CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217150Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	217150		
Applicant Name	Sandoz Inc.		
Drug Product Name	Cyclophosphamide Injection		
Dosage Form.	Injection		
Proposed Strength(s)	500 mg/5 mL, 1000 mg/10 mL, 2000 mg/20 mL		
Route of Administration	Intravenous		
Maximum Daily Dose	1750 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Cyclophosphamide is indicated in adults for the treatment of: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma, multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of the ovary, retinoblastoma, and carcinoma of the breast.		
Drug Product Description	The drug product, Cyclophosphamide Injection, 100 mg/mL is a sterile, ready-to-dilute, clear, colorless to pale-yellow solution in a multiple-dose vial requiring dilution prior to use. Cyclophosphamide Injection is available in the following strengths: 500 mg/5 mL, 1000 mg/10 mL, and 2000 mg/20 mL.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	Store vials refrigerated at 2°C to 8°C (36°F to 46°F).		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Kabir Shahjahan, Ph. D.	Haripada Sarker, Ph.D.

	Drug Product/ Labeling	Yang Nan, Ph.D.	Sherita D. McLamore, Ph.D.
	Manufacturing	Golam Kibria, Ph.D.	Kshitij Patkar, Ph.D.
	Biopharmaceutics	Gerlie Gieser, Ph.D.	Anitha Govada, Ph.D.
	Microbiology	Hemlata Tamta, Ph.D.	Denise Miller, Ph.D.
	RBPM	Dahlia A. Walters, M.S	
	ATL	Yang Nan, Ph.D.	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Deficiencies

None

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends APPROVAL of NDA 217150 for the commercialization of Cyclophosphamide Injection, 100 mg/mL in three strengths of 500 mg/5 mL, 1000 mg/10 mL, and 2000 mg/20 mL. Based on our evaluation of the available information, the Applicant provided sufficient information to support an approval recommendation from the drug product quality perspective. The Applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

Please note that compared to the other approved, ready-to-dilute Cyclophosphamide Injection drug products, this drug product approved under NDA 217150 has the following two key differences:

1. (b) (4)

2. *The drug product is indicated for the treatment of adult patients only, no pediatric indication due to the risk of exposure to ethanol and propylene glycol.*

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None

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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:

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	Established name: CYCLOPHOSPHAMIDE injection, for intravenous use
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	Dosage form: Injection Strengths: 500 mg/5 mL, 1000 mg/10 mL, 2000 mg/20 mL
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	Package term: multiple-dose
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the	N/A	

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

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	It is recommended to include the following instruction under "Storage of Undiluted Cyclophosphamide Injection": *Each vial is recommended for no more than a total of eight (8) dose withdrawals.* (b) (4) [redacted]
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	
If there is a USP monograph for the drug product and it contains a labeling requirement,	N/A	

ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).		
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	Cyclophosphamide injection is a hazardous drug. The Applicant is recommended to include a numerical citation to the "OSHA Hazardous Drugs" in the section 15.

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	The appropriate term "multiple-dose" is listed.

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	The Applicant did not list excipient names and quantities of ethanol and propylene glycol; thus the drug product description is recommended for revision as follows: • 500 mg vial contains 534.5 mg cyclophosphamide monohydrate equivalent to 500 mg cyclophosphamide, 2.92 g dehydrated alcohol (equivalent to __% v/v) and 0.96 g propylene glycol. • 1000 mg vial contains 1069.0 mg cyclophosphamide monohydrate equivalent to 1000 mg cyclophosphamide, 5.85 g dehydrated alcohol (equivalent to __% v/v) and 1.92 g propylene glycol. • 2000 mg vial contains 2138.0 mg cyclophosphamide monohydrate equivalent to 2000 mg cyclophosphamide, 11.69 g dehydrated alcohol (equivalent to __% v/v) and 3.84 g propylene glycol.

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	See above.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Adequate	The Applicant is recommended to include the amount of alcohol in percentage. See above.
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	

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	

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	
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	

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	Store vials refrigerated at 2°C to 8°C (36°F to 46°F).
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

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

No Patient Labeling is provided in the submission.

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]	N/A	
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	N/A	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	N/A	
Alphabetical listing of inactive ingredients (if applicable)	N/A	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	N/A	

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

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

500 mg/5 mL (as an example):

3.2 Carton Labeling

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

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

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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[3], (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	
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	The Applicant is recommended to revise the carton label to include quantitative inactive ingredient information for each strength. See the wording in section 11 for details.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Adequate	The Applicant is recommended to include alcohol content (v/v). DMEPA review team was notified. See section 11 for details.
Linear Bar code	Adequate	

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

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 provided the Applicant adequately address the FDA's recommendations.***

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Approval provided the update on the USPI, container and carton labels per FDA recommendations. See evaluation above.

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

Secondary Assessor Name and Date: Sherita McLamore, Ph.D.

Yang Nan

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Sherita McLamore

Digitally signed by Sherita McLamore
Date: 8/14/2023 03:37:21PM
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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	NDA-217150-ORIG-1
Assessment Cycle Number	1 (Original NDA)
Drug Product Name/ Strength	Cyclophosphamide Injection, 100 mg/mL (Presented as 500 mg/5 mL, 1000 mg/10 mL and 2000 mg/20 mL vials)
Route of Administration	Intravenous (Direct bolus Injection or Infusion)
Applicant Name	Sandoz
Therapeutic Classification/ OND Division	Anti-Cancer/ Division of Oncology 2
LD/RS Numbers	Listed Drug Relied Upon: Cytoxan® (500 mg, 1000 mg, and 2000 mg per vial); NDA 012142 Reference Standard: Cyclophosphamide for Injection (500 mg, 1000 mg, and 2000 mg per vial); ANDA 040745
Proposed Indication	Treatment of malignant diseases (b) (4) (b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

Background:
This 505(b)(2) NDA for Cyclophosphamide (Ready-To-Dilute/Concentrate Solution) Injection, 100 mg/mL relies for approval, at least in part, on the FDA's efficacy and safety findings for Cytoxan® for Injection, which is listed in the Orange Book as the Reference Listed Drug (RLD). Since Baxter's Cytoxan (NDA 012142) was discontinued (not for reasons related to efficacy or safety), the comparative *in vitro* testing studies to support scientific bridging were performed using Baxter's Cyclophosphamide for Injection (ANDA 40745) as the Reference Standard (RS).

The proposed drug product, the relied upon LD product, and the RS are all supplied in three presentations that contain equivalent amounts (i.e., 500 mg, 1000 mg, and 2000 mg) of the active ingredient (cyclophosphamide, in the form of cyclophosphamide monohydrate) per vial. The proposed drug product is intended to be diluted (b) (4), and then administered via direct intravenous (IV) injection or intravenous IV infusion at the same final drug concentrations as approved for the reference LD and RS drug products.

The LD, Baxter's Cytoxan® (NDA 012142) and the RS, Baxter's Cyclophosphamide for Injection (ANDA 040745) are both (lyophilized or non-lyophilized sterile) powders for reconstitution and further dilution. On the other hand, the proposed injectable drug product is a Ready-To-Dilute (RTD) or Concentrate solution. In addition, the proposed RTD solution drug product differs mainly from the reference drug products in terms of ***i***) formulation composition [contains ethanol and propylene glycol, as additional ingredients (b) (4), respectively, which are not present in the excipient-free formulation of the RS) or in place of mannitol ((b) (4) in the LD's latest formulation prior to discontinuation)]; ***ii)*** long-term storage conditions during shelf-life (refrigerated instead of room temperature); ***iii*)** packaging format (multiple-use/multiple-dose vial versus single-use/single-dose vial); ***iv*)** additional diluents to prepare the 20 mg/mL IV bolus injection (can also use the same diluents as recommended to prepare the less concentrated 2 mg/mL IV infusion solution), unlike the LD and RS; **(*v*)** physico-chemical properties of the final dilutions for direct IV and/or IV infusion (e.g., in terms of difference in impurities/degradants profiles during product shelf-life, and higher osmolality of the admixtures of the proposed drug product).

To justify that the aforementioned pharmaceutical quality differences between the proposed RTD solution drug product and the relied upon LD would not significantly impact the clinical PK/efficacy/safety/tolerability of the proposed drug product, the Applicant provided comparative *in vitro* physicochemical, comparative *in vitro* protein binding, comparative *in vitro* hemolysis and plasma compatibility data (using the RS as comparator), as well as antimicrobial effectiveness testing (AET) data (for the undiluted drug product in vial), physico-chemical data (after first opening) and additional CMC on stability data/information for the proposed RTD solution drug product. Initially, the Applicant also provided justification for not submitting data of the proposed drug product from *in vivo* animal toxicology studies for impurities and extractables/leachables qualification, and *in vivo* animal local tolerance studies, etc.

<u>Integrated Assessment of Data/Information Submitted to Support the Scientific Bridge:</u>

During NDA review, the Biopharmaceutics Reviewer requested additional *in vitro* physico-chemical characterization data of the proposed solution drug product (before and after dilution with all label-recommended diluents), comparative *in vitro* protein binding data, and comparative *in vitro* hemolysis and plasma compatibility data from adequately designed *in vitro* studies. The results of these additional <u>*in vitro*</u> studies indicated that as compared to the RS, the proposed drug product's 20 mg/mL admixtures (final dilutions in label-proposed vehicles) exhibited a significantly higher osmolality, and a numerically lower surface tension and higher viscosity. Additionally, the Drug Product Reviewer noted that the proposed RTD solution drug product exhibited impurities/degradants during shelf-life that were of different profile and/or

required specifications that were different or higher than the tolerance limits specified in the USP monograph for 'Cyclophosphamide for Injection'. It was also revealed from the results of the newly conducted studies that the proposed drug product's admixtures and the excipients alone have significant *in vitro* hemolytic (i.e., red blood cell lysis) and plasma incompatibility potential, i.e., when using 0.9% Sodium Chloride Injection as the vehicle/diluent.

Per the Pharmacology/Toxicology Review Team, the notably higher *in vitro* hemolytic potential of the proposed cyclophosphamide formulation as compared to the RS is not considered high enough to be of concern. Additionally, per the Pharm/Tox Reviewer, the impurities/degradants tolerance limits of the proposed drug product were adequately justified from a safety perspective.

(b) (4)

Furthermore, the Biopharmaceutics Reviewer notes that based on the results of the additional *in vitro* protein binding study, the plasma protein binding of cyclophosphamide is low and (when averaged over the studied drug concentration range), and appears similar between the proposed drug product and the RS. This finding suggests that cyclophosphamide PK and efficacy are anticipated to be comparable between the proposed drug product and the RS (and thus, the relied upon LD).

During NDA review, to address the Microbiology Reviewer's information request, adequate Antimicrobial Effectiveness Test (AET) data for the undiluted product in the vial was submitted to support multi-dose labeling claims.

Moreover, FDA's systemic safety-related concerns associated with the combination of alcohol and propylene glycol (i.e., at the levels present in the proposed drug product formulation) were sufficiently addressed after the Applicant decided to add labeling language to (***i***) (b) (4) (b) (4) and (***ii***) warn older patients regarding the proposed product's alcohol content which could exert CNS effects thereby impairing ability to drive or use machines immediately after infusion. (b) (4)

(b) (4)

Conclusion:
Based on FDA's overall assessment of the data/information submitted in the application, the scientific bridge between the proposed drug product and the

relied upon Listed Drug product has been established in accordance with 21 CFR 320.24(b)(6).

Recommendation:
From the Biopharmaceutics perspective, provided there is satisfactory resolution of labeling review issues, the submitted data/information are deemed adequate to support approval of NDA 217150.

List of Submissions Assessed:

Document(s) Assessed	Date Received
SN-1 (Original NDA)	8/12/2022
SN-2 (Response to Process IR: (b) (4))	9/22/2022
SN-3 (Response to Clinical IR: (b) (4))	9/28/2022
SN-4 (Response to Microbiology IR: multi-use product)	10/7/2022
SN-6 (Withdrawal of (b) (4); revised labeling)	11/3/2022
SN-5 (Response to Early Biopharm IR - set 1)	11/3/2022
SN-7 (Response to Follow-up Biopharm IR)	12/7/2022
SN-8 (Response to Micro IR)	1/20/2023
SN-9 (Response to Biopharm IR)	1/20/2023
SN-10 (Response to Process/Facilities IR	1/20/2023
SN-11 (Response to Drug Product IR)	1/23/2023
SN-12 (Response to Biopharm IR)	2/14/2023
SN-13 (Response to Micro IR)	3/16/2023
SN-14 (Response to Process IR – (b) (4) leachables, (b) (4))	4/7/2023
SN-15 (Response to Drug Product IR – CCIT, in-use stability for multi-use claim, (b) (4))	4/10/2023
SN-16 (Response to Clinical Information Request – alcohol/PG)	4/12/2023
SN-17 (Response to Drug Product IR – no change in (b) (4) (b) (4) specification)	4/25/2023
SN-18 (Response to OPMA IR – (b) (4)	4/28/2023
SN-19 (Response to Drug Product IR -analytical methods)	5/1/2023
SN-20 (Response to Biopharm IR – submission date now June 12, 2023)	5/4/2023
SN-24 (Response to Biopharm IR)	6/5/2023
SN-25 (Response to Pharmacology/Toxicology IR)	6/22/2023
SN-27 (Response to Medical IR)	7/14/2023
SN-28 (Response to Biopharm IR)	8/4/2023

Concise Description of Outstanding Issues:
-None (Note that labeling negotiations are in progress)

B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

Note that the proposed drug product was not tested in any *in vivo* human studies.

The Applicant confirmed that the proposed commercial formulation is the same as the formulation that was used in *in vitro* bridging studies and other *in vitro* studies supporting registration. Specifically, the three bulk solution batches (KX0975, KX2522, KX2523) used in the production of the 500 mg/5 mL, 1000 mg/10 mL, and 2000 mg/20 mL presentations of the packaged drug product lots tested in the comparative *in vitro* (physicochemical characterization, *in vitro* protein binding, and *in vitro* hemolysis) studies, registration/stability studies, and other CMC studies supporting registration (e.g., in-use physico-chemical stability testing after first opening, and infusion stability testing) were manufactured using the proposed commercial formulation and process (at the proposed commercial scale, (b) (4)) by the proposed commercial drug product manufacturer [FAREVA Unterach GmbH, Austria]. Additionally, the proposed commercial container-closure system was used to package the proposed RTD solution drug product that was investigated in stability studies.

> *In the Major Amendment submission dated 6/5/2023, the Applicant mentioned about having conducted a preliminary in vivo animal toxicity study to justify the hyperosmolality of the proposed drug product's dilutions. This in vivo animal study also used the same drug product lot that was used in the in vitro protein binding and in vitro hemolysis studies.*

The drug substance (cyclophosphamide monohydrate, USP) produced by the proposed commercial API supplier ((b) (4)) was used in the manufacture of the drug product lots evaluated in stability, comparative *in vitro* studies, as well as in a 5-day preliminary *in vivo* animal dose range finding toxicity study. Per the Drug Substance Reviewer, the batch analysis data of the drug substance batches used to manufacture the drug product registration batches are adequate.

The batch analyses data of the NDA registration batches of the proposed RTD solution drug product are provided in Table 2 and Table 3 of 3.2.P.5.4.

The Drug Product Reviewer confirmed that the change in color of the plastic flip-off cap of the drug product container from (b) (4) (for the NDA registration batches) to (b) (4) (for the commercial batches) is not anticipated to impact stability of the final to-be-marketed drug product,

specifically because the flip-off cap is not in direct contact with the solution drug product.

B. 13 BIOWAIVER REQUEST OR CROSS-PRODUCT BRIDGING

Assessment: Bridging of Proposed and Listed Drug Products – ***Adequate***

In Section 1.12.5 of the NDA, a waiver of *in vivo* bioequivalence studies was requested for all three proposed commercial presentations of the proposed drug product versus the Reference Standard (ANDA 040745), pursuant to 21 CFR 320.22(b)(1).

> *Note that in the Pre-NDA Type B meeting held on 4/29/2022, the Sponsor was informed that reliance on an approved ANDA is not acceptable to support the proposed 505(b)(2) NDA. The Sponsor's proposal to rely on Cytoxan® (NDA 012142) as the Listed Drug (LD) product was deemed acceptable by FDA. Since Cytoxan® was discontinued from marketing, FDA recommended that the ANDA 40745 product be used as the Reference Standard (RS) in the bridging studies to be conducted.*
>
> *Note that in the Biopharmaceutics Information Request dated 10/03/2022, the Applicant was informed that a biowaiver request via 21 CFR 320.22(b)(1) is not feasible because the proposed injectable solution drug product is not qualitatively and quantitatively (Q1/Q2) the same as the LD being relied upon. FDA reminded the Applicant that the adequacy of the scientific bridge between the proposed and relied upon LD drug product can be granted in accordance with 21 CFR 320.24(b)(6), provided the supporting data/information is deemed adequate during NDA review. Additionally, the proposed and the LD drug products do not have the same (shelf-life) dosage forms (RTD solution versus i.e., powder for reconstitution and further dilution), but at the point of patient administration are both injectable solutions with the same drug concentrations.*

This 505(b)(2) NDA for Cyclophosphamide (Ready-To-Dilute/RTD Solution for) Injection, 100 mg/mL, relies for approval, at least in part, on the FDA's findings of efficacy and safety for Cytoxan® (cyclophosphamide monohydrate) powder for Injection.

(b) (4)

(b) (4)

(b) (4)

The proposed RTD product was developed to eliminate the reconstitution step required for the Cytoxan lyophilized powder (prior to the dilution to the minimum concentration, i.e., 20 mg/mL for direct IV infusion or 2 mg/mL for IV infusion).

The noted similarities and differences between the proposed drug product and the relied upon Listed Drug product and the Reference Standard are shown in Reviewer Table 1 below. To justify that the formulation, dosage form/presentation, and other quality differences would not impact efficacy and safety of the proposed drug product (and thus, enable scientific bridging to the LD product), comparative physicochemical characterization, *in vitro* protein binding and *in vitro* hemolysis studies (versus the RS product), as well as stability, in-use stability, and special CMC studies on the proposed RTD solution drug product, and toxicological risk assessments were conducted by the Applicant.

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Gerlie Gieser

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Anitha Palamakula Govada

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

Product Information	Indicated for treatment of malignant diseases: malignant lymphomas, Hodgkin's lymphoma RLD is CYTOXAN (Cyclophosphamide for injection, 500 mg/vial, 1 g/vial, and 2 g/vial) NDA 012142
NDA Number	217150
Assessment Cycle Number	1
Drug Product Name/ Strength	Cyclophosphamide Injection, 100 mg/ mL (500 mg/5 mL, 1000 mg/10mL and 2000mg/20 mL)
Route of Administration	Intravenous
Applicant Name	Sandoz Inc.
Manufacturing Site	FAREVA Unterach GmbH Mondseestraße 11, Unterach, Austria 4866
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: N/A

Assessment Summary: *Cyclophosphamide Injection, 100 mg/ mL is* (b) (4)

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
001	08/12/2022
004	10/27/2022
008	01/20/2023
013	03/16/2023

0022	05/22/2023

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

Remarks: This is an eCTD submission. Information request (IR1) was conveyed on 12/16/2022 and the response received on 01/20/2023. IR2 was conveyed on 02/16/2023 and the response was received on 03/16/2023. IR3 was conveyed on 05/09/2023 and the response was received on 05/22/2023. The IR responses were incorporated in the review.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

Supporting Documents:

- Type V DMF (b) (4) owned by (b) (4) and microbiology review (b) (4), dated 02/01/2023 (adequate) (b) (4)
- Microbiology review (b) (4) dated 06/07/2022 (adequate) for (b) (4).

Select Number of Approved Comparability Protocols: 0

S DRUG SUBSTANCE

Assessment: N/A. Drug substance is supplied non-sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(3.2.P.1 Description and Composition of the Drug Product.pdf)

- **Description of drug product –** Cyclophosphamide injection, 100mg/mL is a clear colorless to pale yellow, sterile, non-pyrogenic solution for intravenous administration.
- **Drug product composition –**

Component	Function	Quality Standard	Cyclophosphamide injection, 100 mg/mL				Concentration (% w/w)
			Amount per mL (mg/mL)	Amount per Unit (500 mg/5 mL)	Amount per Unit (1000 mg/10 mL)	Amount per Unit (2000 mg/20 mL)	
Cyclophosphamide (Cyclophosphamide monohydrate)	Drug substance	USP and in-house	100.00 mg (106.9 mg)	500.0 mg (534.5 mg)	1000.0 mg (1069.0 mg)	2000.0 mg (2138.0 mg)	11.32 % (12.11)
Ethanol absolute[2]	(b) (4)	USP	584.67 mg	2.923 g	5.847 g	11.693 g	66.22 %
Propylene glycol[2]		USP	191.73 mg	958.7 mg	1.917 g	3.835 g	21.71 %
Total weight			883.3 mg	4.42 g	8.83 g	17.67 g	/

- **Description of container closure system –**

Component	Strength	Description	Manufacturer
Glass vial	500 mg/5mL	(b) (4)	
	1000 mg/10mL		
	200 mg/20mL		
Stopper	500 mg/5mL		
	1000 mg/10mL		
	200 mg/20mL		
Seal	500 mg/5mL		
	1000 mg/10mL		
	200 mg/20mL		

Exhibit Batches (500 mg/5 mL, 1000 mg/10mL and 2000mg/20 mL): (b) (4)
Proposed Commercial Batch Size (500 mg/5 mL, 1000 mg/10mL and 2000mg/20 mL): (b) (4)

Assessment: *Adequate*
The applicant provided an adequate description of the drug product composition and container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

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Post-Approval Commitments: None

Assessment: N/A

MICROBIOLOGY LIST OF DEFICIENCIES: None

Primary Microbiology Assessor Name and Date:
Hemlata Tamta, Ph.D., 05/25/2023

Secondary Assessor Name and Date:
Denise Miller, SPQA, Senior Microbiologist, 05/25/2023

Hemlata Tamta

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Denise Miller

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