CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210852Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 210852 (Resubmission#6)
Review #7

Drug Name/Dosage Form	Cyclophosphamide Injection
Strength	500mg/ml; 1g/2ml; 2g/4ml
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Dr. Reddy's Laboratories Limited
US agent, if applicable	Srinivasa Rao

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	09/28/2017	API/DP/Process/Biopharm/ Microbiology/Facility
Class 2 Resubmission#6 23	12/16/22	API, OPMA, DP, OPMA, Biopharm, Micro
24	2/24/2023	DP
25	3/10/2023	DP
26	4/25/2-23	DP, Biopharm

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Rajan Pragani	Haripada Sarker
Drug Product	Yang Nan	Xiao Hong Chen
OPMA Facility/Process	Ruth Moore	Kris (Kshitij) Patkar
Microbiology	Dionne Coker-Robinson	Denise Miller
Biopharmaceutics	Gerlie Gieser	Anitha Govada
Regulatory Business Process Manager	Kristine Leahy	
Application Technical Lead	Xiao Hong Chen	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	4/14/2023	Review by Rajan Pragani
	Type II			Adequate	3/24/3023	Review by Rajan Pragani
	Type V			Adequate	8/1/2021	Review by D. Bateman
	Type III			Adequate	No DMF review is needed.	Adequate info in the NDA
	Type III			Adequate	No DMF review is needed.	Adequate info in the NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Pre IND	129593	Submitted on 4/27/2016
NDA	12142	LD

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA 210852, Cyclophosphamide Injection, is recommended for Approval by the Office of Pharmaceutical Quality (OPQ) review team based on adequate CMC information provided in the resubmission. All deficiencies identified in the previous review cycles have been adequately resolved. All manufacturing and controls facilities are in Acceptable status. Include the following statement in the action letter:

A 24-month expiry is granted for the drug product stored at 2° to 8°C (36° to 46°F) is granted.

II. Summary of Quality Assessments

A. Product Overview

Cyclophosphamide is an alkylating drug substance and is indicated for the treatment of malignant diseases such as lymphomas and other cancers as well as (b) (4) (b) (4) The cyclophosphamide drug product listed drug (LD) used in this application is the Baxter Cyclophosphamide for Injection USP (NDA 12142). The LD is supplied as a sterile white powder product for reconstitution in vials containing 500mg, 1g, or 2g of cyclophosphamide. The proposed drug product is an injection concentrate intended for further dilution prior to intravenous administration.

Proposed Indication(s) including Intended Patient Population	Cyclophosphamide is an alkylating drug indicated for treatment of: **Malignant Diseases**: malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	**Malignant Diseases: Adult and Pediatric Patients** Intravenous: Initial course for patients with no hematologic deficiency: 40 mg per kg to 50 mg per kg in divided doses over 2 to 5 days. Other regimens include 10 mg per kg to 15 mg per kg given every 7 to 10 days or 3 mg per kg to 5 mg per kg twice weekly.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

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. the "unacceptable" recommendation was due to the OAI inspection for Dr. Reddy's Laboratories Limited FEI 3006549835, which renders the facility unacceptable.

The applicant resubmitted the NDA on 11/5/2018 and provided its response to the facility deficiency listed in the CR letter. The facility reviewer evaluated the response to the deficiency regarding the OAI status for Dr. Reddy's Laboratories Limited FEI 3006549835 and determined that it is acceptable based on the OAI status being downgraded to VAI. There was a recent GMP inspection on the drug substance manufacturing site, (b) (4) concluded on (b) (4) Based on the inspection outcome, the status of (b) (4) has changed to OAI during the review cycle. The NDA resubmission was issued a Complete Response letter on 05/03/2019 based on the incompliant GMP status of the API facility.

The applicant submitted 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 submitted 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. While the DP manufacturing facility was found acceptable in the review cycle, 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 5/21/2020.

The applicant submitted a fourth 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 facility, (b) (4) was still in OAI status, and a "withhold" recommendation was made by OPMA. The resubmission was issued a DR letter on 11/6/2020.

The applicant submitted a 5th resubmission on 11/3/2021 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 facility was still in OAI status, and a "withhold" recommendation was made by OPMA. The resubmission was issued a DR letter on 4/18/2022.

Resubmission (Seq#23) Dated 12/16/2022

For the current 6th resubmission, the applicant added an alternate API manufacturer, (b) (4) and an alternate manufacturing site for the current API manufacturer, (b) (4) Later in the review cycle, the applicant withdrew both (b) (4) (FEI (b) (4) and (b) (4)

from the 356h form as the commercial API manufacturer. (b) (4) (b) (4) will be the sole commercial API supplier.

The drug substance information for the commercial supplier, (b) (4) (b) (4) is provided in DMF (b) (4) and it has been reviewed by the API reviewer and found adequate. Note the drug substance information from both withdrawal facility (b) (4) and (b) (4) are also found to be adequate.

The DP manufacturing process and site remain mostly unchanged except the following changes: an increase of the commercial batch size for each of the presentations (within 10 fold increase) and the addition of a new manufacturing line, (b) (4) (b) (4) FEI (b) (4) was withdrawn as a commercial drug substance manufacturer. Developmental data and data for submission batches were generated while the site was in acceptable compliance status. In addition, there are no data integrity issues identified at the (b) (4) site. Hence the submission data can be relied on for regulatory decision-making. Two alternate drug substance manufacturing facilities were submitted to the application in Seq #0022. (b) (4) FEI (b) (4) is acceptable for commercial manufacturing in this review cycle. (b) (4) FEI (b) (4) and its associated facilities for testing of drug substance manufactured by (b) (4) were subsequently withdrawn in seq # 0025.

The applicant manufactured DP batches using the proposed new API supplier (b) (4) and tested against the DP regulatory specifications. All results conform to the specifications. The results showed the DP batches manufactured using the (b) (4) API are comparable to those DP batches made with (b) (4) in the original NDA submission. In addition, six month accelerated stability data for the DP batches manufactured using the (b) (4) API and (b) (4) API also demonstrate comparability. A 24-month expiry is granted for the DP stored at 2° to 8°C (36° to 46°F) is granted.

To support the proposed new changes in the commercial drug substance manufacturer (i.e., from (b) (4) to (b) (4) and in the drug product batch size/manufacturing line/processing time (as well as to extend the scientific bridge to the final to-be-marketed drug product), biopharma reviewer requested additional comparative in vitro physico-chemical characterization data using the proposed drug product manufactured with (b) (4) rug substance. Based on the additional comparative in vitro physico-chemical characterization data of these post-change drug product lots, the link between the Listed Drug and the pre-change drug product lots can be extended to the final proposed to-be-marketed drug product. Additionally, the submitted drug substance batch analyses data and the drug product stability data support comparability of the pre-change and post-change drug substance/drug product lots. Thus, based on the evidence provided in this NDA resubmission, it can be concluded that the scientific bridge between the final proposed to-be-marketed drug product and the relied upon LD product is adequate in accordance with 21 CFR 320.24(b)(6).

In the previous review cycle, the application was recommended to approve for microbiology by DMA (refer to N210852MR01.docx, dated 03/14/2018, by J. Patro). This submission includes changes related to sterility assurance include the addition of a new manufacturing line, [redacted] for the manufacturing of the 500mg/mL and 1g/2mL presentations. [redacted] remains unchanged for the manufacturing of the 2g/4mL presentation. In addition, an increase of the commercial batch size for each of the presentations is proposed as following: 500mg/mL strength: change from [redacted] to [redacted]; 1g/2mL strength: change from [redacted] to [redacted]; 2mg/4mL strength: change from [redacted] to [redacted]. The total manufacturing time from [redacted] from NMT [redacted] hours to NMT [redacted] hours. There is also a change in the Type V DMF No. [redacted] for the [redacted]. Specifically, there is a change in manufacturing site of the [redacted] from [redacted] to [redacted] The sponsor provided adequate validation data to support the addition of the new manufacturing line and changes that are most likely to impact sterility assurance of the drug product. Therefore, the submission is recommended for approval on the basis of sterility assurance.

C. Special Product Quality Labeling Recommendations (NDA only)
N/A

D. Final Risk Assessment (see Attachment)
N/A

Application Technical Lead Name and Date:
Xiao Hong Chen, Ph.D.
23-May-2023

Xiao Chen

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	NDA-210852-ORIG-1-RESUB-23
Assessment Cycle Number	NDA Resubmission #6
Drug Product Name/ Strength	Cyclophosphamide Injection, 500 mg/mL (presented as 500 mg/1 mL, 1000 mg/2 mL, 2000 mg/4 mL)
Route of Administration	Intravenous (Direct Injection or Infusion)
Applicant Name	Dr. Reddy's Laboratories Limited
Therapeutic Classification/ OND Division	Anti-Cancer/ Division of Oncology 1
Listed Drug (LD) Relied Upon/Reference Standard (RS)	LD: Cytoxan® (lyophilized powder) for Injection (500 mg, 1000 mg, and 2000 mg per vial); Baxter, NDA 012142 RS: Cyclophosphamide for Injection (500 mg, 1000 mg, and 2000 mg per vial); Baxter, ANDA 040745
Proposed Indications and Dosage	For treatment of malignant diseases in adults and pediatric patients

Assessment Recommendation: **Adequate**

Assessment Summary:

Background:

Per the Biopharmaceutics Review of the original 505(b)(2) NDA submission (dated 9/28/2017), NDA 210852 was recommended for approval because adequate information was provided to support the scientific bridge between Dr. Reddy's proposed ready-to-dilute/concentrate injectable solution drug product and the relied upon Listed Drug product (LD; Cytoxan® powder for Injection; discontinued) pursuant to 21 CFR 320.24(b)(6). Note that all *in vitro* and *in vivo* nonclinical bridging studies conducted to support this scientific bridge were performed using Baxter's Reference Standard (RS) drug product and the proposed drug product lots that were manufactured using the active pharmaceutical ingredient (API) sourced from (b) (4) However, the original submission and resubmissions #1 through #5 of NDA 210852 received Complete Response (CR) Action Letters citing deficiencies related to the Withhold-OAI recommendations for the Drug Product Manufacturing Facility (Dr. Reddy's Laboratories Limited/India) and/or the Drug Substance Manufacturing Facility (b) (4) In the latest of these CR Letters (dated 4/18/2022), the FDA cited outstanding deficiencies in the (b) (4) facility.

In the current 505(b)(2) NDA (Class 2) Resubmission #6 (submitted on 12/16/2022), the Applicant decided to withdraw (b) (4) and proposed (b) (4) (b) (4) and (b) (4) (b) (4) as the new commercial drug substance manufacturing facilities. On

2/24/2023, per the Drug Product Reviewer's recommendation, the Applicant also withdrew (b) (4) as an alternate drug substance manufacturing facility.

Review Objective:
This Biopharmaceutics review focuses on the evaluation of the adequacy of the scientific bridge to the final to-be-marketed drug product.

Review Assessment Summary:
Note that based on the evaluation of the Office of Pharmaceutical Manufacturing Assessment (OPMA) Reviewer of the current NDA Resubmission #6 [and consistent with the advice received from the Office of Policy for Pharmaceutical Quality (OPPQ)], FDA determined that the data generated using the (b) (4) API drug product lots (as provided in the initial NDA submission) can still be used to support NDA approval. Thus, even though (b) (4) was withdrawn as a commercial drug substance manufacturing facility and additional CMC changes were introduced in the NDA *resubmission*, this Reviewer did not request the Applicant to repeat the full range of *in vitro* and *in vivo* bridging studies performed to support the original NDA submission.

To support the proposed new changes in the commercial drug substance manufacturer (i.e., from (b) (4) to (b) (4) and in the drug product batch size/manufacturing line/processing time (as well as to extend the scientific bridge to the final to-be-marketed drug product), additional comparative *in vitro* physico-chemical characterizatio were requested using the proposed drug product manufactured with (b) (4) drug substance. Based on the additional comparative *in vitro* physico-chemical characterization data of these post-change drug product lots submitted in Sequence Number (SN)-25 (date: 4/25/2023), the link between the LD/RS product and the pre-change drug product lots (tested in the comparative *in vitro* physico-chemical characterization, *in vitro* hemolysis studies and comparative *in vivo* animal PK and local tolerance studies) can be extended to the final proposed to-be-marketed drug product. Additionally, per the Drug Substance and Drug Product Reviewers, the submitted drug substance batch analyses data and the drug product stability data support comparability of the pre-change and post-change drug substance/drug product lots. Thus, based on the evidence provided in this NDA resubmission, it can be concluded that the scientific bridge between the final proposed to-be-marketed drug product and the relied upon LD product is adequate in accordance with 21 CFR 320.24(b)(6).

Recommendation:
From the Biopharmaceutics perspective, NDA 210852 is recommended for APPROVAL.

List of Submissions Assessed:

Document(s) Assessed	Date Received
SN-22 or SDN-23 (Original NDA Resubmission after Complete Response Action)	12/16/2023
SN-23 or SDN-24 (Response to Quality IR)	2/24/2023
SN-24 or SDN-25 (Response to Quality IR)	3/10/2023
SN-25 or SDN-26 (Response to Quality IR)	4/25/2023

Highlight Key Issues from Last Cycle and Their Resolution:

- Drug Substance (DS) Manufacturing Facility with Withhold recommendation (Official Action Indicated) status (i.e., (b) (4) was withdrawn and then replaced with the proposed new commercial DS manufacturing facility (b) (4)

Concise Description of Outstanding Issues:

None

BIOPHARMACEUTICS REVIEW

Background:

Cyclophosphamide (ready-to-dilute solution) Injection, 500 mg/mL (presented as 500 mg/1 mL, 1000 mg/2 mL, 2000 mg/4 mL) relies for approval, at least in part, on the FDA's findings of efficacy and safety for the Listed Drug (LD) product, Baxter's Cytoxan® (cyclophosphamide) lyophilized powder for Injection (500 mg/vial, 1000 mg/vial, 2000 mg/vial; NDA 012142) which was discontinued from sale[1] (not for reasons related to efficacy and safety. In the original NDA (dated 9/28/2017), the Applicant submitted the results of comparative *in vitro* and *in vivo* studies, using Baxter's Cyclophosphamide (sterile powder) for Injection (500 mg/vial, 1000 mg/vial, 2000 mg/vial) as the Reference Standard for establishing a scientific bridge. The original NDA's Biopharmaceutics Reviewer (Dr. Joan Zhao) determined that adequate data were submitted to establish the scientific bridge between the proposed and the LD/RS products. However, the original submission and resubmissions #1 through #5 of NDA 210852 received Complete Response (CR) Action Letters (on 7/24/2018, 5/3/2019, 11/20/2019, 5/21/2020 and 4/18/2022) citing deficiencies related to the Withhold-OAI recommendations for the Drug Product Manufacturing Facility (Dr. Reddy's Laboratories Limited/India) and/or the Drug Substance Manufacturing Facility (b) (4)

Current NDA Resubmission #6:

To address the remaining Complete Response (CR) Letter deficiency (related to the Withhold – OAI recommendation for the original API manufacturing

[1] Drugs@FDA and Electronic Orange Book states "Federal Register determination that product was not discontinued or withdrawn for safety or effectiveness reasons"

facility, [redacted], the Applicant decided to replace [redacted] with [redacted] and [redacted] NDA Resubmission #6 included API equivalency data to support [redacted] and [redacted] as the proposed new commercial drug substance manufacturers, stability data for the [redacted] API drug product exhibit batches, as well as pharmaceutical equivalency data to support comparability of the [redacted] API drug product exhibit batches to the Reference Standard (RS) drug product. Since stability data for the [redacted] API drug product lots could not be provided, per the Drug Product Reviewer's recommendation, on 2/24/2023 the Applicant withdrew [redacted] as an alternate commercial API manufacturing site.

Proposed CMC Changes in NDA Resubmission #6:
Note that in addition to the change in API/drug substance manufacturing site, in the current NDA resubmission, the Applicant also implemented changes to the drug product's batch size/manufacturing line/processing and hold times; refer to the Summary of Changes (Annexure 2) document.

Biopharmaceutics Assessment for NDA Resubmission #6 (Bridging):
At the time of original NDA submission (first cycle) review, the Biopharmaceutics Reviewer determined that the scientific bridge between the [redacted]-API drug product lots (*pre-change* drug product) and the relied upon LD was adequately established per 21 CFR 320.24(b)(6). However, because of the introduction of new CMC changes related to the drug substance and the drug product attributes at the time of NDA resubmission#6, the adequacy of the scientific bridge (specifically, as it applies to the *post-change* or the final to-be-marketed drug product) had to be revisited.

Comparative *In Vitro* Physico-Chemical Characterization:
The current NDA resubmission includes the results of a Pharmaceutical Equivalence Study (in 3.2.P.2) that compared the appearance, assay, impurities of the LD's 20 mg/mL solution to the proposed drug product's [redacted] mg/mL or [redacted] mg/mL dilutions of the three commercial presentations. This Reviewer does not consider the design of the completed comparative physico-chemical characterization study adequate (e.g., in terms of physicochemical properties measured, drug concentrations of the final and test solutions evaluated, dilution of the final IV infusion solutions into volumetric flasks instead of using IV infusion bags). Thus, the Applicant was requested to repeat the comparative *in vitro* physicochemical characterization study by measuring the pH, osmolality, viscosity, specific gravity, surface tension, assay, impurities, appearance, etc., of all proposed/approved presentations of the post-change test drug product and the reference product before dilution (as applicable) and after dilution to the final direct IV and IV infusion solutions (with concentrations of 20 mg/mL and 2 mg/mL, respectively), prepared precisely according to the proposed/approved labeling instructions using all label recommended diluents. For physicochemical testing of the proposed RTD solution/concentrate drug

product, characterization of both the initial/freshly manufactured or released and the "end-of-shelf-life (EOS)" samples was recommended.

In SN-25, the Applicant submitted the requested additional comparative *in vitro* physico-chemical characterization data of the pre-dilution and post-dilution samples of the MSN-API (post-change) drug product versus unexpired Reference Standard. The provided data (in Annexure 1) supported comparability of the pre-change and post-change lots of the proposed drug product, and confirmed the conclusion of the original NDA's Biopharmaceutics Reviewer regarding the adequacy of the scientific bridge between the proposed drug product and the relied upon Listed Drug product. Of note, at the time of original NDA review, FDA previously determined that the higher impurity levels in the proposed drug product than the LD were qualified by animal toxicity studies. Based on *in vivo* animal local tolerance data, FDA also previously determined that the relatively higher osmolality of the 20 mg/mL dilution of the proposed drug product compared to the LD (when using 0.9% Sodium Chloride Injection) is justified, as explained in the Applicant's report. Based on the data provided in SN-25, this Reviewer does not consider the hypo-osmolality of the 2 mg/mL admixtures of the proposed drug product (when using 0.45% Sodium Chloride Injection as the diluent) to be a concern when considering the even lower osmolality of the RS admixtures in the same diluent. Additionally, this Reviewer determines that the slightly lower viscosity of the dilutions and admixtures of the proposed drug product (relative to those of the LD) would not be detrimental to the product's usability (e.g., syringeability, infusibility). This Reviewer notes that during the same long-term (refrigerated) stability period (Months 0 to 6), it appears that the (undiluted) post-change drug product lots packaged in vials exhibited physico-chemical properties (i.e., appearance, cyclophosphamide assay, total impurities, container content) that were comparable to the pre-change drug product lot, and were well within the proposed acceptance criteria (compare the data in Sections 3.2.P.8.3 of the original NDA submission and the current NDA resubmission). Additionally, the pH and osmolality values reported for the dilutions/admixtures of the 18-month old 'pre-change' lots and the 9-month old 'post-change' lots of the proposed drug product were similar (refer to the dilution study reports in SN-1 and SN-25). Thus, this Reviewer determines that is reasonable to consider the full physico-chemical characterization data (i.e., pH, osmolality, viscosity, specific gravity, surface tension, appearance, assay and total impurities) of the 20 mg/mL and 2 mg/mL dilutions/admixtures of the 9-month old post-change (MSN-API)/final to-be-marketed drug product lots to be representative of the physico-chemical properties of the pre-change (b) (4) API) drug product lots that were tested in the initial *in vitro* and *in vivo* bridging studies and CMC studies.

Based on evidence of comparable *in vitro* physicochemical properties between the pre-change and post-change drug products (and the input received from both OPMA and OPPQ), this Reviewer determined that it was not necessary to

submit additional *in vivo* animal local tolerance data, *in vitro* human blood hemolysis data and *in vivo* animal PK data to confirm comparability of the post-change/final proposed commercial drug product to the LD/RS product. Additional *in vitro* human plasma protein binding data were also not pursued because in the original NDA submission the Applicant provided justification regarding the appropriateness of the selected *in vivo* animal PK model. [Note: Per the Process/Facilities Reviewer (Dr. Ruth Moore), the Withhold Approval - OAI status of (b) (4) was not due to data integrity (but rather to (b) (4) contamination) issues related to another drug product class (i.e., the "(b) (4)"). Additionally, (b) (4) was cGMP compliant during the time that the API submission batches for NDA 210852 were manufactured). Thus, per Dr. Moore, even if (b) (4) was withdrawn on the 356H form, it would still be acceptable to rely on the previously submitted *in vitro* and *in vivo* bridging data (as well as the stability data) that were generated using the pre-change drug product lots that were manufactured using the (b) (4) supplied API. Additionally, Dr. Moore confirmed that (***i***) the post-change drug product exhibit lots evaluated in the bridging and stability studies were manufactured within one-tenth of the proposed commercial batch size using the commercial manufacturing process comprised by the same unit operations and equipment of the same design and operating principles, and in-process controls, and (***ii***) all proposed commercial facilities are acceptable/adequate. Furthermore, OPPQ was consulted regarding this policy issue, and they confirmed that it was acceptable to rely on the data previously submitted for the (b) (4) API drug product lots.]

Additional CMC Information Supporting the Extension of the Scientific Bridge:
Note that the NDA Resubmission includes stability data for both the pre-change (b) (4)-API) drug product lots and the post-change (b) (4) API, commercial scale) drug product lots. The Drug Product Reviewer (Dr. Yang Nan) confirmed (***i***) comparability of the stability profiles of the original (pre-change) and the final proposed-to-be-marketed (post-change) drug products, (***ii***) adequacy of the total stability data to support an expiration dating period of 24 months for the final proposed to-be-marketed RTD solution drug product when stored under refrigeration, (***iii***) adequacy/acceptability of the proposed finished product QC specifications for batch release and for shelf-life/stability testing, and (***iv***) product compatibility with the IV infusion bags. Additionally, the Microbiology Reviewer (Dr. Dionne Coker-Robinson) confirmed that (***a***) adequate validation data was submitted to support the addition of the new manufacturing line and the other CMC changes (e.g., (b) (4) (b) (4) (b) (4) that are most likely to impact sterility assurance of the final to-be-marketed drug product, (***b***) there are no changes to the sterility and bacterial endotoxins (BET) specifications of the finished product, and (***c***) the (b) (4) API drug product lots conformed to the sterility and BET specifications.

Note also that the NDA Resubmission includes data to demonstrate equivalence between API from the proposed new commercial sources (b) (4) and (b) (4) and the original source (b) (4) refer to the API Equivalency Report in 3.2.S.4.5. The Drug Substance Reviewer (Dr. Rajan Pragani) confirmed comparability of the drug substance batch analysis data between the pre-change/original and the post-change/final proposed API manufacturers.

Conclusion/Recommendation:
Note that per the Biopharmaceutics review of the original NDA dated 9/28/2017, the comparative *in vitro* and *in vivo* animal data/information/justification previously submitted are sufficient to establish the scientific bridge between the proposed drug product and the relied upon LD product, i.e., in accordance with 21 CFR 320.24 (b)(6).

The additional comparative *in vitro* data provided in the current resubmission #6 of NDA 210852 (dated 12/16/2022) and subsequent information amendments are considered adequate to extend this scientific bridge to the final proposed to-be-marketed drug product, and to support the CMC changes proposed at the time of this NDA resubmission#6.

From the Biopharmaceutics perspective, NDA 210852 is recommended for Approval.

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R. REGIONAL INFORMATION

Comparability Protocols

Not Applicable

Post-Approval Commitments

None

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date: Gerlie Gieser, Ph.D. (5/3/2023)

Secondary Assessor Name and Date (and Secondary Summary, as needed): Anitha Govada, Ph.D. (5/8/2023)

Gerlie Gieser

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Anitha Palamakula Govada

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

IQA ANDA Assessment Guide Reference

Product Information	Sterile solution indicated for use as treatment for malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma. Filled as a 500mg/mL, 1g/2mL, or 2g/4mL fill in a 2mL or 5mL vial; single-dose.
NDA Number	210852 (S/N 0022)
Assessment Cycle Number	2
Drug Product Name / Strength	Cyclophosphamide Injection 500 mg/mL, 1 g/2mL, and 2 g/4 mL
Route of Administration	Intravenous Infusion
Applicant Name	Dr. Reddy's Laboratories Limited
Manufacturing Site	Dr. Reddy's Laboratories Limited Plot No. P1 to P9, Q1 to Q5, Phase- III Duvvada, VSEZ, Visakhapatnam, Andhra Pradesh- 530 046, India
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Theme:

☒ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: *view justification statements found at:* **Justification Statements**

N/A

Other (Requires Division Director Approval) – *Assessor writes-in justification here if "other" selected as theme.*

Assessment Summary: The submission is in response to a Complete Response Letter, dated 04/18/2022. In the previous review cycle, the application was recommended to approve by DMA (refer to N210852MR01.docx, dated 03/14/2018, by J. Patro). This submission includes changes related to sterility assurance include the addition of a new manufacturing line, (b) (4) for the manufacturing of the 500mg/mL and 1g/2mL presentations. (b) (4) emains unchanged for the manufacturing of the 2g/4mL presentation. In addition, an increase of the commercial batch size for each of the presentations is proposed as following: 500mg/mL strength: change from (b) (4)L to (b) (4)L; 1g/2mL strength: change from (b) (4)L to (b) (4)L; 2mg/4mL strength: change from (b) (4)L to (b) (4)L. The total manufacturing time from (b) (4) is increased from NMT (b) (4) hours to NMT (b) (4) hours. There is also a change in the Type V DMF No. (b) (4) for the (b) (4) . Specifically, there is a change in manufacturing site of the (b) (4) from (b) (4) to (b) (4) The sponsor provided adequate validation data to support the addition of the new manufacturing line and changes that are most likely to impact sterility assurance of the drug product. Therefore, the submission **is recommended** for approval on the basis of sterility assurance.

List Submissions Being Assessed (table):

Date Submitted to FDA	Date Received by FDA	Date Assigned to Reviewer
12/16/2022	12/16/2022	12/22/2022

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The submission is in e-CTD format. The original microbiology review was completed and determined to be adequate in N210852MR01.docx, dated 03/14/2018, by J. Patro.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): N/A

Supporting Documents:

- (b) (4)
-

Select Number of Approved Comparability Protocols: 0

The submission is in response to a Complete Response Letter, dated 04/18/2022. In the previous review cycle, the application was recommended by DMA (refer to N210852MR01.docx, dated 03/14/2018, by J. Patro). However, in the response to the Complete Response Letter, the sponsor has provided updated information related to CMC changes that impact sterility assurance. The changes since the previous DMA review that are related to sterility assurance include the following:

- New manufacturing line (b) (4) for the manufacturing of the 500mg/mL and 1g/2mL presentations. (b) (4) remains unchanged for the manufacturing of the 2g/4mL presentation.
  - ➢ Validation information related to the manufacturing equipment associated with (b) (4) and (b) (4) studies are reviewed below.

- The commercial batch is increased for each of the presentations. Refer to table below for details related to batch size changes.

Presentation	Approved		Proposed	
	Batch Size	Filling Line	Batch Size	Filling Line
500mg/mL	(b) (4)	(b) (4)	(b) (4)	(b) (4)
1g/2mL				

2g/4mL	[redacted]	[redacted]	[redacted]

  - To accommodate the increased batch size of the 2g/4mL a larger [redacted] will be used.

- The total manufacturing time from [redacted] NMT [redacted] hours to NMT [redacted] hours.
  - Hold time study data are provided for Exhibit Batches H220548 and H220523. The data demonstrate that [redacted] (NMT [redacted] CFU/ [redacted] mL) and BET (NMT [redacted] EU/mg and NMT [redacted] EU/mg) were met.

- Change in the Type V DMF No. [redacted] for the [redacted]. Note, there is a change in manufacturing site of the [redacted] from [redacted] to [redacted]
  - The Type V DMF [redacted] from [redacted] is referenced for the [redacted] A letter of authorization for access to the DMF for the [redacted] is provided and dated 11/16/2022. The letter states that the information pertaining to the [redacted] is located in [redacted] Information pertaining to the [redacted] was reviewed and determined to be adequate in D [redacted] M21R01.docx, dated 08/01/2021, by D. Bateman.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –**
  There are no changes proposed to the drug product composition. There are changes to the batch size (summarized below).

Presentation	Approved Batch Size	Proposed Batch Size
500mg/mL	[redacted]	[redacted]
1g/2mL	[redacted]	[redacted]
2g/4mL	[redacted]	[redacted]

- **Description of container closure system –**
  There are no proposed changes to the components of the CCS. For ease of reference, CCS information is summarized in the table below.

Component	Drug Product	Vial Size	Description	Manufacturer
Vial	500mg/mL	2mL	(b) (4) clear glass	(b) (4)
	1g/2mL	2mL		
	2g/4mL	5mL		
Stopper	All Presentations	-	(b) (4)	
Seal	All Presentations	-	(b) (4) flip-off seal	

Assessment: The drug product composition and CCS are the same. The batch size is the only proposed change.

Adequate

P.3 MANUFACTURE

(b) (4)

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Denise Miller

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Date: 1/31/2023 08:25:36AM
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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The drafted PI submitted on March 10, 2023 is provided here.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	
If the drug product contains an active ingredient that is a	N/A	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	Adequate	This statement is included. To be consistent with the labeling in NDA 210735, Cyclophosphamide Injection, the following statement was recommended by OOD-labeling to be included: "Do not use Cyclophosphamide Injection vials if there are signs of particulate matter". The Applicant accepted the recommendation.

If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	Adequate	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Adequate	

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	The Applicant was recommended to include the quantity (in mg) for alcohol. Also, addition of "USP" after cyclophosphamide and alcohol is not necessary as it clutters up the labeling. The firm was requested to remove "USP". The Applicant accepted the recommendations.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Adequate	The firm was recommended to include alcohol in volume percentage. The Applicant accepted the recommendation (alcohol equivalent to 63% v/v).
Sterility statement (if applicable)	Adequate	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	

If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	

2. Section 11 (DESCRIPTION) Continued

Item	**Items in Proposed Labeling** (choose "Adequate", "Inadequate", or "N/A")	**Assessor's Comments** (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	The drug product is a new drug product.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	The firm was recommended to use a tabular format to summarize the NDC number, strength and container closure system. The Applicant accepted the recommendation.
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	The proposed storage condition of [redacted] (b) (4) is not necessary. Firm was recommended to revise as follows: *Store vials refrigerated at 2°C to 8°C (36°F to 46°F).* Dr. Reddy accepted the recommendation.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.**- N/A**

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information): N/A

There is no Medication Guides, Instructions for Use, or Patient Information provided in the submission.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

(Copy/paste or refer to a representative example of a proposed container)

(b) (4)

3.2 Carton Labeling

(Copy/paste or refer to a representative example of a proposed carton labeling)

Carton Label 500 mg/mL (updated, see submission SD#27 dated May 16, 2023)

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	The storage temperature was recommended to be revised as follows: *Store vials refrigerated at 2°C to 8°C (36°F to 46°F).* The Applicant accepted the recommendation.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	Firm was recommended to include alcohol quantities in carton labels. The Applicant accepted the recommendation.

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Adequate	Firm was recommended to include alcohol in percentage in carton label. The Applicant accepted the recommendation.
Linear Bar code	Adequate	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	Adequate	

Assessment of Carton and Container Labeling: ***Adequate***

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3. ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Based on the above assessment, the prescribing information, carton and container labels are adequate.

Primary Labeling Assessor Name and Date: Yang Nan, Ph.D.

Secondary Assessor Name and Date (and Secondary Summary, as needed): *XiaoHong Chen, Ph.D.*

Yang Nan

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Xiao Chen

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/s/

XIAOHONG CHEN
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Recommendation: Complete Response

NDA 210852 (Resubmission#4)
Review #5

Drug Name/Dosage Form	Cyclophosphamide Injection
Strength	500mg/ml; 1g/2ml; 2g/4ml
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Dr. Reddy's Laboratories Limited
US agent, if applicable	Srinivasa Rao

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	09/28/2017	API/DP/Process/Biopharm/ Microbiology/Facility
Class 2 Resubmission	11/5/2018	OPMA
Class 2 Resubmission#2	5/21/2019	OPMA
Class 2 Resubmission#3	12/4/2019	OPMA
Class 2 Resubmission#4	6/18/2020	OPMA
Class 2 Resubmission#5	11/3/2021	OPMA

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Facility	Ruth Moore	Yiwei Li
Regulatory Business Process Manager	Kristine Leahy	N/A
Application Technical Lead	Xiao Hong Chen	N/A

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:
N/A

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Pre IND	129593	Submitted on 4/27/2016
NDA	12142	LD

2. CONSULTS

N/A

Executive Summary

I. 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 [redacted] FEI [redacted] The following deficiency comments should be included in the action letter:

During a recent inspection of the [redacted] FEI [redacted] 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.

II. Summary of Quality Assessments

A. Product Overview

Cyclophosphamide is an alkylating drug substance and is indicated for the treatment of malignant diseases such as lymphomas and other cancers as well as [redacted] The cyclophosphamide drug product listed drug (LD) used in this application is the Baxter Cyclophosphamide for Injection USP (NDA 12142). The LD is supplied as a sterile white powder product for reconstitution in vials containing 500mg, 1g, or 2g of cyclophosphamide. The proposed drug product is an injection concentrate intended for further dilution prior to intravenous administration.

Proposed Indication(s) including Intended Patient Population	Cyclophosphamide is an alkylating drug indicated for treatment of: **Malignant Diseases**: malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	**Malignant Diseases: Adult and Pediatric Patients** Intravenous: Initial course for patients with no hematologic deficiency: 40 mg per kg to 50 mg per kg in divided doses over 2 to 5 days. Other regimens include 10 mg per kg to 15 mg per kg given every 7 to 10 days or 3 mg per kg to 5 mg per kg twice weekly.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

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. the "unacceptable" recommendation was due to the OAI inspection for Dr. Reddy's Laboratories Limited FEI 3006549835, which renders the facility unacceptable.

The applicant resubmitted the NDA on 11/5/2018, and provided its response to the facility deficiency listed in the CR letter. The facility reviewer evaluated the response to the deficiency regarding the OAI status for Dr. Reddy's Laboratories Limited FEI 3006549835, and determined that it is acceptable based on the OAI status being downgraded to VAI. There was a recent GMP inspection on the drug substance manufacturing site, (b) (4) concluded on (b) (4) Based on the inspection outcome, the status of (b) (4) has changed to OAI during the review cycle. The NDA resubmission was issued a Complete Response letter on 05/03/2019 based on the incompliant GMP status of the API facility.

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. While the DP manufacturing facility was found acceptable in the review cycle, 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 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.

Resubmission Dated 11/3/2021

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) The applicant stated the following: "FDA has inspected (b) (4) (FEI (b) (4) from (b) (4) Form 483 was issued by Agency on (b) (4) with few inspectional observations. (b) (4) has evaluated all the observations and response has been submitted to FDA on (b) (4) " The applicant 's response and facility status have been reviewed by Dr. Ruth Moore, the OPMA reviewer. Based on the OAI status for (b) (4), OPMA recommended "**withhold**" for the NDA.

C. Special Product Quality Labeling Recommendations (NDA only)
N/A

D. Final Risk Assessment (see Attachment)
N/A

Application Technical Lead Name and Date:
Xiao Hong Chen, Ph.D.
23-March-2022

Xiao Chen

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XIAOHONG CHEN
03/23/2022 12:35:41 PM

Recommendation: Complete Response

NDA 210852 (Resubmission#4)
Review #5

Drug Name/Dosage Form	Cyclophosphamide Injection
Strength	500mg/ml; 1g/2ml; 2g/4ml
Route of Administration	Intraveneous
Rx/OTC Dispensed	Rx
Applicant	Dr. Reddy's Laboratories Limited
US agent, if applicable	Srinivasa Rao

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	09/28/2017	API/DP/Process/Biopharm/ Microbiology/Facility
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Class 2 Resubmission#3	12/4/2019	OPMA
Class 2 Resubmission#4	6/18/2020	OPMA
Amendment 0020	11/2/2020	OPMA

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Facility	Aditi Thakur	Ying Zhang
Regulatory Business Process Manager	Kristine Leahy	N/A
Application Technical Lead	Xiao Hong Chen	N/A

Quality Review Data Sheet

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A. DMFs:
N/A

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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NDA	12142	LD

2. CONSULTS

N/A

Executive Summary

I. 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) (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.

II. Summary of Quality Assessments

A. Product Overview

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Proposed Indication(s) including Intended Patient Population	Cyclophosphamide is an alkylating drug indicated for treatment of: **Malignant Diseases**: malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	**Malignant Diseases: Adult and Pediatric Patients** Intravenous: Initial course for patients with no hematologic deficiency: 40 mg per kg to 50 mg per kg in divided doses over 2 to 5 days. Other regimens include 10 mg per kg to 15 mg per kg given every 7 to 10 days or 3 mg per kg to 5 mg per kg twice weekly.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

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. the "unacceptable" recommendation was due to the OAI inspection for Dr. Reddy's Laboratories Limited FEI 3006549835, which renders the facility unacceptable.

The applicant resubmitted the NDA on 11/5/2018, and provided its response to the facility deficiency listed in the CR letter. The facility reviewer evaluated the response to the deficiency regarding the OAI status for Dr. Reddy's Laboratories Limited FEI 3006549835, and determined that it is acceptable based on the OAI status being downgraded to VAI. There was a recent GMP inspection on the drug substance manufacturing site, (b) (4) concluded on (b) (4) Based on the inspection outcome, the status of (b) (4) has changed to OAI during the review cycle. The NDA resubmission was issued a Complete Response letter on 05/03/2019 based on the incompliant GMP status of the API facility.

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. While the DP manufacturing facility was found acceptable in the review cycle, 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 5/21/2020.

Resubmission Dated 6/18/2020
For the current 4th resubmission, there are no CMC changes. The pending deficiency is the noncompliant status for the API manufacturing facility, (b) (4) Based on the OAI status for (b) (4) OPMA recommended "**withhold**" for the NDA.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

N/A

Application Technical Lead Name and Date:
Xiao Hong Chen, Ph.D.

4-Nov-2020

APPEARS THIS WAY ON ORIGINAL

Xiao Chen

Digitally signed by Xiao Chen
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/s/

XIAOHONG CHEN
11/04/2020 12:43:13 PM

Recommendation: Complete Response

NDA 210852 (Resubmission#3)
Review #4

Drug Name/Dosage Form	Cyclophosphamide Injection
Strength	500mg/ml; 1g/2ml; 2g/4ml
Route of Administration	Intraveneous
Rx/OTC Dispensed	Rx
Applicant	Dr. Reddy's Laboratories Limited
US agent, if applicable	Srinivasa Rao

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	09/28/2017	API/DP/Process/Biopharm/ Microbiology/Facility
Class 2 Resubmission	11/5/2018	OPMA
Class 2 Resubmission#2	5/21/2019	OPMA
Class 2 Resubmission#3	12/4/2019	OPMA

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Facility	Aditi Thakur	Ying Zhang
Regulatory Business Process Manager	Kristine Leahy	N/A
Application Technical Lead	Xiao Hong Chen	N/A

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:
N/A

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Pre IND	129593	Submitted on 4/27/2016
NDA	12142	LD

2. CONSULTS

N/A

Executive Summary

I. 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, [redacted] (b) (4) FEI [redacted] (b) (4) is found to be **unacceptable.** A withhold recommendation has been made for [redacted] (b) (4) FEI [redacted] (b) (4) The following deficiency comments should be included in the action letter:

During a recent inspection of the [redacted] (b) (4) *FEI* [redacted] (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.*

II. Summary of Quality Assessments

A. Product Overview

Cyclophosphamide is an alkylating drug substance and is indicated for the treatment of malignant diseases such as lymphomas and other cancers as well as [redacted] (b) (4) [redacted] (b) (4) The cyclophosphamide drug product listed drug (LD) used in this application is the Baxter Cyclophosphamide for Injection USP (NDA 12142). The LD is supplied as a sterile white powder product for reconstitution in vials containing 500mg, 1g, or 2g of cyclophosphamide. The proposed drug product is an injection concentrate intended for further dilution prior to intravenous administration.

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. the "unacceptable" recommendation was due to the OAI inspection for Dr. Reddy's Laboratories Limited FEI 3006549835, which renders the facility unacceptable.

The applicant resubmitted the NDA on 11/5/2018, and provided its response to the facility deficiency listed in the CR letter. The facility reviewer evaluated the response to the deficiency regarding the OAI status for Dr. Reddy's Laboratories Limited FEI 3006549835, and determined that it is acceptable based on the OAI status being downgraded to VAI. There was a recent GMP inspection on the drug substance manufacturing site, [redacted] (b) (4) concluded on [redacted] (b) (4) Based on the inspection outcome, the status of [redacted] (b) (4) has changed to OAI during the review cycle. The NDA resubmission was issued a Complete Response letter on 05/03/2019 based on the incompliant GMP status of the API facility.

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.

Proposed Indication(s) including Intended Patient Population	Cyclophosphamide is an alkylating drug indicated for treatment of: **Malignant Diseases**: malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	**Malignant Diseases: Adult and Pediatric Patients** Intravenous: Initial course for patients with no hematologic deficiency: 40 mg per kg to 50 mg per kg in divided doses over 2 to 5 days. Other regimens include 10 mg per kg to 15 mg per kg given every 7 to 10 days or 3 mg per kg to 5 mg per kg twice weekly.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance Adequate
No change has been made to the drug substance section in the resubmission. Refer to the IQA for NDA 210852 dated 7/12/2018.

Drug Product Adequate
No change has been made to the drug product section in the resubmission. Refer to the IQA for NDA 210852 dated 7/12/2018.

Manufacturing Inadequate
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 [redacted] (b) (4) FEI [redacted] (b) (4)

Dr. Reddy's Laboratories Limited (FEI: 3006549835)
The firm was inspected from August 12 to 20, 2019. The inspection type was surveillance current good manufacturing practice (CGMP) and pre-approval. The inspection was

initially classified as pOAI and had implications on the commercial products given that there were (b) (4) at the facility. This inspection was later downgraded to VAI CMS #597595 after the review of the firm response. For this particular drug product apart from the expected risk of manufacturing an (b) (4) product into (b) (4) no additional process risks were identified with this product. Given the manufacturing process is low risk from the compounding perspective and the recent inspection covered the facility capability to manufacture the (b) (4) DP therefore no PAI inspection is required. This facility is found to be acceptable for this NDA.

(b) (4) FEI: (b) (4)

Based on the firm's current unacceptable compliance status, a **Withhold** is recommended for the facility for NDA 210852. During the next review cycle, the Facility Reviewer should assess the need for a Pre-approval inspection, or surveillance coverage of operations based on the facility's current status and capabilities.

Microbiology Adequate
No change has been made to the process section in the resubmission. Refer to the IQA for NDA 210852 dated 7/12/2018.

Biopharmaceutics Adequate
No change has been made to the Biopharmaceutics information in the resubmission. Refer to the IQA for NDA 210852 dated 7/12/2018.

C. Special Product Quality Labeling Recommendations (NDA only)
N/A

D. Final Risk Assessment (see Attachment)
Refer to the Drug Product review

Application Technical Lead Name and Date:
Xiao Hong Chen, Ph.D.
5-May-2020

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Recommendation: Complete Response

NDA 210852 (Resubmission#2)
Review #3

Drug Name/Dosage Form	Cyclophosphamide Injection
Strength	500mg/ml; 1g/2ml; 2g/4ml
Route of Administration	Intraveneous
Rx/OTC Dispensed	Rx
Applicant	Dr. Reddy's Laboratories Limited
US agent, if applicable	Srinivasa Rao

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	09/28/2017	API/DP/Process/Biopharm/ Microbiology/Facility
Class 2 Resubmission	11/5/2019	OPMA
Class 2 Resubmission#2	5/21/2019	OPMA

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Facility	Aditi Thakur	Ying Zhang
Regulatory Business Process Manager	Kristine Leahy	N/A
Application Technical Lead	Xiao Hong Chen	N/A

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:
N/A

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Pre IND	129593	Submitted on 4/27/2016
NDA	12142	LD

2. CONSULTS

N/A

Executive Summary

I. 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 "withhold" recommendation from the Office of Pharmaceutical Manufacturing Assessment. Specifically, 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) (b) (4) FEI (b) (4) and Dr. Reddy's Laboratories Limited (FEI 3006549835). The following deficiency comments should be included in the action letter:

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.

II. Summary of Quality Assessments

A. Product Overview

Cyclophosphamide is an alkylating drug substance and is indicated for the treatment of malignant diseases such as lymphomas and other cancers as well as (b) (4) (b) (4) The cyclophosphamide drug product listed drug (LD) used in this application is the Baxter Cyclophosphamide for Injection USP (NDA 12142). The LD is supplied as a sterile white powder product for reconstitution in vials containing 500mg, 1g, or 2g of cyclophosphamide. The proposed drug product is an injection concentrate intended for further dilution prior to intravenous administration.

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. the "unacceptable" recommendation was due to the OAI inspection for Dr. Reddy's Laboratories Limited FEI 3006549835, which renders the facility unacceptable. The applicant resubmitted the NDA on 11/5/2018, and provided its response to the facility deficiency listed in the CR letter. The facility reviewer evaluated the response to the deficiency regarding the OAI status for Dr. Reddy's Laboratories Limited FEI 3006549835, and determined that it is acceptable based on the OAI status being downgraded to VAI. There was a recent GMP inspection on the drug substance manufacturing site, (b) (4) concluded on (b) (4) Based on the inspection outcome, the status of (b) (4) has changed to OAI during the review cycle. The NDA resubmission was issued a Complete Response letter on 05/03/2019 based on the incompliant GMP status of the API facility.

In the current resubmission (#2), the applicant stated that the drug substance facility deficiencies have been addressed and requested the FDA to evaluate the current status of the facility.

Proposed Indication(s) including Intended Patient Population	Cyclophosphamide is an alkylating drug indicated for treatment of: **Malignant Diseases**: malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	**Malignant Diseases: Adult and Pediatric Patients** Intravenous: Initial course for patients with no hematologic deficiency: 40 mg per kg to 50 mg per kg in divided doses over 2 to 5 days. Other regimens include 10 mg per kg to 15 mg per kg given every 7 to 10 days or 3 mg per kg to 5 mg per kg twice weekly.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance
No change has been made to the drug substance section in the resubmission. Refer to IQA for NDA 210852.

Drug Product
No change has been made to the drug product section in the resubmission. Refer to IQA for NDA 210852.

Manufacturing
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).

Specifically, Dr. Reddy's Laboratories Limited (FEI: 3006549835) that is responsible for drug product manufacturing has unacceptable compliance status from the recent inspection of 8/12-21/2019 have implications on the commercial products given that there were (b) (4) at the facility. (b) (4) (FEI: (b) (4) that is responsible for drug substance manufacturing was deemed unacceptable in the last review cycle. In the current review cycle, the outstanding deficiencies have not been

satisfactorily addressed by the firm. During the next review cycle, the Facility Reviewer should assess the need for a Pre-approval inspection, or surveillance coverage of operations based on the facility's current status and capabilities.

Microbiology
No change has been made to the process section in the resubmission. Refer to IQA for NDA 210852.

Biopharmaceutics
No change has been made to the Biopharmaceutics information in the resubmission. Refer to IQA for NDA 210852.

C. Special Product Quality Labeling Recommendations (NDA only)
N/A

D. Final Risk Assessment (see Attachment)
Refer to the Drug Product review

Application Technical Lead Name and Date:
Xiao Hong Chen, Ph.D.
13-Novermber-2019

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/s/

XIAOHONG CHEN
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