CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214657Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ **Approval**
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 214657
Review #2

Drug Product Name	Pemetrexed Injection
Dosage Form	Solution for Intravenous Injection
Strength(s)	25 mg/mL (100 mg/4 mL, 500 mg/20 mL, 1000 mg/40 mL)
Route of Administration	Intravenous Injection
Rx/OTC Dispensed	Rx
Applicant	Sandoz Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SN-25 Resubmission NDA Class 2	11/26/2021	All
SN-26 Labeling Amendment	02/04/2022	All
SN-27 Labeling Amendment	03/23/2022	All
SN-28 Labeling Amendment	05/05/2022	All
SN-29 Labeling Amendment	05/06/2022	All
SN-30 Labeling Amendment	05/11/2022	All

QUALITY ASSESSMENT TEAM

DISCIPLINE	PRIMARY REVIEWER/ SECONDARY REVIEWER	BRANCH/DIVISION
Drug Substance	Paresma Patel	OPQ/ONDP/DNDAPI
Drug Product	Rajiv Agarwal/Xing Wang	OPQ/ONDP/DNDPI
Facility/Process	Steve Hertz/James Norman	OPQ/OPMA/DMAIV
Microbiology	Jason God/Julie Nemecek	OPQ/OPF/DMA
Biopharmaceutics	Gerlie Gieser	OPQ/ONDP/DB
Regulatory Business Process Manager	Rabiya Haider	OPQ/OPRO/RBPMI
Application Technical Lead	Mei Ou	OPQ/ONDP/DBI
Laboratory (OTR)	NA	NA
ORA Lead	NA	NA

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)	(b) (4)	Adequate	DMF (b) (4) reviewed by Donglei Yu 01/04/2022. Remain adequate. Original NDA submission reviewed by Katherine Windsor 02/18/2021. Remain adequate.	MAPP 5015.5 (Rev.1)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
ALIMTA	NDA 021462	Listed Drug Product

2. CONSULTS

None

Executive Summary

Recommendations and Conclusion on Approvability:

From a Pharmaceutical Quality perspective, NDA 214657-ORIG-1-RESUB-27 is recommended for APPROVAL.

Summary of Quality Assessments

A. Product Overview

Sandoz Inc. submitted the original NDA 214657 on July 7, 2020, for Pemetrexed injection solution, 25 mg/mL (100 mg/4 mL, 500 mg/20 mL, 1000 mg/40 mL). This 505(b)(2) NDA relies on the FDA's privious findings of safety and efficacy for the Listed Drug (LD) product, ALIMTA® (pemetrexed) lyophilized powder for injection (NDA 021462), for approval. ALIMTA was approved on February 04, 2004, for the treatment of patients with locally advanced or metastatic non-squamous non-small cell lung cancer as well as mesothelioma and is available as a lyophilized powder (containing 100 mg and 500 mg pemetrexed per vial).

The proposed Pemetrexed injection is a clear colorless to yellow or green-yellow ready-to-dilute (RTD) solution for intravenous administration. Proposed Pemetrexed injection is available in three presentations of 100 mg/4 mL, 500 mg/20 mL and 1000 mg/40 mL. The proposed drug product differs from LD product in terms of dosage form (i.e., RTD solution formulation vs. lyophilized powder formulation for reconstitution and further dilution) drug substance hydrate form (i.e., hemipentahydrate vs. heptahydrate), and excipients (i.e., absence of mannitol, and addition of sodium thiosulfate pentahydrate (b) (4) (b) (4) and propylene glycol (b) (4)

The original NDA received a Tentative Approval Letter on May 06, 2021. The Applicant resubmitted the NDA 214657 on July 23, 2021 but withdraw the resubmission on November 18, 2021. The Applicant resubmitted this NDA again on November 26, 2021 and requested the final approval upon the expiry of the pediatric exclusivity expiry (May 24, 2022).

Quality review cycle #2 addresses the Applicant's product correspondence to notify the agency of a potential out of specification (OOS) result for impurities for the 100 mg/4 mL presentation at the 24-month time point.

Proposed Indication(s) including Intended Patient Population	• in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations. • in combination with cisplatin for the initial treatment of patients with locally advanced or

	metastatic, non-squamous, non-small cell lung cancer (NSCLC). • as a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. • as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy. Limitations of Use: Pemetrexed injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer. • in combination with cisplatin, for the initial treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.
Duration of Treatment	The recommended dose of Pemetrexed Injection administered with pembrolizumab and platinum chemotherapy in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m^2 as an intravenous infusion over 10 minutes, administered after pembrolizumab and prior to platinum chemotherapy, on Day 1 of each 21-day cycle.
Maximum Daily Dose	500 mg/m^2
Alternative Methods of Administration	NA

B. Quality Assessment Overview

DRUG SUBSTANCE: No Action Indicated (NAI)
This NDA was recommended for approval during review of the original submission by Katherine Windsor on 18-Feb-2021. The current resubmission provides no additional drug substance information. The cross referenced DMF (b) (4) was last reviewed by Donglei Yu on 04-Jan-2022. There are no unreviewed amendments. The DMF remains adequate. *The Drug Substance remains **Approval**.*
DRUG PRODUCT: ADEQUATE
Applicant has performed a root cause analysis. (b) (4)

(b) (4) [redacted]
The newly proposed acceptance criteria for impurities are consulted to the assigned Pharmacology/Toxicology (P/T) reviewer and on 7/27/2021, P/T reviewer confirmed that the newly proposed acceptance criteria for (b) (4) [redacted] and total impurities are safe from a P/T standpoint. Therefore, widening of the acceptance criteria for these impurities is acceptable. *The Drug Product recommends for **Approval**.*
PROCESS and FACILITIES: NAI
*The Process and Facilities remains **Approval**.*
MICROBIOLOGY: NAI
*The Microbiology remains **Approval.***
BIOPHARMACEUTICS: NAI
*The Biopharmaceutics remains **Approval**.*

C. Special Product Quality Labeling Recommendations

Provided information is adequate from product quality standpoint.

D. Risk Assessment

FROM INITIAL RISK IDENTIFICATION			REVIEW ASSESSMENT		
Attribute	**Factors that can impact the CQA**	**Initial risk ranking**	**Risk mitigation approach**	**Final risk evaluation**	**Lifecyle consideration**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		L	
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		L	
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		L	
Assay (b) (4)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		L	
Uniformity of Dose (Fill Volume/ deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		L	
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		L	
pH	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		L	

Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		L	
Appearance (Color /turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		L	

E. List of Deficiencies for Complete Response
None

Application Technical Lead Name and Date for NDA-214657-ORIG-1-RESUB-27:
Mei Ou, Ph.D. 05/13/2022

Mei Ou

Digitally signed by Mei Ou
Date: 5/13/2022 10:24:54AM
GUID: 54ca9d7000073c57d2eb7cc6e42c05bb

Memo

From: Rajiv Agarwal, Ph.D., Ph.D., Review Chemist

Through: Anamitro Banerjee, Ph.D., Branch Chief

IND: NDA 214657 (amendment 24 (5/12/2021) and 25 (7/23/2021))

Date: 08/16/2021

Re: Review of newly proposed impurities acceptance criteria in **injection** Drug Product

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Background: Via amendments 24 and 25, a reference is made to an original New Drug Application (NDA 214657) for Pemetrexed Injection, 25 mg/mL (100 mg/4 mL, 500 mg/20 mL and 1000 mg/40 mL) submitted on 7/7/2020.

Sandoz Inc. submits product correspondence to notify the agency of a potential out of specification (OOS) result for impurities for the 100 mg/4 mL presentation at the 24-month time point. Similar findings were encountered in the CMC review of the original NDA. Refer to the CMC review in Panorama.

The testing parameter which is not meeting the tentatively approved specification are for (b) (4) (D) (4) and Total Impurities (NMT (b) (4)%). Following table summarizes the results obtained for these tests at 24 months.

Batch	Storage Condition / Orientation	Time point	(b) (4)
31741527	25°C/60% RH inverted	24 months	
	25°C/60% RH upright		
	30°C/75% RH inverted		
31743055	25°C/60% RH inverted	24 months	
	25°C/60% RH upright		
	30°C/75% RH inverted		
31742988	25°C/60% RH inverted	24 months	
	25°C/60% RH upright		
	30°C/75% RH inverted		

Via amendment 25, Sandoz submits a proposal for changes in the finished product specifications. Sandoz is proposing to widen the release and shelf life specification limits for four parameters in Drug Product Specification (3.2.P.5.1) (b) (4) and *total*

impurities for which out of specification (OOS) results at 24-months' time-point were observed.

Discussion: Considering the OOS results at 24-months' time point, Applicant is proposing to widen specification acceptance criteria for (b) (4) (b) (4) total impurities for all three presentations (100 mg/4 mL, 500 mg/20 mL, 1000 mg/40 mL). The limits for the proposed impurities have been set based on the data collected to date, the toxicological summary and statistical analysis. The table below summarizes the current specifications and the proposed specifications in this amendment.

	Present (release and shelf life specification limits) 100 mg/4 mL, 500 mg/20 mL, 1000 mg/40 mL	Proposed (release and shelf life specification limits) 100 mg/4 mL, 500 mg/20 mL, 1000 mg/40 mL
(b) (4)	NMT (b) (4)	NMT (b) (4)
	NMT	NMT
	NMT	NMT
Total impurities	NMT	NMT

In order to qualify Pemetrexed related impurities, a toxicology study was performed. For more information, please refer to the *Module 3.2.P.5.5* (Chapter 3.1 - *Attachment 1 – Qualification of impurities in Pemetrexed LIVI 25 mg/mL, TOXR-PEM_14*) and corresponding literature references in Module 4.3.
Sandoz believes that there is negligible risk on patient safety for exposure to potential impurities administered with Pemetrexed 25 mg/mL.

Evaluation: *Applicant has performed a root cause analysis.* (b) (4)

(b) (4)

The newly proposed acceptance criteria for impurities is consulted to the assigned Pharmacology/Toxicology (P/T) reviewer and on 7/27/2021, P/T reviewer confirmed

that the newly proposed acceptance criteria for [redacted] *total impurities are safe from a P/T standpoint.*

Therefore, widening of the acceptance criteria for these impurities is acceptable.

Adequate

Rajiv Agarwal

Digitally signed by Rajiv Agarwal
Date: 4/25/2022 07:59:59AM
GUID: 504fa29c0000100b83d3aaa4905783c1
Comments: This memo is currently in “NDA-214657-ORIG-1-AMEND-25” task #10.

Xing Wang

Digitally signed by Xing Wang
Date: 4/25/2022 09:45:29AM
GUID: 525daca300039122a4daaad45e49c6fb

Memo

From: Rajiv Agarwal, Ph.D., Ph.D., Expert Regulatory Review Scientist

Through: Xing Wang, Ph.D., SPQA

IND: NDA 214657 (amendment SDN 27 (11/26/2021))

Date: 4/25/2022

Re: Resubmission/Class 2

CMC information was originally reviewed on 2/23/2021 and on 8/16/2021 and provided information was deemed adequate. No additional CMC information is submitted via this amendment/Resubmission.

Adequate

Xing Wang

Digitally signed by Xing Wang
Date: 4/25/2022 10:42:17AM
GUID: 525daca300039122a4daaad45e49c6fb

Rajiv Agarwal

Digitally signed by Rajiv Agarwal
Date: 4/25/2022 10:41:07AM
GUID: 504fa29c0000100b83d3aaa4905783c1

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	Pemetrexed
Route(s) of administration	Adequate	IV, Injection
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Dosage form: Injection Strengths: 100 mg/4 mL, 500 mg/20 mL and 1000 mg/40 mL
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	Drug product is an injection
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.	N/A	Single-dose (b) (4)
If the drug product contains an active ingredient that is a 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).	Adequate	(b) (4)

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

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	Yes, dilution instructions are in place • Further dilute Pemetrexed Injection with 0.9% Sodium Chloride Injection, USP (preservative–free) to achieve a total volume of 100 mL for intravenous infusion.
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	No specific instruction
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	Yes • Visually inspect for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard if particulate matter or discoloration is observed.
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	N/A	There is no USP monograph for the drug product

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	Not applicable
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".	N/A	Yes, citation is in place in How Supplied section

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	Injection
Strength(s) in metric system	Adequate	Strengths: 100 mg/4 mL, 500 mg/20 mL and 1000 mg/40 mL
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	Refer to Section 11 and Carton labelling
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	Clear, colorless to yellow or green-yellow solution
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Drug product is an injection
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.	N/A	Single-dose vial

Section 11 (DESCRIPTION)

(b) (4)

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	Pemetrexed
Dosage form(s) and route(s) of administration	Adequate	Injection, IV
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)"	Adequate	Each mL contains 25 mg pemetrexed which is equivalent to 30.2 mg pemetrexed disodium 2.5 hydrate.
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	Provided
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.	Inadequate	Provided
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Adequate	N/A
Sterility statement (if applicable)	Adequate	Sterile vials
Pharmacological/Therapeutic class	Adequate	Folate analog metabolic inhibitor
Chemical name, structural formula, molecular weight	Adequate	Yes
If radioactive, statement of important nuclear characteristics.	N/A	Not applicable
Other important chemical or physical properties (such as pKa or pH)	N/A	Not applicable

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	Not applicable
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	Not applicable
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	Not applicable

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

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	Injection
Strength(s) in metric system	Adequate	Yes
Available units (e.g., bottles of 100 tablets)	Adequate	Vials
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	Clear colorless to yellow or green-yellow solution
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not applicable
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.	N/A	Single-dose
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	Protect from light. Keep the vial in the carton box until the time of use. **Comment:** This information is added to the USPI and carton labels.

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 solution at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
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	Not applicable
Include information about child-resistant packaging	N/A	Not applicable

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.

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	**Manufactured by:** FAREVA Unterach GmbH **Manufactured for**: Sandoz Inc., Princeton, NJ 08540

2.0 PATIENT LABELING

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

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	Yes
Special preparation instructions (if applicable)	N/A	N/A
Storage and handling information (if applicable)	N/A	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	Not Applicable
Active ingredient(s) (if applicable)	N/A	Pemetrexed
Alphabetical listing of inactive ingredients (if applicable)	N/A	Yes
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	N/A	**Manufactured by:** FAREVA Unterach GmbH **Manufactured for:** Sandoz Inc., Princeton, NJ 08540

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

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)

100 mg/4 mL:

500 mg/20 mL:

3 Page(s) of Draft Labeling have 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[3], (font size and prominence)	Adequate	Pemetrexed
Strength(s) in metric system	Adequate	Provided
Route(s) of administration	Adequate	For Intravenous infusion (b) (4)
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Adequate	Each mL contains 25 mg pemetrexed which is equivalent to 30.2 mg pemetrexed disodium 2.5 hydrate.
Net contents (e.g., tablet count, volume of liquid)	Adequate	Yes
"Rx only" displayed on the principal display	Adequate	Yes
NDC	Adequate	Yes
Lot number and expiration date	Adequate	Space is provided
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Yes
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	Single-dose vial
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	Each mL contains 25.0 mg pemetrexed, 0.5 mg of sodium thiosulfate pentahydrate, 50.0 mg propylene glycol, water for injection.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Adequate	n/a
Linear Bar code	Adequate	Provided on both vial and carton labels

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	**Manufactured for:** Sandoz Inc., Princeton, NJ 08540
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	No medication guide
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	Not applicable
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Not applicable
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	Not applicable
And others, if space is available.	N/A	Not applicable

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

ATL, once the labelling is finalized, will add the final labelling and labels to their assessment.

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

ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See Carton/Container Labeling Specific Resources for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g.,

[3] Established name = [**Bendamustine HCl**] [IV] [injection]

established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

Overall Assessment and Recommendation:

Provided information is Adequate from an ONDP-DP standpoint.

Following information is added to the carton labels and color mock-ups are provided on 5/12/2022:

- Each mL contains 25 mg pemetrexed which is equivalent to 30.2 mg pemetrexed disodium 2.5 hydrate.

Primary Labeling Assessor Name and Date: Rajiv Agarwal 5/12/2022

Secondary Assessor Name and Date: Xing Wang

Rajiv Agarwal

Digitally signed by Rajiv Agarwal
Date: 5/12/2022 11:18:28AM
GUID: 504fa29c0000100b83d3aaa4905783c1

Xing Wang

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Recommendation: Approval

NDA 214657
Review #1

Drug Name/Dosage Form	Pemetrexed Injection/Injection, ready-to-dilute solution,
Strength(s)	25 mg/mL (100 mg/4 mL, 500 mg/20 mL, and 1000 mg/40 mL),
Route of Administration	Intravenous Injection (infusion)
Rx/OTC Dispensed	Rx
Applicant	Sandoz

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	07/07/2020	ONDP-All
Quality Amendment	08/25/2020	Biopharmaceutics, Microbiology
Quality Amendment	8/26/2020	Biopharmaceutics
Quality Amendment	9/16/2020	Drug Product, Microbiology
Quality Amendment	9/18/2020	Drug Product
Labeling/Container Carton Draft, Package Insert	10/06/2020	Labeling
Quality Amendment	10/23/2020	Drug Product
Clinical Pharmacology	12/07/2021	Biopharmaceutics
Quality Amendment	01/08/2021	Drug Substance, Drug Product, Process and Facilities
Labeling/Container Carton Draft, Package Insert	01/13/2021	Labeling
Quality Amendment	01/14/2021	Drug Product
Labeling, Package Insert	02/11/2021	Revised USPI, and CC
Quality Amendment	03/30/2021	Process and Facilities

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER/ SECONDARY REVIEWER	BRANCH/DIVISION
Drug Substance	Katherine Windsor Ali Al Hakim	OPQ/ONDP/DNDPAPI
Drug Product	Rajiv Agarwal/ Anamitro Banerjee	OPQ/ONDP/DNDPI
OPMA/Facility	Steven Hertz/Yiwei Li	OPQ/OPMA/DMAIV
Microbiology	KellyAnn Miller/Julie Nemecek	OPQ/OPF/DMA
Biopharmaceutics	Gerlie Gieser/Banu Zolnik	OPQ/ONDP/DB/

Regulatory Business Process Manager	Kristine Leahy	OPQ/OPRO/RBPMI
Application Technical Lead	Banu Zolnik	OPQ/ONDP/DB
Laboratory (OTR)	NA	NA
ORA Lead	Caryn McNabb	ORA

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	09/16/2016 by Donglei Yu	
	Type III			Adequate		
	Type III			Adequate	08/16/2010 by Sheldon B Markofsky	MAPP 5015.5 (Rev.1)
	Type III			Adequate	6/15/2017 by Daneli Lopez Perez	
	Type V			Adequate	5/26/2016 by Helen Ngai	

B. Other Documents: *IND or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Alimta Label	NDA 021462	Listed Drug, Alimta

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

From a Pharmaceutical Quality perspective, NDA 214657 is recommended for APPROVAL.

Summary of Quality Assessments

A. Product Overview

Sandoz has submitted this NDA 214657 for Pemetrexed injection. Pemetrexed injection is a sterile, ready-to-dilute solution.

This 505(b)(2) NDA for Pemetrexed Injection, 25 mg/mL relies for approval, at least in part, on the FDA's efficacy and safety findings for the Listed Drug (LD) product, ALIMTA® (pemetrexed) For Injection (NDA 021462). ALIMTA was approved on February 04, 2004 for the treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer as well as mesothelioma and is available as a lyophilized powder (100 mg and 500 mg per vial).

Pemetrexed injection, 25 mg/mL is a clear colorless to yellow or green-yellow solution for intravenous administration. Proposed Pemetrexed injection is available in three presentations of 100 mg/4mL, 500 mg/20mL and 1000 mg/40mL. The proposed ready-to-dilution solution product contains two excipients (sodium thiosulfate and propylene glycol (b) (4)) that are not in the relied upon LD product. Alimta contains mannitol (b) (4).

Proposed Indication(s) including Intended Patient Population	• in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations. (1.1) • in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC). (1.1) • as a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. (1.1) • as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy. (1.1)

	Limitations of Use: Pemetrexed injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer. (1.1) • initial treatment, in combination with cisplatin, of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery. (1.2)
Duration of Treatment	The highest recommended duration of treatment in the label for Non-Squamous NSCLC: Day 1 of each 21-day cycle until disease progression or unacceptable toxicity after four cycles of platinum-based first-line chemotherapy
Maximum Daily Dose	500 mg/m^2
Alternative Methods of Administration	NA

B. Quality Assessment Overview

DRUG SUBSTANCE: ADEQUATE
Pemetrexed disodium is a folate analog metabolic inhibitor. The drug substance is isolated as the hemipentahydrate, which is freely soluble in water. There is a USP monograph for pemetrexed disodium (listing heptahydrate, anhydrous, and free acid forms, but not the hemipentahydrate form). The Applicant cross-referenced the CMC information for pemetrexed disodium drug substance to DMF (b) (4) DMF (b) (4) was reviewed by Donglei Yu Ph.D. (final signature 08-JAN-2021) and was found adequate to support ANDA-202111-ORIG-1-AMEND-20. There have been no quality amendments submitted since the last assessment; the DMF remains adequate to support NDA 214657. Specified and unspecified impurity controls are sufficient. Stability data in the referenced DMF support the proposed retest period of (b) (4) for pemetrexed disodium drug substance (b) (4) The Drug Substance Reviewer recommended for **approval**.
DRUG PRODUCT: ADEQUATE
Pemetrexed injection, 25 mg/mL is a clear colorless to yellow or green-yellow solution for intravenous administration. **Pemetrexed injection is available in three presentations of 100 mg/4mL, 500 mg/20mL and 1000 mg/40mL**. Each 1 mL contains 25 mg Pemetrexed. The dosage form "injection" has been used for drug products available as solutions that will be injected, regardless of whether or not they need further dilution before administration. Correct dosage form has been used. Injection drug product are packaged into clear, colorless Typ (b) (4) glass vials, closed with (b) (4) rubber stoppers. The vials will be

sealed with an aluminum (b) (4) cap with a flip-off. The drug product is supplied as single-use (b) (4) vials. Glass vial and stopper are qualified per USP <660> <211> and USP <381> testings which cover extractables. However, a very extensive study is carried out under EXT-400-2 report summarizing the results over **the entire shelf-life of 24 months (Report TE 150911) for the leachable study and results deemed acceptable**. Also, **Extractables/leachables** in Pemetrexed drug product derived from (b) (4) **are also evaluated and deemed acceptable**.

All excipients used for Pemetrexed injection formulation **were of pharmacopoeia grade (USP). The amounts of Sodium thiosulfate and propylene glycol excipients appears to be higher than what is listed in IID for IV route of administration. Applicant has provided the justification via safety report in 3.2.P.2 (document 2020_TRA_163_MW**). Pharmacology/Toxicology reviewer is contacted to comment on the safety of these excipients. The Pharmacology/Toxicology (P/T) team has no safety issues with the levels of excipient used in the formulation.

No reactions between the excipients, sodium thiosulfate (STS), (b) (4) and propylene glycol, (b) (4) in aqueous solution are known. Stability data from formulation development studies does not indicate any incompatibilities between the chosen excipients.
Per Salt Policy, the strength is based on base. Sodium thiosulfate pentahydrate concentration in the injection is 0.05% (b) (4). Propylene glycol is (b) (4) (b) (4)
CoAs of each excipient are provided and they are adequate. **Stability data from formulation development does not indicate any incompatibilities between the excipients**.

Commercial images of the labels are self-explanatory and different color boxes around each strength are used to distinguish various strengths: Green (100 mg/4mL), Red (500 mg/20mL), and Yellow (1000 mg/40mL). **Route of administration (For intravenous Infusion (b) (4) after dilution) is prominently displayed on each label.** Originally, applicant proposed two sets of release and shelf life specification. Per ICH Q6A, one set of regulatory specification for release and stability are recommended and applicant accepts the proposal. In the revised drug product release/stability specifications, the proposed limit of NLT (b) (4)% for assay of sodium thiosulfate (STS) is not consistent with the data provided in the submission. Therefore, a second IR was communicated on 11/27/2020 to amend the assay to (b) (4)%. Applicant responded on 1/14/2021. During development screening studies (VERB-GAL 015-2015) design of experiment (DoE) was carried out to study suitable STS concentration. Based on the stability data it is determined that total impurities were (b) (4)% when the assay of STS was between (b) (4) %. Therefore, based on the real time stability on the developmental batches, **applicant tighten the lower limit of NLT (b) (4) % to NLT (b) (4) % and this is adequate.**
(b) (4) Similarly, **elemental impurities** in the final drug product **are in compliance** with the USP General Chapter <232> Elemental

Impurities – Limits and ICH Q3D Guideline for Elemental Impurities and also meets Q3D Option 3 requirements.
Applicant states that the Osmolality of the solution is (b) (4) mOsm and the calculated Osmolality of the IV admixture is (b) (4) mOsm. Clinical Division agrees with the Osmolality of the admixture.

Stability study of Pemetrexed injection, 25 mg/mL contains testing at 25°C ± 2°C / 60% ±5% RH, 30°C ± 2°C/75% ± 5% RH and at 40°C ± 2°C/75% ± 5% RH (accelerated condition) in both inverted and upright configurations. Over the 18 months (500 mg and 1000 mg presentations) and 12 months (100 mg presentation) testing times, the parameters, such as, color, assay, chromatographic purity, pH and (b) (4) content were found to be within the shelf-life specification limits. There was no change observed in (b) (4), identity, sub-visible particles, clarity, microbial testing (sterility and bacterial endotoxins) and extractable volume. Tightness of closure (Container Closure Integrity Test) was performed at initial time point. All tested vials were leak tight and no sample showed any blue coloration.Under the thermal stress conditions, the tested parameters remained within the release specification limits over the period of cycles 1, 2 and 3 at -20°C to 40°C/75% RH and within the shelf life specification limits over the tested time period of 12 months. Based on the results of the present study, it can be concluded that temperature variations had no impact on the stability of Pemetrexed injection, 25 mg/mL.
During photo stability testing, data indicate that the drug product is light sensitive as impurity levels are higher in illuminated samples. Therefore, the use of a carton box for storage of the drug product until the moment of use is proposed by the applicant as it provides protection from light. This information is captured in all drug product labels.
Infusion solutions: Infusion solutions prepared from Pemetrexed injection, 25 mg/mL were stable for 7 days at room temperature protected from light and for 14 days at refrigerated condition (2-8 °C, protected from light) for the 500 mg and 1000 mg presentations. For the 100 mg presentation the prepared infusion solution was stable for 3 days at refrigerated condition (2-8 °C, protected from light). In PI label, the recommendation will be captured as (b) (4) Based on the 24 months of real time stability, a 24 months expiration dating period may be granted for 100 mg, 500 mg and 1000 mg presentations.
Original drug vial: The proposed expiration dating period of 24 months for drug product when stored at 25°C (77°F), excursions permitted to 15° - 30°C (59° - 86°F) in the proposed primary container and secondary closure system may be granted.

The Drug Product Reviewer recommended for **approval.**

PROCESS and FACILITIES: ADEQUATE

The manufacturing process development was performed applying a QbD approach, and manufacturing process parameters were proposed based on laboratory studies. A 704a4 was performed for the drug product facility, and after reviewing the facility's 704a4 responses, the primary manufacturing reviewer and lead ORA officer determined that the 704a4 response mitigates the need for a PAI.

The Process and Facilities Reviewer recommended for **approval.**

MICROBIOLOGY: ADEQUATE

The microbiology review covers sterility assurance and microbiological quality of the drug product. The applicant has met regulatory expectations regarding the information related product quality microbiology.

The Microbiology Reviewer recommended for **approval**.

BIOPHARMACEUTICS: ADEQUATE

The proposed injectable drug product is a Ready-To-Dilute (RTD) solution. The proposed RTD product was developed to eliminate the reconstitution step required for the ALIMTA lyophilized powder, prior to dilution with 0.9% NaCl Injection to the final infusion solution. In addition to dosage form during shelf-life (powder vs. concentrate) and additional presentation (1000 mg/vial), the proposed RTD solution drug product differs mainly from the LD in terms of i) drug substance polymorphic hydrate form (hemipentahydrate instead of heptahydrate); ii) formulation composition (contains (b) (4) sodium thiosulfate and (b) (4) propylene glycol in place of (b) (4) mannitol); iii) physico-chemical properties of the RTD solution (b) (4) and the final infusion product (b) (4)) as compared to the LD's reconstituted and final infusion solutions; iv) minor difference in characteristics of immediate container-closure system; v) light sensitivity, and vi) a higher level of measured specific and total impurities during long-term storage at controlled room temperature. The Applicant provided adequate comparative in vitro data, additional CMC and nonclinical data/information, and published literature 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.

Overall, the submitted comparative and additional supporting data/information/ justification are deemed 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 Biopharmaceutics Reviewer recommended for **approval**.

C. Special Product Quality Labeling Recommendations

NA

D. Final Risk Assessment

FROM INITIAL RISK IDENTIFICATION			REVIEW ASSESSMENT		
Attribute	**Factors that can impact the CQA**	**Initial risk ranking**	**Risk mitigation approach**	**Final risk evaluation**	**Lifecyle consideration**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	H	(b) (4)	L	
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipment • Site	M	(b) (4)	L	
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		L	Controls are in place, continue stability monitoring post approval
Uniformity of Dose (Fill Volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		L	
Assay (b) (4)	Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		L	
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		L	

pH-	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		L	Controls are in place

Banu S. Zolnik, Ph.D.
Application Technical Lead, NDA 214657

Banu Zolnik

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U.S. FOOD & DRUG ADMINISTRATION

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CHAPTER III: ENVIRONMENTAL

IQA NDA Assessment Guide Reference

R REGIONAL INFORMATION

EA assessment is covered under Chapter 2 Drug Product review

LABELING

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section:

(b) (4)

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section:

(b) (4)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

(b) (4)

(b) (4)

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)?
☒ Yes ☐ No ☐ N/A

If "No," explain.

R Regional Information

1.14 Labeling (Commercial packaging):

Immediate Container Label (100 mg/mL):

(b) (4)

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(b) (4)

[redacted]

Reviewer's Assessment: *During photostability per ICH Q1B testing (refer to SR-PEMLIV!23 document), the total impurities range for 500 mg/20 mL presentation was between* (b) (4) *% whereas in the 100 mg/4 mL presentation, values between* (b) (4) *% were shown. The total impurity amount of* (b) (4) *% for exposed samples indicates a sensitivity of the drug product to light, which is most pronounced in the 4 mL presentation (worst case for photostability). Stability data indicate that the drug product is light sensitive as impurity levels are higher in illuminated (light exposed) samples for one strength. Therefore, the use of a carton box for storage of the drug product until the moment of use is recommended as it provides protection from light. This information will be captured in product labels.*

Therefore, applicant proposed and this reviewer accepted the following recommendation:

Keep the vial in the carton box until the moment of use.

*The similar information is placed on the **carton box** labels. This is not a precedent, several products under NDA and BLA has this statement on PI and CC label.*

***Infusion solutions** prepared from Pemetrexed injection, 25 mg/mL were stable for 7 days at room temperature protected from light and for 14 days at refrigerated condition (2-8 °C, protected from light) for the 500 mg and 1000 mg presentations. For the 100 mg presentation the prepared infusion solution was stable for 3 days at refrigerated condition (2-8 °C, protected from light).*

From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would not normally be longer than 24 hours at 2 to 8°C, unless dilution has taken place under controlled and validated aseptic conditions.

Therefore, in "How Suuplied" section, one of the following two statement should be included:

When added to an infusion bag containing 0.9% Sodium Chloride Injection, USP, solution may be stored up to 24 hours at 2-8°C.

Reviewer's Assessment: *The deficiencies on PI and CC lables are identified and were communicated to the applicant by DDMAC/OND. Applicant accepts all the CMC recommendations. A final version of the agreed upon PI and container labels (carton box) is provided via amendment dated 2/11/2021.*

Conclusion: *Labels and Labeling are modified as recommended, from a CMC stand point USPI and CC labels deemed adequate.*

Primary Labeling Reviewer Name and Date:

Rajiv Agarwal, Ph.D, 2/12/2021

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Anamitro Banerjee, PhD, 2/23/2021

Rajiv Agarwal

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Anamitro Banerjee

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	214657
Assessment Cycle Number	Original 505(b)(2) NDA
Drug Product Name/ Strength	Pemetrexed Injection 25 mg/mL (presented as 100 mg/4 mL, 500 mg/20 mL,1000 mg/40 mL Ready-To-Dilute/RTD solution in single-dose vials)
Route of Administration	For Intravenous Infusion
Applicant Name	Sandoz, Inc.
Therapeutic Classification/ OND Division	Anticancer: Folate analog metabolic inhibitor DO2
Listed Drug Product Relied Upon	ALIMTA® lyophilized powder for reconstitution and further dilution [NDA 21462]
Proposed Indication	Treatment of non-squamous, non-small cell lung cancer

Assessment Recommendation: **APPROVAL**

Assessment Summary:

This 505(b)(2) NDA for Pemetrexed Injection, 25 mg/mL relies for approval, at least in part, on the FDA's efficacy and safety findings for the Listed Drug (LD) product, ALIMTA® (pemetrexed) For Injection (NDA 021462).

Unlike ALIMTA® which is a lyophilized powder for reconstitution and further dilution, the proposed injectable drug product is a Ready-To-Dilute (RTD) solution. The proposed RTD product was developed to eliminate the reconstitution step required for the ALIMTA lyophilized powder, prior to dilution with 0.9% NaCl Injection to the final infusion solution. In addition to dosage form during shelf-life (powder vs. concentrate) and additional presentation (1000 mg/vial), the proposed RTD solution drug product differs mainly from the LD in terms of ***i***) drug substance polymorphic hydrate form (hemipentahydrate instead of heptahydrate); ***ii***) formulation composition (contains (b) (4) (b) (4) sodium thiosulfate and (b) (4) propylene glycol in place of (b) (4) (b) (4) mannitol); ***iii***) physico-chemical properties of the RTD solution (b) (4)) and the final infusion product ((b) (4)) as compared to the LD's reconstituted and final infusion solutions; ***iv***) minor difference in characteristics of immediate container-closure system; ***v***) light sensitivity, and ***vi***) a higher level of measured specific and total impurities during long-term storage at controlled room temperature.

The Applicant provided adequate comparative *in vitro* data, additional CMC and nonclinical data/information, and published literature 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.

Overall, the submitted comparative and additional supporting data/information/ justification are deemed 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).

List of Submissions Reviewed:

Document(s) Assessed	Date Received
Original NDA	SDN-3, 7/7/2020
Response to Drug Product IR regarding Batch Numbers	SDN-4, 8/25/2020
Response to Biopharmaceutics Pre-Filing Comments (Part I)	SDN-5, 8/26/2020
Response to Biopharmaceutics Pre-Filing Comments (Part II)	SDN-10, 12/7/2020

Concise Description of Outstanding Issues:

None

B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

The comparative *in vitro* physicochemical characterization studies included in the initial NDA submission evaluated representative registration/stability lots of the proposed drug product which were all manufactured using the proposed commercial formulation and process by the proposed commercial drug product manufacturer (EBEWE/Austria) using the drug substance produced by the proposed commercial API supplier (b) (4) (b) (4)

Also used in comparative *in vitro* hemolysis and *in vitro* protein binding studies was a proposed drug product lot (31752677, 500 mg/20 mL) which has the same formulation, process, manufacturer, API supplier, and exhibits similar physicochemical characteristics as the primary registration/stability lots.

The 28-day Repeat Dose Animal Toxicity Study 31777 (conducted to qualify the impurities levels in the proposed drug product) evaluated a drug product lot manufactured by the proposed commercial manufacturer using drug substance from a developmental API supplier (b) (4) (b) (4) which is not the proposed commercial API supplier. The provided appearance

and other physicochemical data of the "active control" lot (pemetrexed 1000 mg/40 mL Batch 31075319) in Study 31777 do not indicate that there are drug product quality attributes that would impact the ability to extrapolate the systemic and local tolerability data in this study to the target drug product manufactured using the API from the proposed commercial supplier [redacted](b) (4) For the Certificate of Analysis of Lot 31075319, refer to Appendix 1 of the Study 31777 report.

The ALIMTA® lots used in comparative *in vitro* physicochemical, hemolysis and protein binding studies were not expired.

Note that the proposed to-be-marketed drug product was not evaluated in clinical studies.

B. 13 BIOWAIVER REQUEST OR CROSS-PRODUCT BRIDGING

Assessment: *BRIDGING OF PROPOSED & LISTED DRUG PRODUCTS* - ***Adequate***

This 505(b)(2) NDA for Pemetrexed (Ready-To-Dilute/RTD Solution for) Injection, 25 mg/mL, relies for approval on the FDA's findings of efficacy and safety for ALIMTA® (pemetrexed disodium) [powder] for Injection. The proposed RTD product was developed to eliminate the reconstitution step required for the ALIMTA lyophilized powder, prior to the dilution step.

The noted similarities and differences between the proposed drug product and the relied upon Listed Drug are shown in Table 1. To justify that the formulation, dosage form and other product quality differences would not impact efficacy and safety of the proposed drug product (and thus, enable scientific bridging to the relied upon LD product), the Applicant conducted comparative physicochemical, comparative *in vitro* protein binding and comparative *in vitro* hemolysis characterization studies, as well as stability testing of the proposed drug product, and a literature-based assessment (i.e., to support the proposed levels of the selected formulation excipients).

Note that in SDN-5, the Applicant acknowledged that the request to waive clinical BE testing of the proposed pemetrexed Ready-To-Dilute (RTD) solution injectable drug product cannot be granted via 21 CFR 320.22(b)(1) because the proposed injectable solution drug product is not qualitatively and quantitatively (Q1/Q2) the same as the relied upon Listed Drug (LD) product. Instead, the scientific bridge to ALIMTA® (Listed Drug product, LD) could potentially be established via 21 CFR 320.24(b)(6).

Table 1. Comparison of the Proposed Drug Product and the Relied Upon Listed Drug Product

	Proposed Drug Product Pemetrexed (Ready-To-Dilute Solution for) Injection, Sandoz, Inc.	**Listed Drug Product Being Relied Upon** ALIMTA® (pemetrexed for injection); NDA 021462, Eli Lilly & Company
Dosage Form; Strength(s)/Presentation	Ready-To-Dilute (RTD) Solution; 25 mg pemetrexed (b) (4) /mL (single-dose vials containing 100 mg/4 mL, 500 mg/20 mL, and 1000 mg/40 mL RTD solution)	Lyophilized Powder for Reconstitution and Further Dilution with preservative-free NSS (single dose 100 mg, and 500 mg (b) (4) /vial)
Formulation Composition	Each glass vial of 100 mg/4 mL RTD solution contains (in addition to 120.8 mg pemetrexed disodium (b) (4)) Sodium thiosulfate pentahydrate (2 mg) Propylene Glycol (200 mg) Water for Injection (q.s. ad 4 mL) HCl or NaOH to adjust pH	Each glass vial of 100 mg pemetrexed (eq. to 139.8 mg pemetrexed disodium heptahydrate) contains Mannitol (106 mg) HCl or NaOH to adjust pH
Final Concentration at the point of patient contact	For BSA = 1.8 m^2: 9 mg/mL upon dilution with NSS to 100 mL	(25 mg/mL upon reconstitution) For BSA = 1.8 m^2: 9 mg/mL upon dilution with NSS to 100 mL
Proposed Indications/Route of Administration/Dosing Regimen	Indications, Administration Routes, and Dosing Regimens the same as LD; Final dilution administered as 10-min IV infusion	
Physico-chemical properties of the product before and after final dilution for IV infusion[a]		
Appearance	Clear, colorless (to pale yellow) solution; (practically) free from visible particulates	
Assay	- Before dilution: 99.6 - 102% (batch release); 99.5 – 102.1% (24 months) *After dilution: 96.4 – 96.6% (24 months)* [Final Proposed ranges: (b) (4) % (batch release and shelf-life)[b]]	Reconstituted/Before dilution: 95.2 - 102.3%; *After dilution: 94.2 – 96.5%* [Approved range: (b) (4) % of LC]
pH	Before dilution: 8.2 – 8.5 (batch release); 7.70 – 8.34 (24 months) *After dilution: 7.5* [Final Proposed ranges: (b) (4) (release and shelf-life)[b]]	Reconstituted/Before dilution: 6.62 – 7.37 *After dilution: 7.05 – 7.15* [Approved range: (b) (4)
Osmolality (mOsm/kg)	Before dilution: 866 - 875 *After dilution: 494 -496*	Reconstituted/Before dilution: 503 - 526 *After dilution: 373 - 378*
Viscosity (mPa.s)	Before dilution: 2.886 – 3.067 *After dilution: 2.643 – 2.7*	Reconstituted/Before dilution: 2.674 – 2.918 *After dilution: 2.461 – 2.693*
Specific gravity	Before dilution: 1.0247 – 1.0263 *After dilution: 1.0097*	Reconstituted/Before dilution: 1.0247– 1.0263 *After dilution: 1.0138*
Total Impurities	Before dilution: (b) (4) % (500 mg/20 mL); (b) (4) % (100 mg/4 mL)	Reconstituted/Before dilution: (b) (4) % *After dilution:* (b) (4) %

	After dilution: [redacted]% (500 mg/20 mL); ND[c] (100 mg/4 mL)		
In Vitro Protein Binding (%) 250 mcg/mL pemetrexed	79.4		77.4
Recommended storage during product shelf-life and upon preparation[d]	USP Controlled Room Temperature Protect from Light. Keep vial in the carton box until moment of use. (use diluted solution within 24 hours of preparation when kept under refrigeration)		USP Controlled Room Temperature ALIMTA is not light sensitive. (use both reconstituted and diluted solution within 24 hours of preparation when kept under refrigeration)
Container-closure	USP Type [redacted] glass vial with (for 100 mg/4 mL), and USP Type [redacted] glass vial (for other two presentations); [redacted] rubber stopper and aluminum seal with light blue plastic flip off		USP Type [redacted] glass vial [redacted] rubber stopper with aluminium seal
Physico-chemical & microbiological stability			
Total Impurities/Degradants	< [redacted]% (batch release) [redacted]% (up to 24 months of long-term storage)		-
Sterility	[redacted] -maintained during 6 months accelerated and 12 or 18 months of long-term stability testing (inverted and upright positions); container-closure integrity testing (CCIT) conforms at initial and 6 months of accelerated stability time points and during long-term storage.		-
Bacterial Endotoxins (NMT [redacted] EU/mL)	Conforms during initial and at Month 12 stability time points		
Special QC specifications (tests and acceptance ranges) final proposed/approved	1. Fill Volumes – NLT [redacted] target filing volume [redacted] based on [redacted]		Reconstitution time = NMT [redacted]
	2. [redacted] Assay	Batch Release[b] and During Shelf-Life: NLT [redacted]%[e]	-
	3. Impurities	Batch Release[b] and During Shelf-Life	
	[redacted]	NMT [redacted]%	[redacted] NMT [redacted]%
	Other individual identified impurities Unspecified unidentified impurities	NM [redacted] NMT [redacted] NMT [redacted]%	Largest Unspecified Impurity: NMT [redacted]%
	Total impurities	NMT [redacted]%	Total Impurities NMT [redacted]%
	4.Test for Inorganic Impurities in the Drug	[redacted]	-

	Substance Raw Material		
	5 (b) (4)	NMT (b) (4)% (in-process)	

[a] Data shown are for the final infusion solutions with drug concentration of 10 mg/mL (used for dosing 500 mg/m^2 of a 2.0 m^2 patient). Unless otherwise specified, the comparative physicochemical data tabulated above were measured using the proposed drug product's 100 mg/4 mL, and/or 500 mg/20 mL presentations, 24 months at time of analysis), versus the unexpired LD's 100 mg/vial and 500 mg/vial presentations.
[b] In SDN-9, per OPQ recommendation, one set of finished product QC specifications for batch release and shelf-life was adopted by the Applicant.
[c] ND: not determined (but values expected to be similar to "before dilution")
[d] Tentative expiration dating period = 24 months (USP CRT)
[e] In SDN-14, per OPQ recommendation, (b) (4) (sodium thiosulfate) Assay was tightened to "NLT (b) (4)%" for batch release and shelf-life testing.

The Reviewer's assessment of the Applicant's justifications for the differences between the proposed drug product and the Listed Drug product are discussed in detail below.

Justification for

1. *Difference in crystalline hydrate of the API salt (hemipentahydrate vs heptahydrate), and the apparent slight difference in the strength of the proposed product's lowest RTD strength (100 mg/4 mL) and the Listed Drug product's reconstituted powder (100 mg/4.2mL)*

   Pemetrexed disodium exists in either of two crystalline API polymorphic forms, hemipentahydrate and heptahydrate. The proposed drug product uses hemipentahydrate whereas the LD uses heptahydrate.

   Per the Applicant, pemetrexed hemipentahydrate solubility in water is at least 100 mg/mL at 25 ℃. Solubility data of the drug substance in pH 1.2, 4.5, and 6.8 buffer media at room temperature and under refrigeration were requested but not provided by the Applicant because formulation pH during product manufacture and storage (b) (4) are adjusted or maintained to be within the pH (b) (4) range. This Reviewer did not pursue the drug substance solubility data under refrigerated conditions in view of the Applicant's findings in a freeze-thaw study which showed that more extremely low temperature conditions (-20 ℃ to 25℃/60%RH, i.e., that might occur during shipping) did not impact the physical stability (including appearance and freedom from insoluble matter/particulates) and chemical stability of the proposed to-be-marketed drug product.

   In SDN-10, the Applicant provided data to demonstrate comparable pemetrexed assay values of the proposed 100 mg/4 mL RTD solution product ((b) (4)%) and the LD product's 100 mg/vial powder following reconstitution with 4.2 mL (b) (4)). After dilution with 0.9% NaCl solution, the pemetrexed assay values of the proposed and the LD products' final infusion solutions were also reported to be similar (b) (4) % versus (b) (4)%, respectively).

   NOT FOR FOIA (b) (4) (b) (4)

Regarding the history of API suppliers, the Applicant mentioned that the (1) 2nd Technical batch manufactured using the (b) (4) API/drug substance had dissolution issues and later precipitated after 12 months of storage, and similarly, (2) the registration batches manufactured in 2015 using (b) (4) drug substance started precipitating after 18 months of stability testing. The root cause for precipitation was identified (b) (4) Thus, in view of the proposed strength (25 mg/mL) of the proposed concentrate/RTD drug product, (as well as the results of the Applicant's root-cause investigation on storage-time dependent API precipitation), this Reviewer considers reasonable the Applicant's proposal to include (b) (4) (b) (4) as part of the Drug Product Manufacturer's QC Specifications for release (b) (4) The Applicant indicated that the inorganic impurities tolerance limits were established (b) (4) (b) (4)

Note that in the SDN-5 Response to the Biopharmaceutics IR, the Applicant indicated that the requested solubility data of the API in various pH media, in the solvent system, and in the prescribed diluent of the proposed ready-to-use pemetrexed solution at room temperature and under refrigeration for the API materials sourced from various suppliers during development were not available for comparison. The Applicant indicated that regardless of the API supplier, the drug substance raw materials during development exhibited a solubility in water of at least 100 mg/mL at 25 °C. Additionally, the Drug Substance Reviewer (Dr. Katherine Windsor) confirmed acceptability of the proposed acceptance criterion/criteria for ***1***) clarity of solution (b) (4) mg/mL in water) [i.e., NMT (b) (4)], as well as ***2***) the proposed levels of specific inorganic impurities for the API supplied by (b) (4) . Furthermore, this Biopharmaceutics Reviewer notes that the proposed Drug Product QC Specifications at batch release and shelf-life already include a QC test to ensure clarity of solution.

2. *Difference in Formulations/Excipients – Impact on pemetrexed PK*

The proposed RTD solution product contains two excipients that are not in the relied upon LD product. Per the Applicant, sodium thiosulfate and propylene glycol (b) (4) are added, and the final pH of the RTD solution is adjusted to (b) (4) in the proposed liquid drug product.

Per the Applicant, these two added excipients (sodium thiosulfate and propylene glycol) in the proposed formulation (b) (4) that could potentially alter the PK/PD effects of intravenously administered pemetrexed. Additionally, since neither of these two excipients are structurally similar to folates, and thus, are unlikely to interfere with the cellular uptake of pemetrexed. Furthermore, both excipients are not significantly protein bound as evident from the effectiveness of hemodialysis in treating propylene

glycol toxicity and the negligible extent of human serum binding reported in the literature for sodium thiosulfate. Moreover, in the SDN-5 IR Response, the Applicant indicated that even though the excipients propylene glycol and sodium thiosulfate are excreted unchanged in the urine to a significant extent (like pemetrexed), the mechanisms of renal elimination, i.e., glomerular filtration/active tubular secretion as both unchanged and metabolized drug, and glomerular filtration, respectively, (versus active tubular secretion by human organic anion transporter 3) do not appear to overlap in part or completely, and thus the excipients are unlikely to alter the elimination PK and PD kinetics of pemetrexed from the proposed drug product.

In the conducted *in vitro* protein binding study (using equilibrium dialysis), the reported percentage of protein binding between the test/proposed product (Batch# 31752677) and reference product (ALIMTA, Batch# S19L025A) were comparable (79.4% versus 77.4%, respectively) at the studied drug concentration (250 mcg/mL, post-addition of the pemetrexed infusion solution into plasma), suggesting that no significant difference in drug distribution between the proposed and the reference drug products is to be anticipated. This Reviewer acknowledges that the Applicant provided protein binding data also for two "pemetrexed API in placebo" formulations (PEME-LIVI and PEME-LYVI) to achieve final drug concentrations in spiked plasma ranging from 0.5 mcg/mL to 200 mcg/mL. Note that this Reviewer did not officially report in the comparative summary Table 1 above the *in vitro* protein binding data generated using these extemporaneously prepared formulations. Nevertheless, it can be inferred from the protein-binding data generated for PEME-LIVI and PEME-LYVI that the percentage of *in vitro* protein binding appears to trend numerically lower at higher final pemetrexed concentration in the spiked plasma (i.e., 85% – 87% at 0.5 mcg/mL versus 80% – 81% at 200 mcg/mL). For the detailed *in vitro* protein binding data, refer to Table 4-2 of the report for Study DMPK R8453172.

This Reviewer believes that the removal of mannitol and the addition of (b) (4) in the proposed drug product would not be anticipated to result in a difference in pemetrexed PK/disposition (occurring mainly via renal elimination as unchanged drug) between the proposed and the reference drug products, for the following reasons: (***i***) The maximum dose of mannitol in ALIMTA (1.06 grams in 1000 mg) is approximately 14-fold lower than the mannitol dose required to induce diuresis in a 70 kg patient given a maintenance (mannitol) dose of 200 mg/kg via IV infusion (3 – 5 min). Thus, this Reviewer assumes that the mannitol (added as (b) (4) excipient) in ALIMTA does not significantly influence the drug's renal elimination. (***ii***) Additionally, based on this Reviewer's literature survey, it appears that neither sodium thiosulfate nor propylene glycol has diuretic or anti-diuretic activity, and substantially higher daily propylene glycol intravenous doses (e.g., 50 grams/day) than that deliverable from the proposed drug product were associated with nephrotoxicity in humans. Furthermore, the similarity of the proposed and LD products in terms of *in vitro* protein binding data suggests anticipated similarity with respect to drug interaction potential where protein binding displacement/competition is the mechanism involved.

3. *Difference in Formulations/Excipients – Impact on drug product systemic safety and local tolerability*

Per the Applicant, the levels of the sodium (b) (4) and propylene glycol excipients in the proposed formulation are justified [from a systemic safety perspective] because their maximum daily doses (MDDs) as received by an adult patient with BSA = 1.8 m^2 (1810 mg/day propylene glycol and 18.1 mg/day sodium thiosulfate) are either 690-fold lower than the 12.5 gram intravenous dose of sodium thiosulfate when used as an antidote for cyanide poisoning, or >10-fold lower than the European Medical Agency's permitted daily exposure (PDE) of adults to parenterally administered propylene glycol (500 mg/kg/day = 25000 mg/day for a 50 kg patient). This Reviewer notes that Yaucher et al. (2003) cited literature that recommend a lower maximum daily permissible intake value for propylene glycol as a food additive (i.e., 25 mg/kg = 1875 mg/day for a 75 kg patient); thus, considering this more conservative PDE value, the amount of propylene glycol in the proposed pemetrexed RTD drug product (and the corresponding MDD of 1810 mg/day for a typical patient with BSA of 1.8 m^2) appears acceptable from a systemic safety perspective. Additionally, this Reviewer notes that the level of propylene glycol in the proposed drug product is approximately 80% lower than the level (and thus, deliverable intravenous infusion dose) of propylene glycol from administration of an already approved pemetrexed RTD drug product, Pemfexy® (50 mg/mL versus 260 mg/mL propylene glycol), which further supports the proposed level of propylene glycol present in the proposed pemetrexed RTD injectable drug product, i.e., from a safety/tolerability perspective. Furthermore, the Drug Product Reviewer (Dr. Rajiv Agarwal) and the Pharmacology/Toxicology Review Team (led by Dr. Whitney Holmes) consider the type and level of added excipients in the proposed formulation acceptable for the following reasons: (1) both excipients are USP grade, and (2) there were adequate literature data provided to support safety of these two excipients; refer to table below.

Component	Function	Quality Standard	Pemetrexed injection, 25 mg/mL				Concentration (% w/w or % w/v)	Maximum Daily Intake (MDI)	IID[1] Limit for intravenous Route of Administration
			Amount per mL (mg/mL)	Amount per Unit (100 mg/4 mL)	Amount per Unit (500 mg/20 mL)	Amount per Unit (1000 mg/40 mL)			
Pemetrexed (Pemetrexed Disodium 2.5 hydrate)	Active ingredient	USP and in-house	25.0 mg (30.2 mg)	100.0 mg (120.8 mg)	500.0 mg (604.2 mg)	1000.0 mg (1208.3 mg)	2.5 %	900 mg	N/A
Sodium thiosulfate pentahydrate[2]	(b) (4)	USP	0.5 mg	2.0 mg	10.0 mg	20.0 mg	0.05 %	18.1 mg[2]	4 mg
Propylene glycol[2]		USP	50.0 mg	200.0 mg	1000.0 mg	2000.0 mg	4.93 %	1810 mg[2]	82.04 % w/v
Hydrochloric acid (b) (4)	pH adjusting agent	NF	q.s.[3]	q.s.[3]	q.s.[3]	q.s.[3]	q.s.[3] to adjust pH between (b) (4)	For pH adjustment	45.63mg
Sodium hydroxide	pH adjusting agent	NF	q.s.[3]	q.s.[3]	q.s.[3]	q.s.[3]	q.s.[3] to adjust pH between (b) (4)	For pH adjustment	250mg
Water for injection	(b) (4)	USP	q.s.[3] to 1 mL	q.s.[3] to 4.0 mL	q.s.[3] to 20.0 mL	q.s.[3] to 40.0 mL	ad[4] to 100%	N/A	N/A

[1] IID refers to the Inactive Ingredient Database posted at the FDA website, **http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm**. Last updated 03/02/2020
[2] Please refer to the excipients safety report attached in *3.2.p.2 - pharmaceutical-development-appendices -US-32* for more information.
[3] *quantum satis, the amount which is enough*
[4] up to

Maximum daily dose (MDD):
= 1.8 m^2 (body surface area) × 500 mg/m^2 (recommended dose)
= 900 mg

In the Applicant's response to the Biopharmaceutics Information Request (SDN-5), it was revealed that the final infusion solution of the proposed RTD product is hypertonic. Additional comparative data in SDN-10 confirmed the hypertonicity of the proposed drug product's final infusion solution (10 mg/mL) (i.e., 494 - 496 mOsm/kg, versus 373 – 378 mOsm/kg for the same final infusion concentration of ALIMTA). Since online references often cite the results of a published literature study (involving adults) reporting a successful reduction of the risk of chemical phlebitis by limiting the infusate osmolality to 450 mOsm/kg (Gazitua et al., 1979), this Reviewer considered additional animal toxicity data submitted in this NDA to evaluate the potential impact of the proposed product's final infusion solution's higher osmolality. Based on the results of a conducted 4-week repeat dose toxicity study in mice, the higher than 450 mOsm/kg osmolality of the proposed product's final infusion solution is not anticipated by this Reviewer to be a local tolerability (i.e. chemical phlebitis) concern because the Applicant reported that there were *no signs of local intolerance reactions* for both slow IV bolus injected pemetrexed 1000 mg/40 mL (Batch 31075319; used as the normal impurity level control) and 0.9% NaCl solution (negative vehicle control); refer to Justification Item #5 (*Difference in Dosage Form and Presentation - Impact on product quality*) below for additional discussion. Although Batch 31075319 used drug substance sourced from a developmental API supplier ((b) (4) and as discussed in Section B.12 above API suppliers changed during early stages of pharmaceutical development (b) (4)), the provided Certificate of Analysis for this test lot confirms that there were no notable (quality attribute differences from the target drug product and there were also no) observed precipitation issues that could have impacted the ability to extrapolate the nonclinical local safety/tolerability findings to the proposed to-be-marketed drug product.

Note that this Reviewer's assessment did not consider the osmolality and other physicochemical data provided for the 1000 mg/40 mL presentation of the Sandoz Pemetrexed Liquid in Vial (LIVI) in the Physicochemical Comparison Study because those LIVI lots were 29 months old (beyond the 24 months proposed drug product shelf-life). All other Sandoz Pemetrexed LIVI lots and all ALIMTA LYophilized powder in Vial (LYVI) lots used in the comparative physicochemical characterization study were not expired. As discussed above, the favorable local tolerability findings for the "active control" product lot (Batch 31075319) in the 4-week animal study also confirms the acceptability from a clinical safety perspective of the slightly higher pH of the proposed product's final infusion solution, i.e., 7.61 – 7.82 (versus 7.05 – 7.15 for ALIMTA's final infusion solution).

Also in SDN-10, the Applicant provided the report of Study 31776 to show that final infusion solutions with concentrations ranging from 0.5 mcg/mL to 2.5 mg/mL do not result in hemolysis of red blood cells *in vitro*. This Reviewer no longer pursued additional *in vitro* hemolysis data for drug concentrations as close as feasible to that achieved at the point of patient administration (i.e., 9 mcg/mL or 10 mcg/mL) because (***i***) the more recently provided comparative *in vitro* osmolality data already confirmed that the proposed product's final infusion solutions are hypertonic, and hemolytic

potential are more often expected to be associated with hypotonic (rather than hypertonic) solutions, and also because (***ii***) the "clinical" significance of the proposed drug product's hypertonicity could be more appropriately addressed by the results of the conducted 28-day local (and systemic) tolerability study in mice (as discussed above).

4. *Difference in Dosage Form and Presentation – Impact on Clinical Outcomes*

   The proposed higher fill volume (delivering as much as 1000 mg per vial) of the proposed drug product is reasonable because the recommended dose is 500 mg/m^2, therefore, up to 1000 mg per dose of IV infusion would be required by a patient with BSA ~ 2 m^2.

   Furthermore, all presentations of the proposed and Listed drug products will have the same pharmaceutical form (solution) at the point of patient contact, the same drug product concentrations prior to final dilution (25 mg/mL) and after final dilution (e.g., 9 mg/mL for a patient with BSA 1.8 m^2), as well as the same administration route and dosing regimens.

   Additionally, both test and reference drug products are presented in a single-dose vial.

5. *Difference in Dosage Form and Presentation - Impact on product quality*

   At the time of comparative *in vitro* testing, the reconstituted Listed Drug 100 mg/vial and 500 mg/vial products exhibited (b) (4)% total impurities/degradants. On the other hand, the exhibit batches of the proposed Ready-To-Dilute Injectable Solution drug product (including the carton as secondary packaging), during 6 months of accelerated (40 ± 2 °C/75 ± 5 RH) and 18 to 24 months of long-term (5 ± 3 °C, and 25°C ± 2°C; RH: 60% ± 5%) stability testing, exhibited NMT (b) (4) (b) (4)[for 100 mg/4 mL: max observed (b) (4)% at 18 months] and NMT (b) (4)% total impurities [for 100 mg/4 mL: max observed (b) (4)% at 18 months]. *It was interesting to note that during stability testing, the proposed product's 100 mg/4 mL presentation exhibited a higher percentage of individual/specific and total impurities/degradants than the 500 mg/20 mL and 1000 mg/40 mL presentations.* Based on the Physicochemical Characterization Study results (in SDN-10), the total impurities levels measured for the 24-month old proposed drug product (500 mg/20 mL) were similar before dilution and after dilution with 0.9% NaCl to the final infusion solution (i.e., (b) (4)% versus (b) (4)%). As compared to the 500 mg/20 mL and 1000 mg/40 mL presentations, the 24-month old 100 mg/4 mL lots of the proposed drug product, the total impurities were higher (b) (4)%) before dilution, consistent with observations in formal long-term stability studies; after-dilution data were not available for this presentation, but the impurities levels post-dilution are also expected to be similar to those measured pre-dilution.

The originally proposed acceptance ranges for finished drug product pH, Assay, and Related Substances were wider or more permissive during shelf-life/stability testing than at batch release of the proposed drug product. However to address the Drug Product Reviewer's Information Request, in SDN-9, the Applicant proposed that the initially proposed shelf-life specifications be used as the one set of finished product QC specifications to be adopted for QC testing of the proposed drug product at batch release and during shelf-life. It is noted that the proposed limit for Total Impurities is higher than that approved for the Listed Drug product (NMT (b) (4)% versus NMT (b) (4)%). Although the levels of (b) (4) degradants in the stability samples were above the ICH Q3H qualification thresholds, the Applicant indicated that based on the results of a 28-day repeated dose toxicity study in mice (Study 31777), there were no signs of local intolerance nor any test or reference-item related local intolerance reactions observed with the [intentionally] degraded pemetrexed (liquid in vial) LIVI product (developmental impurity Batch V2014141, for IV bolus dosing of (b) (4) related impurities once weekly), the "active control" product (Pemetrexed 1000 mg/40 mL Batch 31075319, containing (b) (4)% total impurities), and 0.9% NaCl solution (negative control). Additionally, the Pharmacology/Toxicology Review Team led by Dr. Whitney Helms confirmed that the 28-day toxicity study revealed no real [local and systemic] toxicological differences between the pemetrexed active control product and the pemetrexed enriched with related impurities. To ensure chemical stability of the drug in solution is maintained over the proposed expiration dating period, i.e., 24 months when stored under controlled room temperature conditions, the Drug Product Reviewer recommended tightening of the proposed tolerance limits for assay of the (b) (4) excipient from "NLT (b) (4) " to "NLT (b) (4)%". Also per the Drug Product Reviewer, the proposed overfill volumes for each presentation of the proposed drug product are acceptable as they are aligned with USP<1151> and USP<1> recommendations and will ensure tht each vial will contain sufficient excess liquid to allow withdrawal of the labelled quantity of drug.

Based on the results of the photostability study (performed with and without light exposure and in the presence and absence of the proposed secondary packaging, i.e., the carton box), the Drug Product Reviewer confirmed that the proposed formulation is light sensitive as impurity levels were observed to be relatively higher in the light-exposed formulation that was packaged in *vial* without labels and without carton. In contrast, light-exposed closed carton-packaged product samples did not exhibit an increase in total impurities levels similar to the dark control and non-exposed samples during photostability testing. Thus, to ensure that the proposed formulation's sensitivity to light does not negatively impact the proposed drug product's quality during shelf-life, the Applicant proposed (and the Drug Product Reviewer accepted the proposal) to include in the labeling the following statement: "Protect from Light. Keep the vial in the carton box until time of use".

Additionally, based on the results of physico-chemical (but not microbiological) stability studies on the pierced vials and the infusion solutions, the following were observed: (1) The 100 mg/4 mL presentation of the proposed drug product should be used immediately upon piercing, whereas the pierced vials of the 500 mg/20 mL and 1000

mg/40 mL presentations are stable over 7 days when stored under refrigeration, protected from light. (2) The prepared infusion solution was stable for 3 days for the 100 mg presentation, and for 14 days for the 500 mg and 1000 mg presentations when stored under refrigerated conditions and protected from light. To maximize physicochemical and microbiological stability of the proposed (single-dose) injectable solution drug product, it is appropriate that the labeling and/or labels include precautionary statements similar to those recommended by DMEPA: (1) "Withdraw the calculated dose of Pemetrexed Injection from the vial(s) and discard vial with any unused portion." (2) "If not used immediately, store diluted product under refrigerated conditions [2-8°C (36-46°F)] for no more than 24 hours from the time of dilution. Discard after 24 hours." Per the Microbiology Reviewer (Dr. Kelly Ann Miller), the short duration (24 hours) that the final infusion solution is stored in the refrigerator prior to administration via intravenous infusion poses minimum risk to patient safety and is acceptable from a product quality microbiology standpoint.

As additional measure for ensuring stability of the 100 mg/4 mL presentation of the proposed RTD solution drug product, (b) (4) [redacted]. Per the Applicant, (b) (4) [redacted] stopper (for the closure of all three presentations) was selected (b) (4) [redacted] The Applicant also reported that glass delamination was not observed at 12 months and 24 months of storage at 25 °C. The Drug Product Reviewer confirmed that based on the totality of the evidence provided, there are no concerns related to glass delamination/glass attack.

The Applicant reported (and the Drug Product Reviewer confirmed that) the leachable study over 24 months showed that potential leachables at 25°C or 40 °C were within the safety limits. The Drug Product Reviewer also indicated that ***i***) the glass vial and stoppers used in the primary packaging of the proposed formulation are both qualified per extractables and other analytical tests conducted in accordance with USP<660> and USP<381>, and ***ii***) the extractables/leachables derived from (b) (4) [redacted] were also evaluated.

R. REGIONAL INFORMATION

Post-Approval Commitments

None

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date: Gerlie Gieser, Ph.D. (3/8/2021)

Secondary Assessor Name and Date (and Secondary Summary, as needed): Banu Zolnik, Ph.D. (4/1/2021)

Gerlie Gieser

Digitally signed by Gerlie Gieser
Date: 4/02/2021 09:12:14AM
GUID: 507592ba00003d190b2ea34fe8fb8ccb

Banu Zolnik

Digitally signed by Banu Zolnik
Date: 4/02/2021 08:59:20AM
GUID: 508da7270002a568e175a2c0dd90f334

CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	214657
Assessment Cycle Number	01
Drug Product Name/ Strength	Pemetrexed, 25 mg/mL
Route of Administration	Intravenous Injection
Applicant Name	Sandoz Inc
Therapeutic Classification/ OND Division	CDER/OND/OOD/DO2
Manufacturing Site	EBEWE Pharma Ges m.b.H. Nfg.KG Mondseestrasse 11 4866 Unterach am Attersee, Austria
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0001 SD 3	07/07/2020
0002 SD 4	08/25/2020
0006 SD 8	09/16/2020

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

Remarks: The drug product is a sterile injectable solution for intravenous use that comes in single-dose glass vials (4 mL, 20 mL, and (b) (4) mL). Pemetrexed is a folate analog metabolic inhibitor indicated for treatment of cancer combined with chemotherapy.

Concise Description of Outstanding Issues: N/A

Supporting Documents:

- (b) (4), dated 09/22/2020 for review of the (b) (4) manufacturing process
- (b) (4).docx, dated 6/16/2020 for review of the (b) (4)

S DRUG SUBSTANCE

The drug substance is not provided sterile. Therefore, a product quality microbiology review of the drug substance was not performed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Section 3.2.P.1, p. 2 of 5. The drug product is a clear to yellow or green-yellow solution used for intravenous administration.

- **Drug product composition –** Section 3.2.P.1, p. 2-3 of 5

Ingredient	Quantity per mL	Function
Pemetrexed (Disodium 2.5 hydrate)	25.0 mg (30.2 mg)	API
Sodium thiosulfate pentahydrate	0.5 mg	(b) (4)
Propylene glycol	50.0 mg	
Hydrochloric acid (b) (4)	q.s. to pH	pH adjusting agent
Sodium hydroxide	q.s. to pH	pH adjusting agent
Water for injection	q.s. to 1 mL	(b) (4)
(b) (4)		

- **Description of container closure system –** Section 3.2.P.1, p. 5 of 5, Section 3.2.P.7, p. 2-3 and p.43 of 272. Product codes were located on p. 2 of *process-valid-appendices* pdf (Section 3.2.P.3.5)

Configuration	Component	Description	Manufacturer
100 mg/4 mL	Vial	(b) (4)	
	Stopper		
	Seal		
500 mg/20 mL	Vial		
	Stopper		
	Seal		
1000 mg/40 mL	Vial		

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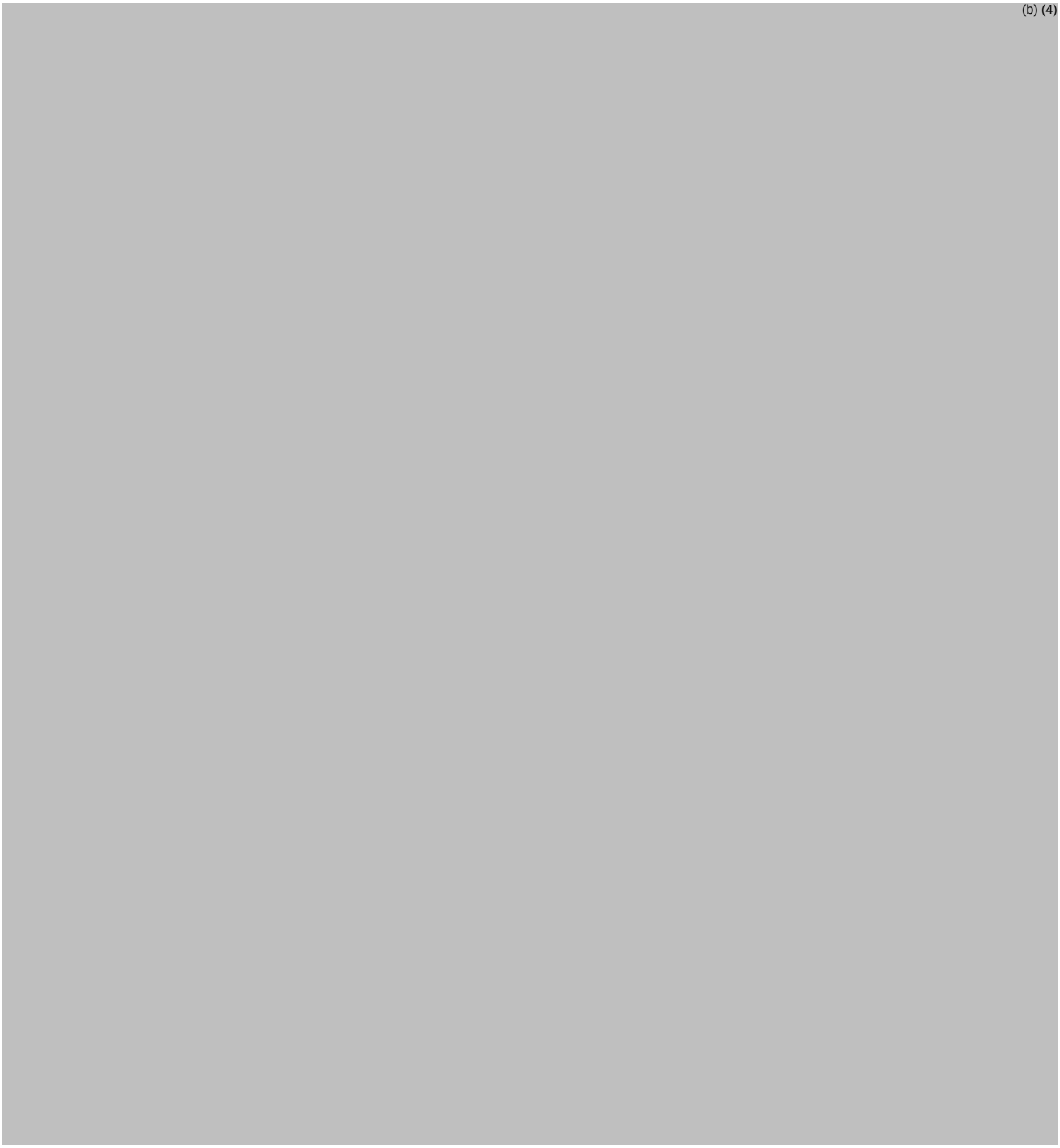

P.7 CONTAINER CLOSURE

See P.1.

P.8 STABILITY

P.8.1 STABILITY SUMMARY AND CONCLUSION

Section 3.8.1, pg. 2, 17 of 56

Stability testing is conducted using accelerated (40°C ±2°C/75%±5%RH), long-term (25°C ±2°C/60%±5%RH), and intermediate (30°C ±2°C/75%±5%RH) conditions.

Proposed Expiry: 24 months at 25°C

Assessment: Adequate
The applicant provides stability data in support of the proposed expiry and storage conditions.

P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

Section 3.2.P.5.1, p. 10 of 10

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Bacterial Endotoxins	USP <85>	NMT (b) (4) EU/mL
Sterility	USP <71>	Sterile

Section 3.8.2, *postapproval-stability* pdf
The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: 25°C ±2°C/60%±5%RH

Test	Time (Months)								
	0	3	6	9	12	18	21	24	36
Bacterial Endotoxins	X				X			X	
Sterility	X				X			X	
Container/Closure Integrity	X				X			X	

Post Approval Stability Commitment

The applicant and manufacturer commit to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

Assessment: Adequate
The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life.

P.8.3 STABILITY DATA

Section 3.8.3, *stability-data* pdf

Stability data was provided from 3 lots of each presentation (4 mL, 20 mL, and 40 mL) under accelerated, intermediate, and long-term conditions. Initial data was provided from the first 12 months of intermediate and long-term conditions and the first 6 months of accelerated conditions. All samples met the acceptance criteria for sterility (sterile) and bacterial endotoxins (NMT (b) (4) EU/mL).

Assessment: Adequate
The stability data submitted to date support the microbiological quality of the drug product.

APPENDICES: N/A

R REGIONAL INFORMATION

Executed Batch Records
Section 3.2.R
Executed lot #(s): JA6439, JA640, JA6441, JA6493, JA6494, JA6495, JA6533, JA6534, JA6536, JJ8138, JK3444, JK3445, JK3480, JK3481, JK3512

(b) (4)

Assessment: Adequate
The applicant has met the regulatory expectations regarding the executed batch records.

Comparability Protocols
No CP was included in the application.

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1
2.A. Prescribing Information
Post-dilution/constitution hold time
Section 1.14.1.3, *package-insert* pdf

Storage temperature: 25°C
Maximum storage time: 24 months
Route of administration: IV
Container: Single dose

Reconstituted/Further Diluted Drug Product

Further product dilution: Dilute with 0.9% sodium chloride injection into a total volume of 100 mL. Administer over 10 minutes. Use immediately or store at 2-8°C for up to 24 hours.

Assessment: Adequate
Once diluted, the drug product is supposed to be used immediately or stored no longer than 24 hours refrigerated. This short duration poses minimum risk to patient safety and is acceptable from a product quality microbiology standpoint.

Post-Approval Commitments: N/A

MICROBIOLOGY LIST OF DEFICIENCIES

Primary Microbiology Assessor Name and Date: KellyAnn Miller, PhD, 09/23/2020

Secondary Assessor Name and Date (and Secondary Summary, as needed): Julie Nemecek, 09/24/2020

KellyAnn Miller

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Julie Nemecek

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Date: 9/24/2020 12:10:12PM
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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