CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214218Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

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

NDA 214218
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	Hospira, Inc., a Pfizer Company

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SN-21 Resubmission NDA Class 2	12/22/2021	All
SN-22 Request for Action Date	02/11/2022	All
SN-23 Labeling Amendment	04/18/2022	All
SN-24 Information Request Response	05/10/2022	Nonclinical and Drug Product
SN-25 Labeling Amendment	05/17/2022	All

QUALITY ASSESSMENT TEAM

DISCIPLINE	PRIMARY REVIEWER/ SECONDARY REVIEWER	BRANCH/DIVISION
Drug Substance	Rajan Pragani/Haripada Sarker	OPQ/ONDP/DNDAPI
Drug Product	Tefsit Bekele/Xing Wang	OPQ/ONDP/DNDPI
Facility/Process	Ruth Moore/Kshitij Patkar	OPQ/OPMA/DPMAIV
Microbiology	Marla Stevens-Riley/ Yeissa Chabrier-Rosello	OPQ/OPMA/DMAI
Biopharmaceutics	Gerlie Gieser	OPQ/ONDP/DBI
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	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 214218-ORIG-1-RESUB-21 is recommended for APPROVAL.

Summary of Quality Assessments

A. Product Overview

Hospira submitted the original NDA 214218 on April 23, 2020, for Pemetrexed injection, a sterile, ready-to-dilute (RTD) solution, 25 mg/mL (100 mg/4 mL, 500 mg/20 mL, 1000 mg/40 mL). This 505(b)(2) NDA relies, at least in part, on the FDA's previous 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 pale yellow (b) (4) 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, presented in 6 mL, 20 mL and 50 mL clear (b) (4) glass vials, representatively.

The proposed drug product differs from LD product in terms of (i) dosage form (i.e., RTD solution formulation vs. lyophilized powder formulation for reconstitution and further dilution), (ii) drug substance hydrate form (i.e., hemipentahydrate vs. heptahydrate), (iii) formulation composition/excipients (i.e., addition of monothioglycerol (b) (4) vs. (b) (4) mannitol), (iv) long-term storage conditions during shelf-life (i.e., refrigerated vs. room temperature), (v) physico-chemical properties of the RTD solution and the final infusion product (has a lower osmolality and slightly higher surface tension, (vi) minor difference in the characteristics of the container-closure system.

The original NDA received a Tentative Approval Letter on February 23, 2021. The Applicant resubmitted the NDA 214218 on November 24, 2021 but withdraw the resubmission on December 22, 2021. The Applicant resubmitted this NDA again on December 22, 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 correspondence to notify minor changes related to drug substance through DMF amendment, drug product (i.e., (b) (4) risk assessment, updated leachable report, minor changes to container closure system and updated stability data), and manufacturing process.

Proposed Indication(s) including Intended Patient Population	• (b) (4) • 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 (b) (4) 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, (b) (4) (b) (4), 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: ADEQUATE
The drug substance pemetrexed disodium was previously reviewed in the original CMC submission (assessment cycle #1) and determined to be adequate (review #1 on 01/07/2021). Since then, cross-referenced DMF (b) (4) has been updated and a quality amendment has also been submitted to this NDA. The most recent DMF major

amendments have been reviewed for an ANDA and the current status of DMF (b) (4) is adequate. Additional test data was submitted to the DMF in response to an additional comment from the last review (R06_AQAC), and the data do not impact the adequate status of the DMF. The CMC information referenced in DMF (b) (4) demonstrates a control of the quality for the manufacture of the drug substance. The NDA amendment was also reviewed and appears reasonable. The drug substance pemetrexed disodium is a disodium salt that is (b) (4) a hydrate. The impurity control strategy follows the USP monograph for pemetrexed disodium. The proposed retest date of (b) (4) from the original submission is still acceptable for pemetrexed disodium.

The Drug Substance recommends for ***Approval****.*

DRUG PRODUCT: ADEQUATE

The CMC updates or changes in this review cycle is related to (b) (4) risk assessment, updated leachable report of pemetrexed injection at the end of its shelf life, minor change to the container closure system and updated stability data. The (b) (4) risk assessment performed per FDA's guidance is adequate and there is no risk for the presence of (b) (4) impurities in the drug product. There is no safety risk with the level of nine leachables identified in pemetrexed injection stored for 24 months at long term storage conditions. For commercial pemetrexed, the (b) (4) top that is not part of the primary packaging will be different in color from the exhibit batches. However, this change in the secondary packaging material will not have an impact on stability of the product. The minor change in the container closure system is acceptable from the CMC perspective. Pemetrexed injection continued to show stability at 2–8 °C for 24 months. No request is made to extend the shelf-life. The 24 months expiration date granted in the first review cycle for pemetrexed remains unchanged.

The Drug Product recommends for ***Approval****.*

PROCESS and FACILITIES: ADEQUATE

(b) (4)

No Pre-approval inspection of facilities were requested. Review of the submission information and inspection history for the drug product manufacturer facility show the site has the capability to manufacture the product and implement the manufacturing

control strategy in compliance with CGMPs. All facilities in the application have satisfactory CGMP compliance status and are recommended for approval.

*The Process and Facilities recommends for **Approval**.*

MICROBIOLOGY: ADEQUATE

Prior to the resubmission, the product quality microbiology information was deemed adequate. The drug product is [redacted] (b) (4). All proposed changes to the drug substance and drug product in current resubmission do not affect sterility assurance/product quality microbiology of the final drug product. The changes to the aluminum seal are not considered to be changes to the primary container closure system. [redacted] (b) (4)

*The Microbiology recommends for **Approval.***

BIOPHARMACEUTICS: ADEQUATE

The Biopharmaceutics Review of the original NDA, APPROVAL was recommended, based on submission of adequate comparative in vitro data and additional supporting data/information/justification 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). For current resubmission, based on the information in the Summary of Changes document and considering the Applicant's updated (24-month) drug product stability summary, it was determined that for the identified minor CMC changes introduced after this NDA's tentative approval, a biowaiver request is not needed. Additionally, submission of in vitro bridging data (e.g., from additional in vitro protein binding, in vitro hemolysis, and physicochemical characterization studies) is not warranted to support the final approval of the proposed drug product.

*The Biopharmaceutics recommends for **Approval**.*

C. Special Product Quality Labeling Recommendations

CMC has no additional comments to provide regarding revised labeling in current resubmission and refer to DMEPA's labeling review.

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) (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-214218-ORIG-1-RESUB-21:
Mei Ou, Ph.D. 05/20/2022

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U.S. FOOD & DRUG ADMINISTRATION

BIOPHARMACEUTICS MEMO

Product Information	
NDA Number	NDA-214218-ORIG-1-RESUB-19 NDA214218 - (0021)
Assessment Cycle Number	505(b)(2) NDA (Class 2) Resubmission After Tentative Approval
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	Hospira
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:

In the FDA Letter dated 2/23/2021, FDA recommended "Tentative Approval" of 505(b)(2) NDA 214218 because the applicant provided a Paragraph III patent certification to the unexpired patent of the relied upon Listed Drug Product, ALIMTA (NDA 021462). Note that in the Biopharmaceutics Review of the Original NDA, APPROVAL was recommended, based on submission of adequate comparative *in vitro* data and additional supporting data/information/justification 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). For details of the Biopharmaceutics Assessment, refer to Chapter 6 of the Office of Pharmaceutical Quality Integrated Quality Assessment of the original NDA 214218 submission.

In the current submission, the Applicant requests final FDA approval of NDA 214218, as well as FDA concurrence on the proposed minor CMC changes after Tentative Approval.

Based on the information in the Summary of Changes document and considering the Applicant's updated (24-month) drug product stability summary, it was determined that for the identified minor CMC changes introduced after this NDA's tentative approval, a biowaiver request is not needed. Additionally, submission of *in vitro* bridging data (e.g., from additional *in vitro* protein binding, *in vitro* hemolysis, and physicochemical characterization studies) is not warranted to support the final approval of Hospira's Pemetrexed (Ready-To-Dilute 25 mg/mL Solution) Injection.

Of note, per the Drug Product Reviewer (Dr. Tefsit Bekele) the submitted updated (24-month) stability data confirm that there are no observed trends, and the proposed drug product is able to conform to the approved finished product QC specifications during its entire shelf-life of 24 months under refrigerated storage. Furthermore, the updated results of the leachables study confirmed the appropriateness of the primary packaging components during the 24 months shelf-life of the proposed commercial drug product.

List of Submissions Reviewed:

Document(s) Assessed	Date Received
SN-19 (Request for Final Approval – withdrawn in SN-20)	11/24/2021
SN-21 (Resubmission of Request for Final Approval)	12/22/2021

Concise Description of Outstanding Issues:

None

Biopharmaceutics Assessor's Name and Date: Gerlie Gieser, Ph.D. (5/10/2022)

Gerlie Gieser

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	214218
Assessment Cycle Number	2
Drug Product Name/ Strength	Pemetrexed Injection, 25 mg/mL
Route of Administration	Intravenous injection
Applicant Name	Hospira, Inc.
Therapeutic Classification/ OND Division	CDER/OOD/DO2
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Seq 0021; SD 21	**12/22/2021 amendment**

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

Remarks: The drug product is indicated for treatment of non-small cell lung cancer (NSCLC). The application had received tentative approval, but in December 2021 the applicant submitted a gratuitous amendment describing changes that they have recently made affecting the drug substance and drug product. Prior to the submission of this amendment, the product quality microbiology information was deemed adequate. The specific changes affecting product quality microbiology are reviewed below.

Concise Description of Outstanding Issues: N/A

Supporting Documents:
DMF (b) (4) (b) (4) and associated microbiology review (b) (4) (adequate, dated 3/31/20).

Product Quality Microbiology Assessment

DRUG SUBSTANCE

Changes are described for the non-sterile drug substance; however, these will not be reviewed because this is a sterile drug product.

Assessment: ***{Adequate}***

The drug product is [redacted] (b) (4). All proposed changes to the drug substance do not affect sterility assurance/product quality microbiology of the final drug product.

DRUG PRODUCT

The following changes proposed for the drug product are related to product quality microbiology:

[redacted] (b) (4)

Assessment: ***{Adequate}***

The drug product is [redacted] (b) (4) Therefore, all proposed changes described above do not affect the product quality or sterility assurance of the drug product. Information associated with [redacted] (b) (4) equipment is typically not assessed for [redacted] (b) (4) products. The changes to the aluminum seal are not considered to be changes to the primary container closure system. [redacted] (b) (4)

LABELING

Although this amendment does not indicate any changes to the drug product labeling, final labeling is included in this amendment. The maximum dose listed in the Dosage and Administration section is 500 mg/m^2. Regarding pediatric use, in Section 8.4 [redacted] (b) (4) [redacted] (b) (4) *Pediatric Use*, there is the statement that "the safety and

effectiveness of the drug product in pediatric patients have not been established." However, there is a description of two clinical trials with pediatric patients stating that (b) (4) "no tumor response was observed."

Assessment: ***{Adequate}***

(b) (4)

(b) (4) N214218MR01 notes that safety and effectiveness of the drug has not been established in pediatric patients.

(b) (4)

MICROBIOLOGY LIST OF DEFICIENCIES

None

Primary Microbiology Assessor Name and Date: Marla Stevens-Riley, Ph.D, (04/20/2022)

Secondary Assessor Name and Date: Yeissa Chabrier-Rosello, Ph.D., (04/20/2022)

Marla Stevens Riley

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Yeissa Chabrier Rosello

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U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM
NDA 214218
Pemetrexed Injection

Hospira, Inc a Pfizer company submitted a 505(b)(2) for Pemetrexed injection on April 23, 2020. The drug product was tentatively approved (TA) on February 23, 2021. The original CMC labeling review for pemetrexed injection 100 mg/4 mL, 500 mg/20 mL, and 1000 mg/40 mL was uploaded in panorama on December 18, 2020. CMC recommended approval pending revision of the prescribing information, container labels and carton labeling as advised in the review. The applicant accepted the recommendation and revised the prescribing information, container labels, and carton labeling accordingly.

The applicant submitted a class 2-resubmission on December 22, 2021, to provide CMC updates. As part of the resubmission, a revised labeling was submitted on March 24, 2022. CMC has no additional comments to provide. Refer to DMEPA's labeling review uploaded in DARRTS on April 06, 2022 for comments sent to the applicant during this review cycle.

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TEFSIT BEKELE

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Recommendation: Approval

NDA 214218
Review #1

Drug Name/Dosage Form	Pemetrexed Injection/Injection, 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	Hospira Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	4/23/2020	ONDP-All
Quality Amendment	7/10/2020	Process and Facilities, Biopharmaceutics
Quality Amendment	8/13/2020	Biopharmaceutics
Quality Amendment	9/23/2020	Microbiology
Quality Amendment	10/13/2020	Process and Facilities
Labeling Amendment	10/20/2020	Labeling
Quality Amendment	11/04/2020	Drug Product, Process and Facilities,
Quality Amendment	11/16/2020	Drug Product, Process and Facilities
Labeling/Container Carton Draft, Package Insert	12/01/2020	Labeling
Labeling/ Package Insert	12/03/2020	Labeling
Labeling/Container Carton Draft,	12/07/2020	Labeling
Clinical Pharmacology	12/10/2020	Biopharmaceutics
Quality Amendment	12/14/2020	Drug Product
Quality Amendment	12/18/2020	Drug Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER/ SECONDARY REVIEWER	BRANCH/DIVISION
Drug Substance	Rajan Pragani/ Ali Al Hakim	OPQ/ONDP/DNDPAPI
Drug Product	Tefsit (Mimi) Bekele/ Anamitro Banerjee	OPQ/ONDP/DNDPI
OPMA/Facility	Ruth Moore/David Anderson	OPQ/OPMA/DMAIV
Microbiology	Christine Craig, Marla Stevens-Riley	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	MAPP 5015.5 (Rev.1)
	Type III			Adequate		
	Type V			Adequate	3/31/20	
	Type III			Adequate	6/15/2017 by Daneli Lopez Perez	

B. Other Documents: *IND or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Alimta Label	NDA 021462	Listed Drug, Alimta
IND	IND 138218	

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

From a Pharmaceutical Quality perspective, NDA 214218 is recommended for APPROVAL.

Summary of Quality Assessments

A. Product Overview

Hospira, Inc a Pfizer company has submitted this NDA 214218 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).

The proposed drug product is supplied as 100 m/4 mL, 500 mg/20 mL, and 1000 mg/40 mL in 6 mL, 20 mL, and 50 mL clear [redacted] (b) (4) glass vials respectively. The vials are stoppered with 20 mm [redacted] (b) (4) rubber closure and 20 mm aluminum [redacted] (b) (4) seal with different colors for different presentations. The drug product is to be stored at 2–8°C and the applicant proposes a shelf life of 24 months. Pemetrexed is prone [redacted] (b) (4) form ketopemetrexed impurity. The proposed product formulation consists of monothioglycerol [redacted] (b) (4) . [redacted] (b) (4) . The drug product formulation does not contain antimicrobial preservatives. The applicant refers to the listed drug,

Proposed Indication(s) including Intended Patient Population	• [redacted] (b) (4) • 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
The drug substance pemetrexed disodium is a disodium salt that is manufactured as a hemipentahydrate. The CMC information referenced in DMF (b) (4) demonstrates a control of the quality for the manufacture of the drug substance. The impurity control strategy follows the USP monograph for pemetrexed disodium. The most recent DMF amendments have been reviewed and the current status of DMF (b) (4) is adequate. Based on the stability data provided in the DMF, a proposed retest date of (b) (4) is acceptable for pemetrexed disodium. The Drug Substance Reviewer recommended for Approval.

DRUG PRODUCT: ADEQUATE
The applicant provided satisfactory drug product information including stability of the product. Pemetrexed is a folate analog metabolic inhibitor indicated for the treatment patients with non-small cell lung cancer. Pemetrexed injection is a sterile solution containing no antimicrobial preservatives. It is supplied as clear colorless to pale yellow solution in 100 mg/4 mL, 500 mg/20 mL, and 1000 mg/40 mL (single-dose) strengths. It is a ready-to-dilute solution for IV infusion administration over 10 minutes. The overall formulation development indicates that the quality and chemical

stability of the proposed product is equivalent to the listed drug. The proposed pemetrexed injection is a (b) (4) product containing no antimicrobial preservatives. (b) (4) . Three registration batches of each strength were manufactured that conform to the proposed specifications. (b) (4) .

The product is required to be diluted in 0.9% NaCl infusion solution before administration. The admixture can be stored under refrigerated conditions for up to 24 hours which is supported by in-use stability data. Pemetrexed injection is stable at 2–8 °C for up to 18 months and up to 6 months at 25 °C/60% RH. Based on the available 18 months stability data at 2–8 °C, the requested 24 months expiration date is granted. This determination is based on ICH Q1A (R2) and ICH Q1E.

The Drug Product reviewer recommended for approval.

PROCESS and FACILITIES: ADEQUATE

(b) (4)

No Pre-approval inspection of facilities were requested. Review of the submission information and inspection history for the drug product manufacturing facility show that the site has the capability to manufacture the drug product and implement the manufacturing control strategy in compliance with CGMPs. All facilities listed in the application have satisfactory CGMP compliance status and are recommended for approval.

The process and facilities are 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), the proposed RTD solution drug product differs mainly from the LD in terms of *i*) drug substance (b) (4) hydrate form (hemipentahydrate instead of heptahydrate); *ii*) formulation composition (contains (b) (4) monothioglycerol in place of (b) (4) mannitol; *iii*) long-term storage conditions during shelf-life (refrigerated instead of room temperature); *iv*) physico-chemical properties of the RTD solution and the final infusion product (has a lower osmolality and slightly higher surface tension, (b) (4) may have a slightly higher pH as compared to the LD's reconstituted and final infusion solutions); *v*) minor difference in the characteristics of the immediate container-closure system.

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

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/equipments • Site	H	(b) (4)	L	
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M		L	
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		L	
Physical stability (solid state) lyophilized small molecule products **molecule products**	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		L	
Uniformity of Dose (Fill Volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		L	
Assay (b) (4)	Formulation • Raw materials • Process parameters •	L		L	

Banu S. Zolnik, Ph.D.
Application Technical Lead, NDA 214218

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

CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	N/A	Adequate
Established name(s)	Pemetrexed Injection	Adequate
Route(s) of administration	For intravenous use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4)	Change to: Injection: 100 mg/4 mL (25 mg/mL) in a single-dose vial (3) Injection: 500 mg/20 mL (25 mg/mL) in a single-dose vial (3) Injection: 1 g/40 mL (25 mg/mL) in a single-dose vial. (3)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	"single-dose" Not included	See comments above

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
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)	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. Visual inspection not included under section *2.7 Preparation and Administration*	Acceptable since a hold time of 24 hours at 2–8 °C has been justified by in-use stability study. However, change the statement to include "if not used immediately, store diluted product…". Include a statement to visually inspect the solution once it has been diluted.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Injection	Adequate
Strength(s) in metric system	(b) (4)	Change to: Injection: 100 mg/4 mL (25 mg/mL) clear colorless to pale yellow ready-to-dilute solution in single-dose vial Injection: 500 mg/20 mL (25 mg/mL) clear colorless to pale yellow ready-to-dilute solution in single-dose vial Injection: 1 g/40 mL (25 mg/mL) clear colorless to pale yellow ready-to-dilute solution in single-dose vial.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not included	Not necessary for section 3
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Incorrect description of the drug product was included	Change to: See above for recommended changes
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Single-dose vial.	Adequate

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	No proprietary name Established name: Pemetrexed Injection	Adequate
Dosage form(s) and route(s) of administration	Injection for intravenous infusion	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	(b) (4)	Change to: Each milliliter (mL) contains 25 mg pemetrexed (equivalent to 27.57 mg pemetrexed disodium)
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	(b) (4)	Change to: Each milliliter (mL) contains 25 mg pemetrexed (equivalent to 27.57 mg pemetrexed disodium), 1.2 mg monothioglycerol, water for injection and may contain sodium hydroxide for pH adjustment.
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.	Included (see above)	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Pharmacological/ therapeutic class	folate analog metabolic inhibitor	Adequate
Chemical name, structural formula, molecular weight	**Chemical name**: *N*-[[4-[2-(2-Amino-4-oxo-4,7-	Adequate

	dihydro-1*H*-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]phenyl]carbonyl]-L-glutamic acid disodium, hemipentahydrate **Structural formula**: $C_{20}H_{19}N_5Na_2O_6 \bullet 2.5H_2O$ **Molecular weight**: 516.41 g/mol	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	(b) (4)	Change to: supplied as a sterile, preservative-free clear, colorless to pale yellow ready-to-dilute solution
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	injection	Adequate
Strength(s) in metric system	100 mg/4mL 500 mg/20 mL 1 g/40 mL	Adequate
Available units (e.g., bottles of 100 tablets)	Carton containing one (1) single-dose vial, 100 mg/4 mL (25 mg/mL).	Adequate

	Carton containing one (1) single-dose vial, 500 mg/20 mL (25 mg/mL). Carton containing one (1) single-dose vial, 1 g/40 mL (25 mg/mL).	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	For all the presentations the following description is included (b) (4) NDC numbers are included for all presentations	Change to: Pemetrexed Injection is a clear, colorless to pale yellow ready-to-dilute solution in a single-dose vial for intravenous infusion. NDC numbers-adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single-dose	Adequate

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	(b) (4)	Change to Storage and Handling Store Pemetrexed Injection at controlled refrigerated temperature, 2°C to 8°C (36°F to 46°F).
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about child-resistant packaging	Not provided	Product is for injection and it is in glass vials sealed. CRP not required.

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured by: Zydus Hospira Oncology Private Ltd. Ahmedabad 382-213, Gujarat, India. Distributed by: Hospira, Inc., Lake Forest, IL 60045 USA	Adequate

2.0 PATIENT LABELING

Assessment patient Labeling: Patient Labeling is adequate from the product quality perspective.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

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

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	No proprietary name Established name: Pemetrexed Injection	Adequate
Dosage strength	100 mg/4 mL (25 mg/mL) 500 mg/20 mL (25 mg/mL) 1 g/40 mL (25 mg/mL)	Adequate
Route of administration	(b) (4)	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance		Change to: Each mL contains 25 mg pemetrexed (equivalent to 27.57 mg pemetrexed disodium), 1.2 mg monothioglycerol, water for injection and may contain sodium hydroxide for pH adjustment.
Net contents (e.g. tablet count)	1 x 4 mL vial 1 x 20 mL vial 1 x 40 mL via	Adequate
"Rx only" displayed on the principal display	Provided	Adequate
NDC number	Provided	Adequate
Lot number and expiration date	Space provided	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	(b) (4)	Change to Store refrigerated at 2°C to 8°C (36°F to 46°C) (DMEPA review has sent an IR regarding storage conditions)
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single-dose vial	Single-dose vial was placed on the carton labeling at three different places. See IR sent by the DMEPA reviewer regarding this
Other package terms include pharmacy bulk package and imaging bulk package which	(b) (4)	Adequate

require "Not for direct infusion" statement.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Provided	Adequate
Name of manufacturer/distributor	Manufactured by: Zydus Hospira Oncology Private Ltd. Ahmedabad 382-213, Gujarat, India. Distributed by: Hospira, Inc., Lake Forest, IL 60045 USA	Adequate
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	No text	Adequate
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	

Assessment of Carton and Container Labeling: Adequate with comments. See information requests below.

Overall Assessment and Recommendation:

The container/carton labeling, and prescribing information comply with all regulatory requirements and they are recommended for approval from a CMC perspective pending revision of what are noted in the Assessor's Comments column above. The following information requests were sent to the applicant on November 30, 2020. See DMEPA's review for additional information requests sent to the applicant.

1. Include "Sterile" on both the container labels and carton labeling.
2. On the container and carton labeling, replace "[redacted] (b) (4) [redacted] (b) (4) with "Each mL contains 25 mg pemetrexed (equivalent to 27.57 mg pemetrexed disodium), 1.2 mg monothioglycerol, water for injection and may contain sodium hydroxide for pH adjustment"

The applicant responded to the information requests on December 07, 2020 and agreed to revise the container labels and carton labeling accordingly. Their responses are acceptable.

Primary Labeling Assessor Name and Date: Tefsit Bekele December 17, 2020

Secondary Assessor Name and Date Anamitro Banerjee, December 09, 2020

TEFSIT BEKELE

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Anamitro Banerjee

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	214218
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	Hospira
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), the proposed RTD solution drug product differs mainly from the LD in terms of ***i***) drug substance (b) (4) hydrate form (hemipentahydrate instead of heptahydrate); ***ii***) formulation composition (contains (b) (4) monothioglycerol in place of (b) (4) (b) (4) mannitol; ***iii***) long-term storage conditions during shelf-life (refrigerated instead of room temperature); ***iv***) physico-chemical properties of the RTD solution and the final infusion product (has a lower osmolality and slightly higher surface tension, (and to improve product stability) may have a slightly higher pH as compared to the LD's reconstituted and final infusion solutions); ***v***) minor difference in the characteristics of the immediate container-closure system.

The Applicant provided adequate comparative *in vitro* and additional CMC and nonclinical data/information 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
SDN-1 (Original)	4/23/2020
SDN-3 (Response to Biopharmaceutics Information Request – Part I)	7/10/2020
SDN-4 (Response to Biopharmaceutics Information Request – Part II)	8/13/2020
SDN-13 (Response to Biopharmaceutics Information Request- Part III)	12/10/2020

Concise Description of Outstanding Issues:

- None

B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

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

The Applicant confirmed that the test drug product lots used in *in vitro* comparative studies and the registration stability lots were manufactured (at the same scale) by the proposed commercial drug product manufacturer [Zydus Hospira Oncology Pvt. Ltd. (ZHOPL) India]. In SDN-3, the Applicant informed FDA that the report of the *in vitro* protein binding study ((b) (4) Study 15N-1832) that identified (b) (4) as the drug product manufacturer of (test) Drug Product Lot PL11801 (a lot also evaluated in registration stability studies) was erroneous.

The drug substance (pemetrexed disodium *hemipentahydrate*) produced by the proposed commercial API supplier (b) (4)) was used in the manufacture of the drug product lots evaluated in stability and *in vitro* studies. Note that post-stability study changes in API manufacturer equipment ((b) (4) and raw material ((b) (4)) supplier occurred; CoAs of the post-change API material (as well as the pre-change API material) were submitted and (based on email discussions) were found adequate by the Drug Substance Reviewer (Dr. Rajan Pragani) to support

the proposed CMC change. Dr. Pragani confirmed that the API manufacturing changes are very low risk in terms of affecting drug product performance (i.e., very minor manufacturing changes, stays in same facility, DS pre- and post-change batch data are comparable, drug product is a solution formulation). Dr. Pragani further indicated that the draft FDA Guidance states that the "manufacture of a batch of drug product using the post-modification drug substance is not always required." Thus, in this case, comparative testing of the pre-change and post-change drug products is not warranted.

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, at least in part, on the FDA's findings of efficacy and safety, as well as nonclinical toxicology, 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 tabulated below. To justify that the formulation, dosage form/presentation, and other quality differences would not impact efficacy and safety of the proposed drug product (and thus, enable scientific bridging to the LD product), comparative physicochemical and in vitro protein binding characterization studies, as well as stability studies on the proposed drug product, and survey of the Inactive Ingredients Database and other publicly available databases worldwide were conducted by the Applicant.

To fulfill the requirements for demonstrating equivalence to the ALIMTA® (Listed Drug product, LD), the Applicant provided data/information to enable scientific bridging of the proposed and the LD products per 21 CFR 320.24 (b)(6).

Note that a biowaiver request via 21 CFR 320.22 is not feasible because the proposed injectable solution drug product is not Q1/Q2 the same as the LD being relied upon. Note also that the proposed and the LD drug products do not have the same (shelf-life) dosage forms (RTD solution versus i.e. powder for reconstitution and further dilution).

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, NDA 214218 Hospira 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 (b) (4) (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 (b) (4) pemetrexed disodium (b) (4) Monothioglycerol (b) (4) Water for Injection (b) (4) 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	(b) (4)	
Proposed Indications/Route of Administration/Dosing Regimen	Proposed/Approved Administration Routes and Dosing Regimen the same as LD; All Proposed Indications the same as LD, but (voluntarily) excluded LD's approved indication for combo therapy with pembrolizumab & platinum Final dilution administered as 10-min IV infusion	
Physico-chemical properties of the final dilution for IV infusion		
Appearance	Clear, colorless to pale yellow (or green-yellow) solution; free from visible particulates	
Assay	100 mg/4 mL: (b) (4) 500 mg/20 mL: (b) (4) 1000 mg/40 mL: (b) (4) [Proposed ranges: (b) (4) of label claim/LC (release); (b) (4) (shelf-life)]	100 mg/vial: (b) 500 mg/vial: (b) (4) [Approved range: (b) (4) of LC]
pH	Before dilution: (b) (4) After dilution (9 mg/mL): (b) (4) [Proposed ranges: (b) (4) (release); (b) (4) (shelf-life)]	Before dilution: (b) (4) After dilution (9 mg/mL): (b) (4) [Approved range: (b) (4)]
Osmolality (mOsm/kg)	Before dilution: ~120 After dilution (9 mg/mL): 235 - 238	Before dilution: 518 After dilution (9 mg/mL): 371
Viscosity (cP)	Before dilution: 1.2 After dilution (9 mg/mL): 1.1	Before dilution: 1.2 – 1.3 After dilution (9 mg/mL): 1.1
Specific gravity	Before & after dilution: 1.01	Before & after dilution: 1.02
Surface Tension (dynes/cm)	Before dilution: 70 – 74 After dilution (9 mg/mL): 65 - 71	61.4 55 - 65

In Vitro Protein Binding (%, mean) 0.5 mcg/mL pemetrexed 5 mcg/mL 50 mcg/mL 200 mcg/mL 1 mg/mL 5 mg/mL 9 mg/mL	85.7 84.5 82.2 80.6 57.6 40.0 35.0			84.8 83.3 80.4 78.3 58.9 35.1 28.4
Recommended storage during product shelf-life[c] and upon preparation	RTD – Refrigerated (use diluted solution within 24 hours of preparation under refrigeration)			Powder – USP Controlled Room Temperature (use both reconstituted and diluted solution within 24 hours of preparation under refrigeration)
Container-closure	(b) (4) glass vial with (b) (4) rubber stopper with aluminium seal; (b) (4) (b) (4)			(b) (4) glass vial with (b) (4) rubber stopper with aluminium seal
Physico-chemical & microbiological stability				
Total Impurities/ Degradants	(b) (4)			
Sterility (Meets USP Requirements)	(b) (4) maintained during 6 months accelerated and 18 months of long-term stability testing of the RTD solution, and after dilution within 24 hours under refrigeration			-
Bacterial Endotoxins (NMT (b) (4) EU/mg of Pemetrexed)	Conforms during initial and later stability time points			
Special QC specifications (tests and acceptance ranges) proposed/approved	1. Minimum Fill Volume/Container Content: NLT nominal (e.g., 4 mL for 100 mg/4mL)[d]			Reconstitution time = NMT (b) (4)
	2. Assay of antioxidant	At Release	During Shelf-Life (refrigerated)	-
	Monothioglycerol	NLT (b) (4) mg/mL	NLT (b) (4) mg/mL	
	3. Impurities	At Release	During Shelf-Life (refrigerated)	
	Ketopemetrexed	NMT (b) (4)	NMT (b) (4)	Compound (b) (4): NMT (b) (4) Largest Unspecified Impurity: NMT (b) (4) Total Impurities NMT (b) (4)
	Any Individual unspecified impurity	NMT (b) (4)	NMT (b) (4)	
	Total impurities	NMT (b) (4)	NMT (b) (4)	

[a]The proposed drug product contains (b) (4) the active ingredient. Mannitol (excipient present in the LD product (b) (4)) was excluded since the manufacture of the proposed drug product does not involve lyophilization.
[b] following reconstitution of 100 mg/vial and 500 mg/vial, per approved ALIMTA®labeling instructions
[c]Tentative expiration dating period = 24 months (Refrigerated)
[d]target fill volumes: (b) (4) corresponding to overfill (b) (4) to facilitate withdrawal and administration of labelled doses/volumes.

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 (b) (4) 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)*

   Per the Applicant, the proposed drug product uses the hemipentahydrate form of pemetrexed sodium whereas the LD uses heptahydrate, and that pH-solubility data for the hemipentahydrate form are available. The difference in hydrate form is not expected to result in a variation between the drug products as the drug substance is (b) (4), and the measured solubility of the hemipentahydrate is well in excess of the (b) (4) solution concentration. Additionally, the proposed RTD drug product and the reconstituted LD yield clear, colorless to pale yellow (or green yellow) solutions that are free from particulates (demonstrating visually complete solubility).

   In SDN-4, the Applicant provided additional data to show that the proposed RTD product's 100 mg/4 mL presentation has comparable assay to the LD's 100 mg/vial when reconstituted with 4.2 mL (instead of 4 mL) vehicle (i.e., both products have assay values within (b) (4) of label claim).

   Not for FOIA: *Based on the ALIMTA NDA data, both hemipentahydrate and heptahydrate forms of pemetrexed disodium are* (b) (4)

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

   Note that the Applicant did not conduct clinical and additional preclinical studies because the results of the originally conducted *in vitro* protein binding study indicated that the formulation/excipient difference between the relied upon Listed Drug product and the proposed drug product, i.e., in terms of the presence of monothioglycerol (and the removal of mannitol) did not impact the *in vitro* protein binding of pemetrexed. Specifically, the Applicant reported that the percentages of unbound pemetrexed to human plasma protein was comparable between the test/proposed product (Batch# PL11801, 100 mg/4mL vial; DOM= 10/2018) and

reference product (ALIMTA, Batch# C804889C; 100mg/vial; expires 7/31/2020) at the studied drug concentrations (0.5 and 5.0 mcg/mL, post-addition of the pemetrexed infusion solution into plasma). In SDN-13, the Applicant provided additional data showing comparable percentage of *in vitro* protein binding for the proposed drug product and the relied upon LD product at higher final infusion concentrations, i.e., 200 mcg/mL and up to 9 mg/mL (representing drug concentration in the final dilution at the point of patient contact). Both proposed and LD products exhibited drug concentration-dependent decreases in extent of plasma protein binding. Refer to Table 1 of the IR Response in SDN-13. Therefore, based on the findings of the comparative in vitro protein binding study, no significant difference in drug distribution between the proposed and the reference drug products is anticipated.

Additionally, in SDN-3, the Applicant explained that the removal of mannitol from the proposed drug product is not expected to affect the PK of pemetrexed because (1) the amount of mannitol in the Listed Drug product is several orders of magnitude lower than the clinical intravenous doses of Mannitol Injection approved for the reduction of intracranial pressure or intraocular pressure via osmotic diuresis, and (2) unlike pemetrexed, mannitol is not secreted by tubular cells and thus will not compete with OAT3 for pemetrexed secretion in the renal tubules. Furthermore, the addition of monothioglycerol (MTG) (b) (4) in the proposed drug product is also not expected to alter the PK of pemetrexed based on the following observations: (i) there are no specific reports found about MTG's effect on drug disposition, especially renal clearance or OAT3 activity. (ii) There is precedence for use of MTG in multiple other parenteral drug products currently approved in the US. In a patient with BSA = 1.8 m^2, the amounts of MTG received following administration of the proposed drug product is comparable to that received following administration of BENDEKA® (43.2 mg versus 43.2 mg per dose, respectively), and the presence/absence of MTG in bendamustine formulations (BENDEKA® versus TREANDA®) was not reported to affect the clearance of bendamustine [NDA 208914]. [However, for proper context this Reviewer notes that the presence/absence of MTG is not the only qualitative difference between the BENDEKA and TREANDA formulations.] Additionally, based on this Reviewer's literature survey, it appears that MTG (unlike high-dose mannitol) does not possess diuretic or anti-diuretic activity, and thus, is not anticipated to adversely impact renal elimination of pemetrexed. Additionally, the similarity of the *in vitro* protein binding data between the proposed and LD products suggests anticipated similarity with respect to drug interaction potential where displacement from protein binding interactions are involved.

3. *Difference in Formulations/Excipients and Physicochemical Properties – Impact on drug product safety/tolerability and quality*

   NDA Table 2.3.P.1-1 (excerpted below) provides the details of the proposed product's formulation. Per the Applicant (b) (4)

(b) (4) monothioglycero (b) (4) was added to the formulation (b) (4). The Applicant uses monothioglycerol that conforms to compendial (NF) standards, and is present at a level (1.2 mg/mL - based on formulation development study results - that is) similar to that found in FDA approved drug products intended for IV administration. Specifically, the level of monothioglycerol does not exceed the FDA Inactive Ingredients Database (IIG) limit for maximum potency per unit dose (b) (4) (b) (4)), as well as the maximum daily dose of the excipient given via the intravenous route. To illustrate precedented use of the proposed amount of the proposed excipient in pharmaceuticals intended for IV use in humans, the Applicant stated that in the case of BENDEKA® (bendamustine hydrochloride) which contains 5 mg monothioglycerol per mL, a typical adult patient with BSA = 1.8 m^2 administered the recommended 120 mg/m^2 bendamustine dose will receive 43.2 mg monothioglycerol intravenously over 10 min on Days 1 and 2 of the 21-day cycle for 8 cycles. The same patient when given the proposed pemetrexed RTD solution drug product will be exposed to the same total monothioglycerol dose IV on Day 1 of each 21-day treatment cycle. It is interesting to note that the monothioglycerol content in all three presentations of the proposed RTD products was reported to be stable at (b) (4) mg/mL during 6 months of accelerated (25°C/60% RH, Inverted) and 18 months of long-term (5°C±3°C, Inverted) storage. Note that the Pharmacology/Toxicology Reviewer Team (led by Dr. Whitney Helms) and the Drug Product Reviewer (Dr. Tefsit Bekele) consider the level of monothioglycerol ((b) (4) in the proposed drug product formulation acceptable from the safety and product stability perspectives, respectively. Refer to the Drug Product Review for the assessment of the adequacy/acceptability of the finished product QC specifications for batch release and shelf-life.

(b) (4)

Table 2.3.P.1-1. Qualitative and Quantitative Composition

Component	Quantity per Milliliter (mL)	Concentration: 25 mg/mL			Function	Reference to Standard
		100 mg/4 mL	500 mg/20 mL	1000 mg/40 mL		
		Nominal quantity per unit[a]	Nominal quantity per unit[a]	Nominal quantity per unit[a]		
Pemetrexed disodium[b] (b) (4)	27.57 mg (25.0 mg)	110.28 (100 mg)	551.40 (500 mg)	1102.80 mg (1000 mg)	Active Ingredient	In-house
Monothioglycerol	1.2 mg/mL	4.80 mg	24.00 mg	48.00 mg	(b) (4)	NF
Water for Injection	(b) (4)					USP
Sodium Hydroxide					pH adjustment	NF
(b) (4)					(b) (4)	NF
Total Volume	q.s. to 1.00 mL	4.00 mL	20.00 mL	40.00 mL	N/A	N/A

a. Each vial of Pemetrexed Injection contains a sufficient excess to allow withdrawal of the labelled quantity of drug substance. The values presented in Table 2.3.P.1-1 refer to the labelled quantities and are not inclusive of this excess. The target excess compared to labelled quantity is (b) (4) for the 100 mg/4 mL presentation, (b) (4) for the 500 mg/20 mL presentation and (b) (4) for the 1000 mg/40 mL presentation. Refer to Section 3.2.P.2.2 formulation development for discussion on overfills.

b. Factored to 100% basis. Refer to Section 3.2.P.2.2 for formulation development.

(b) (4)

q.s. = Quantity sufficient; A.R. = As required; N/A = Not applicable

Per the Applicant, the RTD solution was formulated (b) (4) . The slight differences in pH and osmolality between the proposed Ready-To-Dilute solution drug product and the reconstituted LD product were not deemed by the Applicant as clinically relevant because the proposed and reference solutions are further diluted with 0.9% NaCl Injection prior to IV administration, and the resulting pH and osmolality of the final diluted solutions are "well within clinical recommendations for IV infusions", so the risk of vascular adverse events is expected to be low. Per the Applicant, the lower measured osmolality of the final dilution of the proposed drug product is not a safety concern because "< 500 mOsm/L, the clinical recommendation for peripheral vein tolerance in the upper arms", and "a hypotonic solution of sodium chloride (154 mOsmol/L) is approved for IV infusion". This

Reviewer acknowledges that although the proposed pH range is slightly higher for the proposed drug product than approved for the reference drug product ((b) (4)), the Applicant provided data showing that the final infusion solutions of both products have (b) (4) Furthermore, in SDN-4 , the Applicant reported a numerically higher surface tension of the pre-dilution and post-dilution (final infusion) solutions prepared from the proposed RTD solution drug product versus that of the relied LD product (e.g., for 100 mg/4 mL vs. 100 mg/vial: (b) (4) versus (b) (4) dynes/cm post-dilution). This Reviewer believes that the slightly (b) (4) higher surface tension values for the proposed drug product is not anticipated to significantly impact the miscibility/mixability of the RTD solution with the diluent.

In SDN-13, the Applicant provided data to show that the hypotonicity of the proposed drug product's final infusion solution did not induce *in vitro* hemolysis. It is not clear to this Reviewer why the hypotonicity of the final infusion solution of the proposed drug product was not addressed during formulation development, i.e., by addition of typical tonicity adjusting agents.

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

Pemetrexed Injection 100 mg/4 mL and 500 mg/20 mL presentations have the same amounts of active substance as the 100 mg/vial and the 500 mg/vial presentations, respectively, of the reference product, ALIMTA®. To cater to the 500 mg/m^2 dosage need of a typical adult patient (b) (4) and for that matter any other patient with BSA > (b) (4) a 1000 mg/40 mL single-dose vial presentation of Pemetrexed Injection (as concentrate liquid or RTD solution) is proposed. Per the Applicant, prior to final dilution, all three presentations of the proposed drug products and all two presentations of the Listed Drug product upon reconstitution will have the same drug concentration (25 mg/mL). [Note that the Clinical Pharmacology Review for ALIMTA® includes 1000 mg/40 mL **solution**.]

After final dilution, the proposed drug product and the LD will also have the same dosage form and final drug product concentration (e.g., 9 mg/mL for a patient with BSA = 1.8 m^2) at the point of patient contact, as well as the same administration routes and dosing regimens.

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

At the time of comparative *in vitro* testing, the reconstituted Listed Drug product, ALIMTA® powder (3 – 4 months-to-expiry) had similar or numerically lower levels of impurities/degradants than the 1 – 4 month old Ready-To-Dilute Injectable solution drug product. Note however that during 6 months of accelerated (25°C/60% RH) and 18 months of long-term (5 ± 3 °C) (b) (4), the registration batches of the proposed RTD drug product were observed to exhibit NMT (b) (4) total impurities, NMT (b) (4) ketopemetrexed, and NMT (b) (4) any individual unspecified

impurity. It is also important to note that none of the proposed tolerance limits for total and specific impurities (i.e., NMT (b) (4), NMT (b) (4), and NMT (b) (4), respectively, during shelf-life) in the RTD product exceeds the LD's approved limits (nor those specified in the USP Monograph of Pemetrexed [lyophilized powder] for Injection). No discernible trends were observed with respect to pH, pemetrexed assay, and appearance, although the Applicant reported a statistically significant increasing trend in the 95% confidence intervals of the individual and total impurities levels and the anticipated decreasing trend in the (b) (4) monothioglycerol assay which are expected to remain within the proposed limits over the proposed shelf-life of 24 months (under refrigeration).

Although the proposed acceptance ranges for finished drug product pH, Assay, and Related Substances (i.e., ketopemetrexed and total impurities) are wider or more permissive during shelf-life/stability testing than at batch release of the proposed solution drug product, the proposed ranges appear reasonable because per the Applicant, the proposed finished product QC specifications (except pH) are aligned to the available USP monograph for the lyophilized powder of Pemetrexed For Injection. Additionally, the Drug Product Reviewer confirmed the acceptability of the proposed acceptance criteria for pH, assay and related substances, and recommended a change to the product's appearance/description to be consistent with the actual observed color of the solution during stability testing. The *updated* finished product QC specifications at batch release and during shelf-life were deemed acceptable by the Drug Product Reviewer. Furthermore, based on the additional extractable volume data and the submitted in-process and batch analysis data, the Process Reviewer (Dr. Ruth Moore) concluded that the proposed lower limits for the in-process fill volume ranges (b) (4) were acceptable, thereby assuring sufficient excess volume is available for withdrawal of the labeled nominal fill volume of the drug product.

Based on the results of the extractables and leachables study, the Applicant concluded that the primary packaging components are appropriate for use with the proposed pemetrexed RTD solution formulation. A (b) (4) glass vial has been selected (b) (4). Based on the results of an FDA requested (b) (4) study extension, the Drug Product Reviewer confirmed the Applicant's observation that up to 18 months of long-term and accelerated storage, there is no evidence or early indicators of (b) (4) in reaction zones of the drug product vials, and the drug product was free from visible particulates. Three leachables originating from the rubber stopper have been identified in the drug product; at 12 months of long-term storage, the measured levels of these leachable compounds corresponded to total daily intake (TDI) < 5 mcg/day each, but since the three structures were predicted by *in silico* assessment to be non-mutagenic, the Applicant did not deem further local and systemic toxicological evaluation to be warranted. For these non-mutagenic leachables, the Pharmacology/Toxicology Reviewers consider the TDI levels of < 5 mcg/day measured at 12 months of refrigerated storage acceptable from a safety perspective. Additionally, per the Drug Product Reviewer, additional leachables

testing for the end-of-shelf life product was not requested because the Applicant indicated that the levels of leachables will be monitored over the product's shelf life (currently, 24 months) and will further evaluate if an increase in the level of the impurities is observed.

6. *Difference in Recommended Storage Conditions - Refrigeration (instead of Room Temperature Storage during drug product shelf-life)*

   Per the Applicant, the long-term (refrigerated) stability data over 18 months for the registration batches indicate that the potency and the levels of specific and total impurities in the proposed solution drug product conform to the proposed acceptance criteria [consistent with those specified in the USP monograph for Pemetrexed (powder) for Injection] when stored in the refrigerator during shelf-life (24 months), as well as up to 24 hours after the proposed RTD product is diluted with 0.9% Sodium Chloride Injection. Note that the NDA provided only 6 months (as opposed to at least 12 months) product stability data of the RTD solution drug product under room temperature storage. Additionally, per the Applicant, three freeze/thaw treatment cycles, and exposure to severe lighting conditions did not alter the proposed drug product's quality. The Drug Product Reviewer confirmed the Applicant's stability findings and considers the 24 months expiration dating period for the proposed drug product acceptable.

7. *Difference in Indications*

   Note that the Applicant is not seeking ALIMTA's indication for combination use with pembrolizumab and platinum therapy. Per the Medical Review Team, this indication is being carved out due to patent/exclusivity issue. Thus, the Biopharmaceutics Review Team did not deem it necessary to send out the IR comment to query the Applicant about the possibility that there are any formulation components or other quality attributes of the proposed drug product which might be unsuitable for use in the excluded indication.

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. (12/11/2020)

Secondary Assessor Name and Date (and Secondary Summary, as needed): Banu Zolnik, Ph.D. (12/15/2020)

Gerlie Gieser

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Banu Zolnik

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Date: 12/17/2020 01:09:28PM
GUID: 508da7270002a568e175a2c0dd90f334

CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	214218
Assessment Cycle Number	1
Drug Product Name/ Strength	Pemetrexed Injection, 25 mg/mL
Route of Administration	Intravenous injection
Applicant Name	Hospira, Inc.
Therapeutic Classification/ OND Division	CDER/OOD/DO2
Manufacturing Site	Zydus Hospira Oncology Pvt. Ltd., Gujarat, India.
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Multiple documents	**Submission 4/23/2020** **Submission 9/23/2020 (IR response)**

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

Remarks: The drug product is indicated for treatment of non-small cell lung cancer (NSCLC).

Concise Description of Outstanding Issues: N/A

Supporting Documents:
DMF (b) (4) (b) (4) and associated microbiology review (b) (4) (adequate, dated 3/31/20).

S DRUG SUBSTANCE

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

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(3.2.P.1, Description and Composition of the Drug Product, pg. 1-2)

- **Description of drug product –** A clear, colorless, [redacted], aqueous solution, intended to be further diluted prior to administration. The drug product is manufactured in the following presentations: 6 mL vial (100 mg/4mL), 20 mL vial (500 mg/20 mL), and 50 mL vial (1 g/40 mL).

- **Drug product composition:**

Component	Quantity per Milliliter (mL)
Pemetrexed disodium [redacted]	27.57 mg (25.0 mg)
Monothioglycerol	1.2 mg/mL
Water for Injection	[redacted]
Sodium Hydroxide	[redacted]
[redacted]	
Total Volume	q.s. to 1.00 mL

- **Description of container closure system**

(3.2.P.7, Container Closure System - Solution, pg. 2)

Table 3.2.P.7-1. Summary of Container Closure System

Primary Packaging Component	Description	ZHOPL Commodity No.	Supplier Name and Address
Container	6 mL, [redacted] glass vial	[redacted]	[redacted]
	20 mL, [redacted] glass vial		
	50 mL, [redacted] glass vial		
Closure	20 mm, [redacted] Rubber Stopper		

Assessment: ***{Adequate}***

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity

13 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

R REGIONAL INFORMATION

Executed Batch Records

(3.2.R, Batch Data Summary Tables)
Executed lot #(s):

Batch Number	Presentation
PL11801	100 mg/4 mL
PL11802	
PL11803	
PL21801	500 mg/20 mL
PL21802	
PL21803	
PL31801	1000 mg/40 mL
PL31802	
PL31803	

Assessment: ***{Adequate}***
Detailed executed batch records were provided for three lots of each of the proposed presentations of drug product.

Comparability Protocols

(3.2.R, Comparability Protocols for Pemetrexed Injection)

The applicant confirms that no CP is 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 , pg. of

Storage temperature: 2-8°C
Route of administration: IV infusion over 10 minutes
Container: Single dose vial

Further Diluted Drug Product
The package insert submitted instructs that an appropriate quantity of the drug product is further diluted with 0.9% Sodium Chloride Injection, USP, so that the total volume of solution is 100 mL. The diluted product may be stored for NMT 24 hours under refrigerated conditions (2-8°C) and includes instructions to discard after 24 hours.

Assessment: ***{Adequate}***
The package insert provides appropriate and adequate instructions for storage and dilution of the subject drug product.

MICROBIOLOGY LIST OF DEFICIENCIES

Primary Microbiology Assessor Name and Date: Christine Craig, Ph.D.,11/17/2020

Secondary Assessor Name and Date: Marla Stevens-Riley, Ph.D., 11/18/2020

Christine Craig

Digitally signed by Christine Craig
Date: 11/18/2020 04:07:50PM
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Marla Stevens Riley

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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/

BANU S ZOLNIK
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