.77	High	100
Atenolol*	0.19 \pm 0.05	89.97 \pm 7.58	Low	50
Caffeine	63.61 \pm 16.04	98.97 \pm 2.14	High	100
Carbamazepine	43.04 \pm 6.63	91.81 \pm 3.52	High	100
FITC-dextran*	<0.14	ND	Low	N/A
Fluvastatin ^a	5.69 \pm 0.20	94.57 \pm 8.36	High	~ 100
Furosemide	0.18 \pm 0.01	93.12 \pm 3.33	Low	61
Hydrochlorothiazide	0.55 \pm 0.14	95.67 \pm 2.42	Low	71
Ketoprofen	29.25 \pm 2.94	93.55 \pm 1.31	High	100
Labetalol	13.53 \pm 1.38	86.43 \pm 3.65	High	90
Lincomycin	0.22 \pm 0.09	82.35 \pm 4.06	Low	6 ~13
Mannitol	0.77 \pm 0.15	93.61 \pm 1.60	Low	15
Metoprolol	27.88 \pm 2.51	91.52 \pm 2.83	High	95
Minoxidil*	2.71 \pm 0.42	91.47 \pm 6.76	High	100
Nadolol	0.32 \pm 0.08	91.54 \pm 3.77	Low	35
Naproxen	59.17 \pm 2.64	88.12 \pm 0.87	High	94
Pindolol*	17.00 \pm 4.28	91.99 \pm 6.81	High	90
Propranolol	31.75 \pm 4.33	89.25 \pm 1.92	High	100
Ranitidine	0.28 \pm 0.04	91.20 \pm 3.69	Low	61
Sulfasalazine	0.07 \pm 0.00	88.63 \pm 2.25	Low	13
Theophylline	28.70 \pm 2.29	93.53 \pm 1.83	High	100
Timolol*	18.71 \pm 4.87	94.19 \pm 9.13	High	90
Verapamil	20.17 \pm 1.28	87.57 \pm 13.92	High	100

ND: not determined.

*The P_{app} values are presented as average \pm SD (n=4), except for the compounds used in the ruggedness tests, in which case the permeability values presented are the average results from the ruggedness tests (n=8 to 48).

^aThere are three components of the recovery calculation for fluvastatin: cumulative receiver concentration at 120 minutes, donor concentration at 120 minutes, and concentration in cell lysates.

Regarding the Caco-2 monolayer integrity, the study showed that it passed the post-experiment (PE) test criteria, which were as follows:

- Calculated $P_{app} \leq 1.0 \times 10^{-6}$ cm/s.
- Calculated $P_{app} \geq 3$ times P_{app} for the same monolayer.
- At least three monolayers in each group must meet the acceptance criteria individually.

❖ Reviewer Permeability Conclusions: The average P_{app} value for cyclophosphamide is greater than the P_{app} value of $(b) (4)$ at all three concentrations. The B-to-A P_{app} to A-to-B P_{app} ratios of cyclophosphamide are between 0.745 and 1.02 at all three concentrations and cyclophosphamide

permeates the Caco-2 membrane by passive diffusion. Cyclophosphamide may be classified as a highly permeable compound.

Stability in Gastrointestinal Fluid:

The cyclophosphamide stability in the intestinal tract using gastric and intestinal fluids as per the BCS Guidance was not provided. Based on the FDA Guidance to Industry, *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (BCS)* (August 2000), “Determining the extent of absorption in humans based on mass balance studies using total radioactivity in urine does not take into consideration the extent of degradation of a drug in the gastrointestinal fluid prior to intestinal membrane permeation. In addition, some methods for determining permeability could be based on loss or clearance of a drug from fluids perfused into the human and/or animal gastrointestinal tract either in vivo or in situ.”

The sponsor states that neither of the situations described in the FDA guidance applies to the 11ROXAP4GLPS165 permeability study. During the permeability assays conducted in study 11ROXAP4GLPS165, exact amounts of cyclophosphamide that crossed the membrane were directly measured at each time point using a highly selective LC-MS/MS MRM method free of the interference of degradants. Therefore, the sponsor states that whether cyclophosphamide is stable or not in the GI tract would not have any impact on the conclusion of the study.

- ❖ Reviewer GI Stability Conclusions: The sponsor’s rationale for not conducting gastric stability experiments appears acceptable.

RECOMMENDATION and COMMENTS:

1. The data submitted support that cyclophosphamide is a highly permeable drug.
2. Note that the final recommendation regarding the BCS-Class 1 classification will be given by the FDA’s BCS Committee.

Clinical Pharmacology Review Addendum

NDA:	203856
Drug:	Cyclophosphamide capsule
Strengths:	25 and 50 mg
Sponsor:	Roaxane Lab
Submission Type:	505(b)(2); General Correspondence- Biopharmaceutics Classification System (BCS) Classification Request
Submission Date:	11/30/12
Reviewer:	Sarah J. Schrieber, Pharm.D.
Team Leader:	Qi Liu, Ph.D.

Purpose: This review evaluates the gastric fluid stability data (study #12ROXAP4), which has been submitted by the sponsor in response to the recommendation from the FDA BCS Committee. The data submitted demonstrate that cyclophosphamide is stable when incubated at 37°C for 1 hour in simulated gastric fluid and for 3 hours in simulated intestinal fluid.

Regulatory Background: The sponsor is seeking approval via a 505(b)(2) pathway for the use of Cyclophosphamide capsules (25 mg and 50 mg) for the same indications currently applicable to the sponsor's approved ANDA 040032 Cyclophosphamide Tablets USP (25 mg and 50 mg). A biowaiver was requested by the sponsor for Cyclophosphamide capsules under IND 112446 on 3/12/12 based on the Biopharmaceutics Classification System (BCS). Permeability of cyclophosphamide was evaluated using an *in vitro* monolayer model. Based on the data submitted, the clinical pharmacology reviewer concluded that cyclophosphamide is a highly permeable drug (refer to the review on pages 1-6 above). However, the FDA BCS committee determined that until stability data over the physiologic pH range is evaluated, Cyclophosphamide cannot be classified as BCS Class I (see the clin pharm filing memo by Sarah Schrieber posted on 8/28/12 in DARRTS).

Study #12ROXAP4 Summary:

Title: Stability in Simulated Gastric and Intestinal Fluids of the Customer's Test Compound Cyclophosphamide

Methods:

- The chemical stability of cyclophosphamide was assessed in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) by dissolving cyclophosphamide 0.0556 mg/mL in each fluid, incubating at 37°C, and sampling at two time points (0 and 60 minutes for SGF; 0 and 180 minutes for SIF).
 - A single incubation (n=1) was prepared for each time point per matrix.
 - Time points mimic the physiological residence times in the gastric and intestinal environment.
- At each sampling time point, a 100 µL aliquot was quenched with 1900 µL of diluent (ACN:HBSSg 1:1 (v:v)).
 - Six replicates (n=6) of each sample were prepared and analyzed.
- SGF and SIF were prepared as described in USP35/NF30 (pg 1072).

Result: More than 98% of cyclophosphamide remained intact at the end of each incubation; see Table 1.

Table 1. Stability of Cyclophosphamide in Simulated Gastric and Intestinal Fluids

Cyclophosphamide	Simulated Gastric Fluid		Simulated Intestinal Fluid	
	Measured Concentration (nM)		Measured Concentration (nM)	
	0 min	60 min at 37°C	0 min	180 min at 37°C
Measured Concentration (nM)	199000	207000	180000	159000
	189000	108000	219000	189000
	192000	193000	173000	168000
	196000	196000	179000	195000
	207000	203000	193000	242000
	183000	241000	192000	163000
Mean	194333	191333	189333	186000
SD	8335	44311	16501	31010
Percentage of Remaining (%)	98.5		98.2	

Conclusion: Cyclophosphamide was stable when incubated at 37°C for 1 hour in simulated gastric fluid and for 3 hours in simulated intestinal fluid.

RECOMMENDATION and COMMENTS:

1. The data submitted support that cyclophosphamide is a highly permeable drug.
2. Note that the final recommendation regarding the BCS-Class 1 classification will be given by the FDA's BCS Committee.

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/s/

SARAH J SCHRIEBER
02/25/2013

QI LIU
03/04/2013

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	203856 / 505(b)(2)	Brand Name	Cyclophosphamide
OCPB Division (I, II, III)	V	Generic Name	Cyclophosphamide
Medical Division	DOP1	Drug Class	Alkylating agent
OCPB Reviewer	Sarah J. Schrieber, Pharm.D.	Indication(s)	Malignant diseases
OCPB Team Leader	Qi Liu, Ph.D.	Dosage Form	Capsule (25 mg and 50 mg)
		Dosing Regimen	1 to 5 mg/kg/day
Date of Submission	July 2, 2012	Route of Administration	Oral
Estimated Due Date of OCPB Review		Sponsor	Roxane Labs
PDUFA Due Date	May 3, 2013	Priority Classification	Standard
Division Due Date			

The objective of this NDA 505(b)(2) submission is to seek approval for the use of Cyclophosphamide Capsules, 25 mg and 50 mg for the same indications currently applicable to the sponsor's approved ANDA 040032 Cyclophosphamide Tablets USP, 25 mg and 50 mg. In late 2008, the brand manufacturer of Cytoxan® discontinued production and distribution of their cyclophosphamide product and Roxane Lab's ANDA 040032 became the Reference Listed Drug (RLD).

A biowaiver was requested by the sponsor for Cyclophosphamide Capsules under IND 112446 based on the Biopharmaceutics Classification System (BCS). Permeability of cyclophosphamide was evaluated using an in vitro monolayer model. The FDA BCS committee has determined that until stability data over the physiologic pH range is evaluated, Cyclophosphamide cannot be classified as BCS Class I.

The proposed label will also be under Physician Labeling Rule (PLR) conversion. Several references have been used in the clinical pharmacology sections which have resulted in changes to the data. The label requires clinical pharmacology review.

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

The following information requests should be sent to the Applicant:

1. The FDA Biopharmaceutics Classification System (BCS) committee has determined that stability data over the physiologic pH range are needed to complete the evaluation of your request for a BCS Class 1 assignment for cyclophosphamide drug substance. Once the gastric stability data are generated, please submit this information under both IND 112446 and NDA 203856. In your NDA, please also include a comment stating that FDA requested this information to support your BCS-based biowaiver request for Cyclophosphamide Capsules. We request this information be submitted within one month. If this is not feasible, please provide your proposal with justification.
2. Please submit the individual publications cited within the Moore (1991) reference which supports the relevant updated labeling statements (e.g., regarding the absolute bioavailability, Mathias (1984) and Wagner and Feneberg (1984) are cited within Moore (1991)).

Sarah J. Schrieber, Pharm.D. August 28, 2012

 Reviewing Clinical Pharmacologist Date

Qi Liu, Ph.D. August 28, 2012

 Team Leader/Supervisor Date

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/s/

SARAH J SCHRIEBER
08/28/2012

QI LIU
08/28/2012

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	203-856 - Resubmission/After Refusal to File
Product name, generic name of the active, and dosage form and strength	Cyclophosphamide capsules, 25 and 50 mg (two strengths)
Submission date	July 2, 2012
Applicant	Roxane Laboratories
Medical Division	OODP
Type of Submission	505(b)(2), Original (N-000) Resubmission
Biopharmaceutics Reviewer	Zedong Dong, Ph.D.
Biopharmaceutics Lead	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS				
<u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	X		
2.	Is the dissolution test part of the DP specifications?	X		Proposed dissolution acceptance criterion: Q= (b) (4) USP Apparatus 1 (100 rpm), 900 mL DI water The acceptability of the above proposed acceptance criteria will be a review issue.
3.	Does the application contain the dissolution method development report?		X	The applicant needs to provide dissolution method development report to demonstrate the discriminating capability of the method.
4.	Is there a validation package for the analytical method and dissolution methodology?	X		
5.	Does the application include a biowaiver request?	X		The NDA includes a biowaiver request based on BCS-Class 1 designation of cyclophosphamide drug substance. The BCS information was submitted under IND 112,446 and the FDA Biopharmaceutics Classification System (BCS) committee determined that stability data over the physiologic pH range are needed to complete the evaluation of the BCS Class 1 assignment for cyclophosphamide drug substance. Once the gastric stability data are submitted and reviewed the BCS Committee will provide their final decision. However, the lack of the GI stability information is a review issue, rather than a filing issue.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

6.	Does the application include an IVIVC model?		X	Not applicable
7.	Does the application include information/data on in vitro alcohol dose-dumping potential?		X	Not applicable
8.	Is there any in vivo BA or BE information in the submission?		X	Not applicable
B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
9.	IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		<ul style="list-style-type: none"> ➤ The NDA is filable from the Biopharmaceutics Perspective ➤ The acceptability of the proposed dissolution method and acceptance criteria will be a review issue. ➤ The biowaiver of cyclophosphamide capsules will be a review issue depending on the BCS Committee recommendation on the BCS 1 designation of cyclophosphamide drug substance.
10.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable.
11.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			Fileable
12.	Are there any potential review issues identified?			See comments below. Additionally, GI stability information is needed to complete the BCS-Class 1 assessment, and therefore to support the BCS-based biowaiver request. An IR letter draft by OCP will be send to the Applicant requesting this information.

**PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW**

13.	<p>Reviewer Comments (to be conveyed to the Applicant in the 74 day letter):</p> <ol style="list-style-type: none">1. The dissolution method development report was not included in your NDA submission. Please provide the dissolution method development report demonstrating that the proposed dissolution method has discriminating capability against potential significant manufacturing process changes that may impact the drug product quality.2. Please provide the dissolution profiles (mean, range, and RSD) of the registration batches for both strengths from release as well as stability testing.
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{See appended electronic signature page}

Zedong Dong, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

08/28/2012
Date

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

08/28/2012
Date

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/s/

ZEDONG DONG
08/28/2012

ANGELICA DORANTES
08/28/2012

ONDQA BIOPHARMACEUTICS FILING REVIEW

NDA#:	203-856
Submission Date:	12/21/2011
Brand Name:	N/A
Generic Name:	Cyclophosphamide, USP
Formulation:	Immediate Release Capsule
Strength:	25 mg and 50 mg
Applicant:	Roxane Laboratories, Inc.
Type of submission:	Original NDA, 505(b)(2), Standard Review
Reviewer:	Zedong Dong, Ph.D.

SUBMISSION

NDA 203-856 is submitted under FDC 505(b)(2) category for Cyclophosphamide Capsules 25 mg and 50 mg for the treatment of malignant diseases, often used in combination with other neoplastic drugs, or for the treatment of carefully selected cases of biopsy proven “minimal change” nephritic syndrome in children. The reference drug product for this NDA is Cyclophosphamide Tablets (ANDA 40-032), also manufactured by Roxane Laboratories. This application includes a request for a biowaiver in lieu of a human pharmacokinetic study to support the change in formulation from a tablet to a capsule. The biowaiver is based on the data submitted in the NDA to support the approval of a BCS-Class 1 classification for Cyclophosphamide.

BIOPHARMACEUTICS REVIEW

The Biopharmaceutics review will be focused on the evaluation of the information/data supporting the approval of; 1) the BCS-Class 1 classification for Cyclophosphamide drug substance and fast dissolving characteristics for Cyclophosphamide Capsules drug product; 2) their request for a BCS-Class 1 bioavailability waiver for their product, Cyclophosphamide 25 mg and 50 mg Capsules; and 3) the proposed dissolution method and acceptance criterion.

The applicant submitted solubility, permeability, and dissolution information to support the BCS-Class 1 classification of Cyclophosphamide, drug substance. This information was submitted according to the recommendation given by the Agency in the Pre-IND Meeting (*preliminary comments dated 07/19/2011 in DARRTS*). However, gastrointestinal stability data for Cyclophosphamide was not provided. The applicant considered that this information was not necessary to support the approval of a BCS-Class 1 designation for their drug product.

The proposed dissolution method includes Tier 1 and Tier 2 tests, which are essentially the same as the compendial USP method (Apparatus 1 at 100 rpm, in 900 mL dissolution medium). The dissolution medium for Tier 1 test is DI water, whereas Tier 2 test dissolution medium is DI water with pepsin. The proposed acceptance criterion for dissolution test is $Q = \text{[redacted]}^{(b)(4)}$. The submission did not include the dissolution

development report with data supporting the selected testing parameters and discriminating capability of the selected dissolution method. The analytical procedures of the dissolution method and the method validation report were included in the submission.

COMMENT TO BE CONVEYED TO THE APPLICANT

1. To support the proposed BCS-Class 1 category for Cyclophosphamide, please provide the gastric stability information for cyclophosphamide as outlined in the FDA correspondence for IND 112446 (4.1. Gastric Stability) dated 07/19/2011.
2. Please provide dissolution method development report to justify the instrumental parameters for the dissolution method.
3. Based on the dissolution requirement for the drug product of BCS-Class 1 category, the proposed acceptance criterion for dissolution ($Q = \text{[REDACTED]}^{(b)(4)}$) is not acceptable. Please tighten the acceptance criterion accordingly to support a fast dissolving BCS-Class 1 drug product (i.e., $Q = \text{[REDACTED]}^{(b)(4)}$ at 15 minutes).

RECOMMENDATION

NDA 203-856 for Cyclophosphamide capsules is fileable from the Biopharmaceutics perspective.

Zedong Dong, Ph.D.
Reviewer
ONDQA Biopharmaceutics

Date

Angelica Dorantes, Ph.D.
Supervisory Lead
ONDQA Biopharmaceutics

Date

CC: NDA 203-856
Kim Robertson, Debbie Mesmer

APPENDIX A

Formulation Compositions 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)
Pregelatinized Starch, NF					(b) (4)
Sodium Steryl Fumarate, NF					(b) (4)
					(b) (4)

¹ Equivalent to 25 mg of Cyclophosphamide (Anhydrous)

² Equivalent to 50 mg of Cyclophosphamide (Anhydrous)

APPENDIX B

Proposed Dissolution Acceptance Criteria and Method Conditions

Dissolution	1726-03	Capsules tested with <u>Tier I</u> media meet USP <711> S1, S2 and S3 criteria: NLT (b) (4) (Q) of the labeled amount dissolves in (b) (4)	<u>Tier I</u> 6 capsules tested with Tier I media, meet USP <711> S1 criteria: NLT (b) (4) (Q) of the labeled amount dissolves in (b) (4) If S1 criteria are not met for Tier I, proceed to Tier II. <u>Tier II</u> Capsules tested with Tier II media (with Pepsin) meet USP <711> S1, S2 and S3 criteria: NLT (b) (4) (Q) of the labeled amount dissolves in (b) (4)
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DISSOLUTION CONDITIONS

USP Apparatus:
 Speed:
 Medium:

 Temperature:
 Volume:
 Sampling Times:
 Pull Volume:
 Filter:

(b) (4)

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/s/

ZEDONG DONG
02/09/2012

ANGELICA DORANTES
02/09/2012

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	203856	Brand Name	Cyclophosphamide
OCPB Division (I, II, III)	V	Generic Name	Cyclophosphamide
Medical Division	DOP1	Drug Class	Alkylating agent
OCPB Reviewer	Sarah J. Schrieber, Pharm.D.	Indication(s)	Malignant diseases
OCPB Team Leader	Qi Liu, Ph.D.	Dosage Form	Capsule (25 mg and 50 mg)
		Dosing Regimen	1 to 5 mg/kg/day
Date of Submission	December 21, 2011	Route of Administration	Oral
Estimated Due Date of OCPB Review		Sponsor	Roxane Labs
PDUFA Due Date		Priority Classification	
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				

Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	x	1	1	
(IVIVC):				
Bio-wavier request based on BCS	x			
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1	1	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	x			
Comments sent to firm?	No			
QBR questions (key issues to be considered)	Are the cyclophosphamide solubility and permeability data adequate to grant a BCS classification?			
Other comments or information not included above	None.			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

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SARAH J SCHRIEBER
02/08/2012

QI LIU
02/08/2012