CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210852Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 23, 2022
From	Xiao Hong Chen, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	210852 Resubmission#3
Applicant	Dr. Reddy's Laboratories Limited
Date of Submission	June 18, 2020
PDUFA Goal Date	December 18, 2020
Proprietary Name / Established (USAN) names	Cyclophosphamide Injection
Dosage forms / Strength	500mg/ml; 1g/2ml; 2g/4ml
Proposed Indication(s)	Cyclophosphamide is an alkylating drug indicated for treatment of malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma
Recommended:	Complete Response

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Product Integrated Quality Assessment; in DARRTS, dated March 23, 2022
  - Ruth Moore, Ph.D. for Office of Pharmaceutical Manufacturing Assessment
  - Xiao Hong Chen, Ph.D. as Application Technical Lead

Summary of Review

Background

The original NDA was submitted on 9/28/2017. A Complete Responses (CR) letter was issued to the applicant on 7/24/2018 based on the "unacceptable" recommendation from the facility review. Specifically, the OAI inspection carried out in the first review cycle for Dr. Reddy's Laboratories Limited FEI 3006549835 (responsible for DP manufacturing) renders the facility unacceptable.

In the resubmission received on 11/5/2018, the applicant provided the response to the facility deficiencies outlined in the CR letter. The facility reviewer evaluated the inspection history documents and the then status for Dr. Reddy's Laboratories Limited FEI 3006549835, and recommended the facility acceptable based on the OAI status being downgraded to VAI as well as risk assessment. However, a GMP inspection concluded on (b) (4) on the drug substance manufacturing site, (b) (4) found the facility is not incompliance with GMP. That facility was recommended unacceptable by OPMA. The resubmission was issued a Complete Response Letter dated May 3, 2019.

The applicant made a second resubmission on 5/21/2019, and provided its response to the facility deficiencies listed in the CR letter. However, neither the API nor the DP manufacturing facilities were deemed acceptable, and a "Withhold" recommendation was made by OPMA. The resubmission was issued a DR letter on 11/20/2019.

The applicant made a third resubmission on 12/4/2019, and provided its response to the facility deficiencies listed in the CR letter. There are no other changes provided in the resubmission. The OPMA reviewed the application and other inspectional documents and concluded that the API manufacturing facility, (b) (4) for NDA 210852 is deemed unacceptable. A **withhold** recommendation has been made for (b) (4) FEI (b) (4) The resubmission was issued a DR letter on 5/21/2020.

The applicant made a forth resubmission on 6/18/2020, and provided its response to the facility deficiencies listed in the CR letter. There are no other changes provided in the resubmission. The API manufacturing facilities was still in unacceptable status, and a "withhold" recommendation was made by OPMA. The resubmission was issued a DR letter on 11/6/2020.

For the current 5th resubmission, the applicant did not propose any CMC changes. The pending deficiency is the OAI status for the API manufacturing facility, (b) (4) which has not been addressed adequately.

Recommendations and Conclusion on Approvability
The NDA 210852, Cyclophosphamide Injection, is recommended for **Complete Response** based on the "**withhold**" recommendation from the Office of Pharmaceutical Manufacturing Assessment. A withhold recommendation has been made for (b) (4) FEI (b) (4) The following deficiency comments should be included in the action letter:

> *During a recent inspection of the (b) (4) FEI (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.*

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/s/

XIAOHONG CHEN
03/23/2022 01:36:27 PM

Cross-Discipline Team Leader Review

Date	November 4, 2020
From	Xiao Hong Chen, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	210852 Resubmission#3
Applicant	Dr. Reddy's Laboratories Limited
Date of Submission	June 18, 2020
PDUFA Goal Date	December 18, 2020
Proprietary Name / Established (USAN) names	Cyclophosphamide Injection
Dosage forms / Strength	500mg/ml; 1g/2ml; 2g/4ml
Proposed Indication(s)	Cyclophosphamide is an alkylating drug indicated for treatment of malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma
Recommended:	Complete Response

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Product Integrated Quality Assessment; in DARRTS, dated 11/4/2020
  - Aditi Thakur, Ph.D. for facility
  - Xiao Hong Chen, Ph.D. as Application Technical Lead

Summary of Review

Background

The original NDA was submitted on 9/28/2017. A Complete Responses (CR) letter was issued to the applicant on 7/24/2018 based on the "unacceptable" recommendation from the facility review. Specifically, the OAI inspection carried out in the first review cycle for Dr. Reddy's Laboratories Limited FEI 3006549835 (responsible for DP manufacturing) renders the facility unacceptable.

In the resubmission received on 11/5/2018, the applicant provided the response to the facility deficiencies outlined in the CR letter. The facility reviewer evaluated the inspection history documents and the then status for Dr. Reddy's Laboratories Limited FEI 3006549835, and recommended the facility acceptable based on the OAI status being downgraded to VAI as well as risk assessment. However, a GMP inspection concluded on (b) (4) on the drug substance manufacturing site, (b) (4) FEI (b) (4) found the facility is not incompliance with GMP. That facility was recommended unacceptable by OPMA. The resubmission was issued a Complete Response Letter dated May 3, 2019.

The applicant made a second resubmission on 5/21/2019, and provided its response to the facility deficiencies listed in the CR letter. However, neither the API nor the DP manufacturing facilities were deemed acceptable, and a "Withhold" recommendation was made by OPMA. The resubmission was issued a DR letter on 11/20/2019.

The applicant made a third resubmission on 12/4/2019, and provided its response to the facility deficiencies listed in the CR letter. There are no other changes provided in the resubmission. The OPMA reviewed the application and other inspectional documents and concluded that the API manufacturing facility, (b) (4) for NDA 210852 is deemed unacceptable. A **withhold** recommendation has been made for (b) (4) FEI (b) (4) The resubmission was issued a DR letter on 5/21/2020.

For the current 4th resubmission, there are no CMC other changes. The pending deficiency is the noncompliant status for the API manufacturing facility, (b) (4) Based on OAI status for (b) (4) OPMA made "withhold" recommendation for the NDA.

Recommendations and Conclusion on Approvability
The NDA 210852, Cyclophosphamide Injection, is recommended for **Complete Response** based on the "**withhold**" recommendation from the Office of Pharmaceutical Manufacturing Assessment. A withhold recommendation has been made for (b) (4) FEI (b) (4) The following deficiency comments should be included in the action letter:

> *During a recent inspection of the (b) (4) FEI (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.*

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/s/

XIAOHONG CHEN
11/04/2020 01:44:11 PM

Cross-Discipline Team Leader Review

Date	May 6, 2020
From	Xiao Hong Chen, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	210852 Resubmission#3
Applicant	Dr. Reddy's Laboratories Limited
Date of Submission	December 4, 2019
PDUFA Goal Date	June 4, 2020
Proprietary Name / Established (USAN) names	Cyclophosphamide Injection
Dosage forms / Strength	500mg/ml; 1g/2ml; 2g/4ml
Proposed Indication(s)	Cyclophosphamide is an alkylating drug indicated for treatment of malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma
Recommended:	Complete Response

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Product Integrated Quality Assessment; in Panorama, dated 5/5/2020
  - Aditi Thakur, Ph.D. for facility
  - Xiao Hong Chen, Ph.D. as Application Technical Lead
- DMEPA review (Tingting Gao, PharmD.); in DARRTS, dated 2/20/2020

Summary of Review

Background

The original NDA was submitted on 9/28/2017. A Complete Responses (CR) letter was issued to the applicant on 7/24/2018 based on the "unacceptable" recommendation from the facility review. Specifically, the OAI inspection carried out in the first review cycle for Dr. Reddy's Laboratories Limited FEI 3006549835 (responsible for DP manufacturing) renders the facility unacceptable.

In the resubmission received on 11/5/2018, the applicant provided the response to the facility deficiencies outlined in the CR letter. The facility reviewer evaluated the inspection history documents and the then status for Dr. Reddy's Laboratories Limited FEI 3006549835, and recommended the facility acceptable based on the OAI status being downgraded to VAI as well as risk assessment. However, a GMP inspection concluded on (b) (4) n the drug substance manufacturing site, (b) (4) FEI found the facility is not

incompliance with GMP. That facility was recommended unacceptable by OPMA. The resubmission was issued a Complete Response Letter dated May 3, 2019.

The applicant made a second resubmission on 5/21/2019, and provided its response to the facility deficiencies listed in the CR letter. However, neither the API nor the DP manufacturing facilities were deemed acceptable, and a "Withhold" recommendation was made by OPMA. The resubmission was issued a DR letter on 11/20/2019.

The applicant made a third resubmission on 12/4/2019, and provided its response to the facility deficiencies listed in the CR letter. There are no other changes provided in the resubmission. The OPMA reviewed the application and other inspectional documents and concluded that the manufacturing facility for NDA 210852 is deemed unacceptable. A **withhold** recommendation has been made for (b) (4) FEI (b) (4)

Labeling Review by DMEPA
The proposed Cyclophosphamide Injection PI, container labels, and carton labeling are acceptable from a medication error perspective. DMEPA has no further recommendations.

Recommendations and Conclusion on Approvability
The NDA 210852, Cyclophosphamide Injection, is recommended for **Complete Response** based on the "**withhold**" recommendation from the Office of Pharmaceutical Manufacturing Assessment. Specifically, following a review of the application and other inspectional documents, the manufacturing facility, (b) (4) FEI (b) (4) is found to be **unacceptable.** A withhold recommendation has been made for (b) (4) (b) (4) FEI (b) (4) The following deficiency comments should be included in the action letter:

During a recent inspection of the (b) (4) *FEI* (b) (4) *manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.*

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/s/

XIAOHONG CHEN
05/06/2020 11:47:57 AM

Cross-Discipline Team Leader Review

Date	November 13, 2019
From	Xiao Hong Chen, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	210852 Resubmission#2
Applicant	Dr. Reddy's Laboratories Limited
Date of Submission	May 21, 2019
PDUFA Goal Date	November 21, 2019
Proprietary Name / Established (USAN) names	Cyclophosphamide Injection
Dosage forms / Strength	500mg/ml; 1g/2ml; 2g/4ml
Proposed Indication(s)	Cyclophosphamide is an alkylating drug indicated for treatment of malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma
Recommended:	Complete Response

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Product Integrated Quality Assessment; in Panorama, dated 11/13/2019
  - Aditi Thakur, Ph.D. for facility
  - Xiao Hong Chen, Ph.D. as Application Technical Lead
- Marketing and Advertising (MARITSA SERLEMITSOS-DAY); in DARRTS, dated 9/16/2019
- Medication Error (Tingting Gao, PharmD.); in DARRTS, dated 10/7/2019

Summary of Review

Background

The original NDA was submitted on 9/28/2017. A Complete Responses (CR) letter was issued to the applicant on 7/24/2018 based on the "unacceptable" recommendation from the facility review. Specifically, the OAI inspection carried out in the first review cycle for Dr. Reddy's Laboratories Limited FEI 3006549835 (responsible for DP manufacturing) renders the facility unacceptable. In the following resubmission received on 11/5/2018, the applicant provided the response to the facility deficiencies outlined in the CR letter. The facility reviewer evaluated the inspection history documents and the then status for Dr. Reddy's Laboratories Limited FEI 3006549835, and recommended the facility acceptable based on the OAI status being downgraded to VAI as well as risk assessment. However, a GMP inspection concluded on (b) (4) on the drug substance manufacturing site, (b) (4) FEI (b) (4) found the facility is not incompliance with GMP. That facility was recommended

unacceptable. The resubmission was issued a Complete Response Letter dated May 3, 2019. The Applicant submitted the current resubmission following receiving the CR letter. There are no other changes provided in the resubmission.

Recommendations and Conclusion on Approvability
The resubmission of NDA 210852 dated May 21, 2019, is recommended for **Complete Response** from the Office of New Drug Products, Office of Pharmaceutical Quality, based on the "**withhold**" recommendation made by the Office of Pharmaceutical Manufacturing Assessment.

Following a review of the application and other inspectional documents, the manufacturing facilities for NDA 210852 are found to be **unacceptable.** A withhold recommendation has been made for (b) (4) FEI (b) (4) and Dr. Reddy's Laboratories Limited (FEI 3006549835).

Recommended Comments to Applicant
The following facility deficiencies will be included in the Complete Response letter for this NDA resubmission:

During a recent inspection of the (b) (4) *FEI* (b) (4) *and Dr. Reddy's Laboratories Limited (FEI 3006549835) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.*

Labeling Review by OPDP
OPDP has reviewed the attached proposed carton labeling and container label submitted by the Sponsor to the electronic document room on March 19, 2019, and they do not have any comments.

Labeling Review by DMEPA
Dr. Reddy's Laboratories Class 2 Resubmission contains no labels and labeling, and Dr. Reddy's stated there are no changes to the previously submitted container labels and carton labeling (submitted June 5, 2018) and Prescribing Information (submitted April 27, 2018). DMEPA has determined that the proposed Cyclophosphamide Injection PI, container labels, and carton labeling could be improved to ensure safe product use. DMEPA's comments have been conveyed to the applicant. The applicant has made recommended changes based on the FDA recommendation. The revised container label and carton labeling for Cyclophosphamide Injection are acceptable from a medication error perspective.

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/s/

XIAOHONG CHEN
11/13/2019 04:16:43 PM

Cross-Discipline Team Leader Review

Date	April 24, 2019
From	Xiao Hong Chen, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	210852 Resubmission
Applicant	Dr. Reddy's Laboratories Limited
Date of Submission	November 5, 2018
PDUFA Goal Date	May 5, 2019
Proprietary Name / Established (USAN) names	Cyclophosphamide Injection
Dosage forms / Strength	500mg/ml; 1g/2ml; 2g/4ml
Proposed Indication(s)	Cyclophosphamide is an alkylating drug indicated for treatment of malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma
Recommended:	Complete Response

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Product Integrated Quality Assessment; in Panorama, dated 4/24/2019
  - Aditi Thakur, Ph.D. for facility
  - Xiao Hong Chen, Ph.D. as Application Technical Lead
- Clinical Pharmacology (Huiming Xia, Ph.D.); in DARRTS, dated 4/11/2019
- Marketing and Advertising (Kevin Wright, PharmD.); in DARRTS, dated 3/27/2019
- Medication Error (Tingting Gao, PharmD.); in DARRTS, dated 3/22/2019

Summary of Review

The original NDA was submitted on 9/28/2017. A Complete Responses (CR) letter was issued to the applicant on 7/24/2018 based on the "unacceptable" recommendation from the facility review. Specifically, the OAI inspection carried out in the first review cycle for Dr. Reddy's Laboratories Limited FEI 3006549835 renders the facility unacceptable. In the current resubmission received on 11/5/2018, the applicant provided its response to the facility deficiencies outlined in the CR letter. The facility reviewer evaluated the inspection history documents and the current status for Dr. Reddy's Laboratories Limited FEI 3006549835, and recommended the facility acceptable based on the OAI status being downgraded to VAI as well as risk assessment.

There was a recent GMP inspection on the drug substance manufacturing site, (b) (4) (b) (4) FEI (b) (4) concluded on (b) (4) and recommended as OAI during this review cycle. The facility is deemed unacceptable.

There are no other changes provided in the resubmission.

Recommendations and Conclusion on Approvability
The NDA 210852, Cyclophosphamide Injection, is recommended for **Complete Response** from the Office of New Drug Products, Office of Pharmaceutical Quality, based on the "inadequate" recommendation for the facility review.

During a recent inspection of the (b) (4) FEI (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Recommended Comments to Applicant
The following facility deficiency will be included in the Complete Response letter for this NDA resubmission:

> *Following a review of the application, Pre-approval facility inspection results, and other inspectional documents, the manufacturing facilities for NDA 210852 are found to be unacceptable. A withhold recommendation has been made for* (b) (4) (b) (4) *FEI* (b) (4)

Labeling Review by OPDP
OPDP has reviewed the attached proposed carton labeling and container label submitted by the Sponsor to the electronic document room on March 19, 2019, and they do not have any comments.

Labeling Review by DMEPA
Dr. Reddy's Laboratories Class 2 Resubmission contains no labels and labeling, and Dr. Reddy's stated there are no changes to the previously submitted container labels and carton labeling (submitted June 5, 2018) and Prescribing Information (submitted April 27, 2018). DMEPA has determined that the proposed Cyclophosphamide Injection PI, container labels, and carton labeling could be improved to ensure safe product use. DMEPA's comments have been conveyed to the applicant. The applicant has made recommended changes based on the FDA recommendation. The revised container label and carton labeling for Cyclophosphamide Injection are acceptable from a medication error perspective.

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/s/

XIAOHONG CHEN
04/24/2019 12:28:05 PM

Cross-Discipline Team Leader Review

Date	July 13, 2018
From	Xiao Hong Chen, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	210852
Applicant	Dr. Reddy's Laboratories Limited
Date of Submission	September 28, 2017
PDUFA Goal Date	July 28, 2018
Proprietary Name / Established (USAN) names	Cyclophosphamide Injection
Dosage forms / Strength	500mg/ml; 1g/2ml; 2g/4ml
Proposed Indication(s)	Cyclophosphamide is an alkylating drug indicated for treatment of malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma
Recommended:	Complete Response

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Product Integrated Quality Assessment; in Panorama, dated 12-Jul-2018
  - Mohd Shahjahan Kabir, Ph.D. for drug substance
  - Amit Mitra, Ph.D. for drug product
  - Zhaoyang Meng, Ph.D. for drug product process
  - Jennifer Thomas, Ph.D. for microbiology
  - Aditi Thakur, Ph.D. for facility
  - Zhuojun (Joan) Zhao, Ph.D. for biopharmaceutics
  - Xiao Hong Chen, Ph.D. as Application Technical Lead
- Clinical Pharmacology (Huiming Xia, Ph.D.); in DARRTS, dated 9-Jul-2018
- Pharmacology/Toxicology (Claudia Miller, Ph.D.); in DARRTS, dated 19-Jun-2018
- Marketing and Advertising (Kevin Wright, PharmD.); in DARRTS, dated 3-May-2018
- Medication Error (Tingting Gao, PharmD.); in DARRTS, dated 8-Jun-2018

1. Introduction

AuroMedics Pharma, LLC submitted this 505(b)(2) New Drug Application (NDA) for Cyclophosphamide Injection Concentrate 500 mg, 1 g and 2 g for the same (b) (4) (b) (4) route of administration, dosages, and dosing schedule as Cytoxan®, the listed drug (LD), held by Baxter under NDA 12142. AuroMedics Cyclophosphamide Injection Concentrate differs from Cytoxan® drug product formulation, in that it contains ethanol

(dehydrated alcohol) as an excipient instead of mannitol. The Applicant developed this new formulation of cyclophosphamide to address the issues observed with slow reconstitution and dissolution of the currently marketed powder product. In contrast to the LD formulation, AuroMedics Cyclophosphamide Injection Concentrate is already in solution to facilitate preparation and ensure that the drug substance is completely dissolved at time of administration.

This application relies on the Agency's determination of safety and efficacy for the LD, Cytoxan® Cyclophosphamide Injection, lyophilized powder, which was approved for marketing under NDA 12,142 on November 16, 1959, and currently discontinued.

2. Background

A pre-IND/pre-NDA meeting request (written response only) from the Applicant was submitted under IND 127067 and received on December 12, 2015. A final written response was sent to the Applicant on February 02, 2016. The Applicant indicated that the long-term stability studies have been performed and show cyclophosphamide concentration degradation mechanism leads to (b) (4) based impurities due to the presence of (b) (4) in the formulation. The Applicant acknowledged that TDI of the (b) (4) impurities exceeds the identification and qualification thresholds stipulated in ICH Guideline Q3B (R2) guideline; however, they requested to provide a safety assessment instead of conducting toxicity studies for the drug product. The Agency agreed that providing a safety assessment on the drug product degradants may be an alternative approach to conducting an animal toxicology study to qualify these degradants; however, the acceptability of the safety assessment to support the proposed drug product specifications would be determined after reviewing all available data submitted to the NDA, including referenced published literature and CMC data on the to-be-marketed drug product.

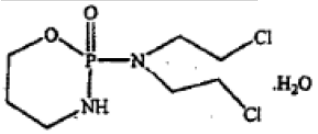
3. Chemistry, Manufacturing and Controls (CMC)

Drug Substance
International Nonproprietary Name (rINN): Cyclophosphamide
f
Pharmacopoeia Monograph Name: Cyclophosphamide

Chemical Name: N,N-bis (2-chloroethyl)-N'-(3-hydroxypropyl) phosphordiamidic acid cyclic ester monohydrate

CAS Registry Number: 6055-19-2

Chemical Structure:



Molecular Formula: C7H15Cl2N2O2P • H2O
Molecular Weight: 279.09

Cyclophosphamide drug substance is a white to almost white powder. It is freely soluble in ethanol and soluble in water. Cyclophosphamide monohydrate is not hygroscopic. Cyclophosphamide Monohydrate contains one chiral center. The intended product is a racemic mixture.

Cyclophosphamide drug substance is manufactured by [redacted] in [redacted] The CMC information for the drugs substance are cross-referenced to Type II DMF [redacted] The DMF [redacted] (Cyclophosphamide Monohydrate, USP) was previously reviewed (Review #3) by Yongjun Gao dated 12/19/2017, and was found to be Adequate as an API supplier for an ANDA; no further significant amendment is noted for the DMF [redacted] The drug substance information for NDA 210852 is deemed acceptable.

Drug Product

The drug product is a sterile, non-pyrogenic, solution of cyclophosphamide, USP in dehydrated alcohol, USP manufactured in three strengths, 500 mg, 1 g, and 2 g per vial. The formulation for the proposed drug product in this NDA is different from the LD, Cytoxan. The LD is a lyophilized drug product with mannitol as the excipient. The proposed drug product is formulated in a vial with dehydrated alcohol to produce 100 mg/ml concentration. The drug product is to be reconstituted with normal saline to produce 20 mg/ml concentration of cyclophosphamide for direct intravenous injection. For infusion, the drug is to be diluted to a final concentration of 2 mg/mL cyclophosphamide with the following options: 1) dilute with 0.45% sodium chloride injection; 2) dilute with 5% dextrose solution; 3) dilute with 5% dextrose and 0.9% sodium chloride injection. The drug product release and stability specifications have been adequately justified. The applicant has provided satisfactory stability data for a maximum of 24 months under long term storage conditions. The photo-stability studies (per ICH Q1(B)) data suggests that there is no substantial impact of light on the potency as well as physical properties of the drug product. Freeze/thaw study indicates that the drug product is not stable under freeze thaw cycle. An expiration dating of 24 months is granted for the drug product stored at 2°C to 8°C (36°F to 46°F). Adequate stability data of the diluted drug product solutions are included in the submission.

Process

The manufacturing process is an [redacted] including: [redacted] CQAs of the drug product have been identified as following: Description, Assay, [redacted] and Sterility. The batch size is the same for both exhibit and commercial scale. The commercial scale process contains the same unit operations and utilizes equipment of the same design and operating principles as that of the equipment used to produce the exhibit batch. The manufacturing and controls for the drug product is deemed adequate.

Microbiology

The drug product is manufactured by [redacted] Cyclophosphamide Injection is prepared by [redacted]

(b) (4) in accordance with batch records and standard operating procedures. The environmental monitoring, (b) (4) monitoring, and product bioburden information are adequate. The validation and requalification of both (b) (4) (b) (4) as well the (b) (4) is adequate. The (b) (4) (b) (4) are adequate. All information pertaining to (b) (4) are adequate. The specification for sterility and endotoxins are adequate. The microbiology information provided for the NDA is found to be acceptable.

Facilities

Following a review of the application and inspectional documents, there are significant outstanding, manufacturing or facility risks that prevent approval of this application. The OAI Warning Letter 320-16-02 was issued on 11/5/2017 following the inspection at Dr. Reddy's Laboratories Limited, FEI 3006549835, in March 2015. The Warning Letter included several observations related to sterile drug manufacturing, including concerns over inadequate investigations, media fills, and lack of adequate visual inspection procedures. The firm subsequently responded to the Warning Letter and requested a Regulatory Meeting to further explain their responses. Following review of the responses, for-cause inspection memos were completed and assignments for reinspection of the firm was created. A re-inspection of the firm was completed in March 2017 and was classified OAI. This renders the facility unacceptable. Therefore, there is currently a lack of confidence in its commercial drug product manufacturing capability for this NDA due to ongoing CGMP compliance issues. No preapproval inspections were requested during the review cycle. The manufacturing facilities listed for NDA 210852 are not acceptable at this time.

Biopharmaceutics

Dr. Reddy's Laboratories Limited's proposed Cyclophosphamide Injection Concentrate, 500 mg, 1 g and 2 g is a ready-to-dilute (RTD) concentrate with same strengths as the LD, Cytoxan® (Baxter's NDA 012142). The LD is formulated as lyophilized powder (500mg, 1 g and 2 g) for IV Injection and infusion, as well as oral administration for treatment of Malignant Disease and Minimal change nephrotic Syndrome in Pediatric Patients

The applicant submitted a request for the waiver of bioavailability/bioequivalence studies of Cyclophosphamide Injection Concentrate under *21CFR320.22(b)(1)*. Due to the difference in the inactive ingredients, a biowaiver under 21 CFR 320.22 is not feasible. However, the applicant has provided sufficient information to support the bridging between the proposed drug product and the LD, Cytoxan® for injection under *21CFR 320.24(b)(6),* justifying the reliance of the proposed drug product on the LD.

The proposed formulation contains the same active ingredient cyclophosphamide, which will be diluted to the same concentration as the LD, and will be administered at the same dose, concentration and volume as the LD. However; the proposed drug product contains dehydrated alcohol, which is not present in the LD, Cytoxan® for injection or the reference standard drug, Baxter's Cyclophosphamide (non-lyophilized) for injection. The dehydrated alcohol level in the proposed Cyclophosphamide Injection is found acceptable based on the previously approved amount for IV injection products. The presence of dehydrated alcohol in the

proposed drug product is not expected to impact the disposition kinetics of cyclophosphamide in humans; therefore, similar cyclophosphamide plasma concentrations are expected after administration of the proposed drug product or the LD. To support the bridging, the Applicant has provided comparative physicochemical data for the proposed and the reference standard drug products, and are deemed acceptable. NDA 210852 for Cyclophosphamide Injection, 500 mg/2.5 mL, 1g/5 mL and 2g/5mL is therefore recommended for acceptable from the Biopharmaceutics perspective.

4. Nonclinical Pharmacology/Toxicology

Dr. Reddy's intends to rely on the FDA's previous findings of safety and efficacy for the listed drug, Cytoxan® (cyclophosphamide for injection) under NDA 012142, which is discontinued. Dr. Reddy's proposed formulation is different from the listed drug (LD) formulation in terms of dosage (from being a solution versus dry powder), and that it uses dehydrated alcohol, as an excipient. The Applicant submitted animal pharmacokinetic and toxicology studies in rodents in support of this NDA. Dr. Reddy's provided a study report for a single dose, bridging toxicity study in male rats (Study No. P264/SE/065) to compare pharmacokinetics between Dr. Reddy's product and the LD. Pharmacokinetic results showed similar exposures with Dr. Reddy's product versus the LD. The Applicant's formulation uses dehydrated alcohol as a vehicle. Volume of distribution and clearance results were similar between test-article and reference product, suggesting ethanol did not influence disposition of kinetics of Dr. Reddy's product versus the LD. To qualify the levels of impurities in Dr. Reddy's product, Dr. Reddy's conducted a 4-week repeat-dose comparative study with their product without or with spiking of impurities compared to the LD in CD-1 mice. The purpose of this GLP study was to qualify the levels of impurities in Dr. Reddy's product when administered once weekly, for a total of 4 doses. From the nonclinical perspective, this NDA is recommended for approval.

5. Clinical Pharmacology

The applicant requested waiver of bioavailability/bioequivalence studies of Cyclophosphamide Injection Concentrate, which is reviewed by Division of Biopharmaceutics in the Office of New Drug product. There is no clinical pharmacology study conducted and no clinical pharmacology related labeling changes are included for this application. From a perspective of clinical pharmacology, no outstanding issues were identified, given that no changes in dose, administration route (intravenous), and dosing interval, and indications, except for the formulation changes from dry powder to a solution. The editorial change of drugs name in Section of 7 Drug Interaction, 8.6 Use in Patients with Renal Impairment, as well as a general statement regarding the use of alcohol in Section of 8.7 Use in Patients with Hepatic Impairment listed below is acceptable from clinical pharmacology perspective.

6. Clinical/Statistical- Efficacy

Not applicable.

7. Safety

Not applicable.

8. Advisory Committee Meeting

Not applicable.

9. Pediatrics

Not applicable.

10. Other Relevant Regulatory Issues

Not applicable.

11. Labeling

DMEPA's review is to evaluate the proposed Cyclophosphamide Injection prescribing information (PI), container labels, and carton labeling to identify areas of vulnerability that could lead to medication errors. The review found that the proposed Cyclophosphamide Injection PI, container labels and carton labeling may be improved to ensure safe use. DMEPA's specific recommendations were conveyed to the applicant. The revised container labels and carton labeling for Cyclophosphamide Injection are acceptable from a medication error perspective, and they have been accepted by the applicant.

OPDP has reviewed the proposed product labeling (PI), container label and carton labeling for the NDA submission, Cyclophosphamide Injection, for intravenous use (Cyclophosphamide). OPDP does not have any comments regarding the proposed PI or container carton labeling.

12. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

Complete Response

- **Risk Benefit Assessment**

The NDA 210852, Cyclophosphamide Injection, is recommended for Complete Response from the Office of New Drug Products, Office of Pharmaceutical Quality, based on the "inadequate" recommendation for the facility review. Specifically, the recent OAI inspection for Dr. Reddy's Laboratories Limited FEI 3006549835 renders the facility unacceptable. There is currently a lack of confidence in its commercial drug product manufacturing capability for

this specific NDA due to ongoing CGMP compliance issues. No preapproval inspections were requested during the review cycle. Refer to the facilities review.

- **Recommendation for Postmarketing Risk Management Activities**

Not applicable.

- **Recommendation for other Postmarketing Study Commitments**

Not applicable.

- **Recommended Comments to Applicant**

The following facility deficiency will be included in the Complete Response letter for this NDA application:

During a recent inspection of the Dr. Reddy's Laboratories Limited (FEI 3006549835) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

XIAOHONG CHEN
07/13/2018