CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215179Orig1s000

SUMMARY REVIEW

Division Director Summary Review

NDA/SDN	215179/34
Memo Date	05/17/2023
Submission Date	08/23/2022
Product	Pemetrexed Injection 10 mg/ml (100 mg/10 mL, 500 mg/50 mL, 1000 mg/100 mL)
PDUFA Goal Date	May 23, 2023
Sponsor/Applicant	Shilpa Medicare LTD

Action Recommended: The Division recommends approval of NDA 215179.

Summary

This is a 505(b) (2) application resubmission by Shilpa Medicare ltd. for Pemetrexed for Injection. Shilpa is not proposing a proprietary name for their product. The reference drug product is Eli Lilly and Company's Alimta (pemetrexed disodium) for injection (NDA 021462). Shilpa proposes the same indications for Pemetrexed for Injection as described for Alimta. See the Clinical Memo (May 2023) for a listing of these indications.

This NDA was re-submitted in response to FDA's complete response (CR) letter dated April 14, 2022. During the review period, the Applicant submitted a major amendment (dated February 15, 2023), which extended the goal date by 3 months.

Drug substance and microbiology were found adequate in the last round of product quality review, and no new related CMC information was submitted. Per OPQ's review:

"Resolution of key product quality issues was attained by manufacturing new vial product batches at a GMP compliant site; establishing and justifying the shelf-life specification criteria; addressed the manufacturing process issues for the 10 mL vial product and submitting adequate and acceptable long term stability studies on vial product batches that are representative of the proposed commercial drug product. The (b) (4) and the L-cysteine content of the drug product are monitored (b) (4) An adequate scientific bridge had been established between the proposed drug product and the LD product, i.e., in accordance with 21 CFR 320.24(b)(6). (b) (4) Cadila is the newly proposed manufacturing site, and it is an approved facility. All associated manufacturing, testing, packaging facilities were deemed acceptable. Overall, the applicant provided sufficient information in this resubmission to assure the identity, strength, purity, and quality of the proposed drug product."

For full details, see the Integrated Quality Review uploaded on April 26, 2023.

No clinical safety or efficacy data were submitted in this NDA application. Product labeling has been updated to align with the listed drug Alimta. This application was reviewed by the 505(b)2 committee at the 505(b)(2) clearance meeting the first week of May 2023 and was cleared for action.

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/s/

ERIN A LARKINS
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Cross-Discipline Team Leader Review

Date	April 1, 2022
From	Mei Ou, Ph.D. OPQ/ONDP/Division of Biopharmaceutics
Subject	Cross-Discipline Team Leader Review
NDA	NDA 215179-ORIG-1-RESUB-20
Type of Submission	505(b)(2)
Applicant	Shilpa Medicare LTD
Date of Submission	October 14, 2021
PDUFA Goal Date	April 14, 2022
Established or Proper names	Pemetrexed Injection
Dosage forms / Strength	Solution for Intravenous Injection 10 mg/mL (100 mg/10 mL, 500 mg/50 mL, 1000 mg/100 mL)
Proposed Indications	The same as Alimta®: • In combination with pembrolizumab and platinum chemotherapy, in 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. Limitations of Use: Pemetrexed injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer. • 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.
Recommendation:	**COMPLETE RESPONSE**

This CDTL review is based on the primary reviews/memos of:

DICIPLINE	PRIMARY REVIEWER/TL	FINAL REVIEW DATE
Quality IQA	Mei Ou (Application Technical Lead)	04/01/2022
Drug Substance	Haripada Sarker	03/11/2022
Drug Product and Labeling	Mike (William) Adams Xing Wang	03/06/2022 and 03/09/2022
Process/Facility	Yan Zheng David Anderson	03/11/2022
Quality Microbiology	Jason God Julie Nemecek	02/17/2022
Biopharmaceutics	Gerlie Gieser	03/09/2022
Clinical	Satinder (Mona) Choudhary Nicole Drezner	03/26/2022
Non-Clinical (Pharmacology/Toxicology)	Sachia Khasar Claudia Miller	03/31/2022
Clinical Pharmacology	Wentao Fu Jeanne Fourie Zirkelbach	N/A
Division of Medication Error Prevention and Analysis	Tingting Gao Janine Stewart	03/25/2022
505(b)(2) Committee	Mary Ann Holovac	N/A

Cross Discipline Team Leader Review

1. Background

This NDA for Pemetrexed Injection (10 mg/mL) relies for approval, at least in part, on the FDA's prior findings of safety and efficacy for the Listed Drug (LD) product, ALIMTA® (pemetrexed) lyophilized powder for injection (NDA 021462), approved on February 4, 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 drug product has the same indications as described for Alimta, as:

- 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.
- 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.

The proposed drug product also has the same route of administration and contains the same active moiety (pemetrexed) as the approved LD. There is no difference in dosing regimen (500 mg/m^2 as an intravenous infusion over 10 minutes).

The proposed drug product differs from the LD product in terms of:

- Pemetrexed disodium polymorphic hydrate form is in hemipentahydrate instead of heptahydrate).
- Formulation composition (contains additional L-cysteine hydrochloride (b) (4) as (b) (4) sodium chloride as (b) (4), and water for injection as (b) (4) and different amount of mannitol and pH adjusting agents presented in the LD).
- Injection solution versus lyophilized powder.

The original 505(b)(2) application by Shilpa Medicare Limited was submitted on August 27, 2020 but received a Complete Response (CR) letter on June 24, 2021 due to insufficient data to support product quality, facilities inspection issues, and labeling deficiencies.

The Applicant resubmitted this NDA on October 14, 2021 to respond the deficiencies cited by FDA in the CR letter issued on June 24, 2021. In the current review cycle, (b) (4) and proposed an alternate drug product manufacturing and control site (Cadila

Healthcare Limited/India) on February 10, 2022, with a change in process (b) (4) (b) (4) In addition, the Applicant changed the name of drug product manufacturing facility from *Cadila Healthcare Limited* to *Zydus Lifesciences Limited* on March 28, 2022.

No clinical pharmacology, safety or efficacy data were submitted in this NDA application.

2. Product Information

Pemetrexed Injection, 10 mg/mL, is a clear, colorless to pale yellow to greenish yellow, sterile solution, presented in a 10 mL (100 mg), 50 mL (500 mg) and 100 mL (1000 mg) single-dose glass vial. The proposed drug product has the same indications, same route of administration and contains the same active moiety (pemetrexed) as the approved LD. There is no difference in dosing regimen.

The chemical composition of the proposed drug product, Pemetrexed Injection 10 mg/mL and the LD product's final infusion solution (prepared from reconstitution of the lyophilized powder and further dilution) are the same, except for the presence of (b) (4) (L-cysteine hydrochloride (b) (4)) in the proposed drug product's formulation (b) (4) To deliver the required pemetrexed dose (calculated based on the patient's body surface area (BSA), 500 mg/m^2), the appropriate volume (i.e., not necessarily 100 mL) of the "ready-to-use" Pemetrexed 10 mg/mL solution requiring no further dilution is to be withdrawn from the vial(s) and then transferred into an empty sterile IV bag immediately prior to IV infusion that is then administered to the patient with the aid of an infusion pump.

3. Pharmaceutical Quality- INADEQUATE

The OPQ review teams recommended for Complete Response for the current resubmission due to:

1) The NDA lacks sufficient finished drug product stability to support approval of the Cadila Healthcare site proposed for drug product manufacture and control, or an acceptable leachables study performed on drug product samples taken from the Cadila Healthcare 12 month stability samples. The 12 month stability samples will be available on 07/31/2022. The drug product review recommended complete response.
2) The additional data/information provided by the Applicant during the current NDA review cycle indicated that the proposed drug product is comparable, i.e., in terms of these attributes to the relied upon LD, ALIMTA. However, the Drug Product Reviewer determined that the long-term stability data and the leachables data provided for the Cadila-manufactured drug product batches are not sufficient to support the new drug product manufacturing site, as well as the proposed drug product expiration dating period of (b) (4) months. There is a potential concern regarding the impact on drug product stability of the difference in the (b) (4) used by the original and new drug product manufacturing sites, respectively. Additionally, the labeling discussions will not be completed during the current NDA review cycle. Thus, although the comparative delivered volume/delivered dose related deficiency cited in the 06/24/2021 CR Letter was addressed, there are still outstanding CMC review issues emergent from the more recent proposal to change the drug product manufacturing site

at the time of the 10/14/2021 NDA Resubmission, and labeling review issues. Therefore, given the unresolved CMC and labeling deficiencies, at the current time, it cannot be concluded that an adequate scientific bridge had been established between the proposed drug product and the relied upon LD, i.e., in accordance with 21 CFR 320.24(b)(6). The biopharmaceutics review recommended complete response.

Drug Substance: ADEQUATE

The NDA is re-submitted in response to FDA's complete response (CR) letter dated June 24, 2021 for non-API issues. API information are cross-referenced to DMF (b) (4), which is reviewed by Katherine Windsor dated 3/11/2021 to support the NDA 215179. In addition to the response to CR letter, the applicant also proposes inclusion of alternate Finished Dosage Form Manufacturing Facility for manufacturing & testing of Pemetrexed Injection, 100 mg/10 mL, 500 mg/50 mL, and 1000 mg/100 mL (10 mg/mL). This NDA was recommended for approval from the CMC perspective during the last review cycle (Review-1) by Katherine Windsor dated 3/11/2021. Drug substance remains adequate.

Drug Product: INADEQUATE

The drug product manufacturing and control site at (b) (4) submitted in amendment SD-001 was found to be out of GMP compliance and classified OAI. The NDA received a CR letter 06/24/2021. The complete response, submitted 10/14/2021, included the addition of Cadila Healthcare as an alternate drug product manufacturing and control site with a change from (b) (4) (b) (4) This review cycle addresses the CMC for the alternate manufacturing site and the submission of sufficient drug product stability data to support approval of that site. The NDA lacks sufficient finished drug product stability to support approval of the Cadila Healthcare site proposed for drug product manufacture and control, and an acceptable leachables study performed on drug product samples taken from the Cadila Healthcare 12 month stability samples. The 12 month stability samples will be available on 07/31/2022. Drug product recommends inadequate.

Process and Facilities: ADEQUATE

Two drug product manufacturing facilities were initially proposed: (b) (4) and Cadila Healthcare Limited. (b) (4) was proposed in the original submission on 08/27/2020. The original submission was CR-ed due to deficiencies including the incompliance status of the (b) (4), but the manufacturing process at (b) (4) was found adequate. (b) (4) Cadila is the newly proposed manufacturing site, and it is an approved facility. The assessment in this review mainly applies to the facility and manufacturing process of the Cadila manufacturing site: (b) (4) (b) (4) Note that the Applicant changed the name of drug product facility from *Cadila Healthcare Limited* to *Zydus Lifesciences Limited* on 03/28/2022. Process and facilities recommend adequate.

Quality Microbiology: ADEQUATE

The subject submission is a response to the Agency's Complete Response letter, dated 24 June 2021. The first cycle DMA review was adequate. However, the subject submission proposes an alternate drug product manufacturing facility. This review covers sterility assurance for the proposed alternate manufacturing facility. Microbiology recommends adequate.

Biopharmaceutics: INADEQUATE

To address the Biopharmaceutics deficiency comment included in the CR Letter issued for the original NDA, the Applicant provided the results of the delivered dose study in the NDA Resubmission. (b) (4) drug product lots evaluated in the in vitro bridging studies submitted to support the original NDA, the Applicant was requested to conduct repeat comparative in vitro physicochemical, protein binding and delivered dose studies using the drug product lots manufactured by the new drug product manufacturing site (Cadila Healthcare Limited/India).The additional data/information provided by the Applicant during the current NDA review cycle indicated that the proposed drug product is comparable, i.e., in terms of these attributes to the relied upon Listed Drug product, ALIMTA. However, the Drug Product Reviewer determined that the long-term stability data and the leachables data provided for the Cadila-manufactured drug product batches are not sufficient to support the new drug product manufacturing site, as well as the proposed drug product expiration dating period of (b) (4) months. Additionally, the labeling discussions will not be completed during the current NDA review cycle. Thus, although the comparative delivered volume/delivered dose related deficiency cited in the 6/24/2021 Complete Response Letter was addressed, there are still outstanding CMC review issues emergent from the more recent proposal to change the drug product manufacturing site at the time of the 10/14/2021 NDA Resubmission, and labeling review issues. Therefore, given the unresolved CMC and labeling deficiencies, at the current time, it cannot be concluded that an adequate scientific bridge had been established between the proposed drug product and the relied upon LD, i.e., in accordance with 21 CFR 320.24(b)(6). Biopharmaceutics recommends complete response.

List of Deficiencies for Complete Response:

1) Per ICH Q1A(R2), provide at least 12 months of long term stability data on the NDA exhibit batches manufactured at the Cadila Healthcare Limited/Zydus Lifesciences Limited site (FEI#3007621329, DUNS#650348852).
2) Provide an acceptable leachables study performed on 12 month samples taken from the long term stability study for the NDA exhibit batches manufactured at the Cadila Healthcare Limited/Zydus Lifesciences Limited site.
3) The product quality deficiencies listed above should be resolved before the adequacy of the scientific bridge between the proposed drug product and the relied upon Listed Drug product can be established, i.e., in accordance with 21 CFR 320.24(b)(6).

4. Nonclinical Pharmacology/Toxicology

The original NDA was approvable from a pharmacology/toxicology perspective. No new pharmacology/toxicology information was included in the resubmission. From a nonclinical perspective, the level of the extractables from (b) (4) is not a safety concern since

pemetrexed is genotoxic and Pemetrexed Injection will be used in an advanced cancer population. In addition, Pemetrexed Injection will be administered once every 21 days; thus, based on the total concentration of extractables at worse-case scenario (b) (4) the daily intake is (b) (4) / 21 days), which is within the safety concern threshold (SCT). From a pharmacology/toxicology perspective, there are no outstanding issues, therefore, the application is recommended for approval.

5. Clinical Pharmacology

No new clinical pharmacology information was included in the resubmission. The clinical pharmacology review for the original NDA was not warranted and there were no clinical pharmacology issues if the scientific bridging is established between the proposed drug product and the relied upon LD product.

6. Clinical

No clinical studies have been conducted under the submitted original NDA and the resubmission and no clinical issues need to be addressed related to this NDA. The clinical team recommended approval upon satisfactory review from other FDA disciplines.

7. Pediatric Research Equity Act Waiver - NAI

8. Advisory Committee Meeting - NAI

9. Other Relevant Regulatory Issues

NDA-215179-ORIG-1-RESUB-20 will receive a CR action. Per email by Mary Ann Holovac dated March 11, 2022, clearance from the 505(b)(2) committee will be needed again for the future submission.

10. Labeling

Labeling is aligned with the LD product Alimta. DMEPA evaluated proposed Prescribing Information (PI), Patient Package Insert (PPI), container labels and carton labeling for areas of vulnerability that may lead to medication errors. DMEPA determined that the proposed Pemetrexed Injection PI, container label, and carton labeling can be improved for clarity. However, labeling comments for this review cycle are deferred due to the planned Complete Response action.

11. Risk Benefit Assessment

Please refer to NDA 021462 (Alimta)

12. Recommendations

The cross disciplinary team lead recommendation for NDA-215179-ORIG-1-RESUB-20 is **Complete Response.**

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Cross-Discipline Team Leader Review

Date	June 15, 2021
From	Banu Zolnik, Ph.D. Biopharmaceutics Team Leader, ONDP/Division of Biopharmaceutics
Subject	Cross-Discipline Team Leader Review
NDA	NDA 215179
Type of Submission	505(b)(2)
Applicant	Shilpa Medicare LTD.
Date of Submission	August 27, 2020
PDUFA Goal Date	June 27, 2021
Established (USAN) names	Pemetrexed Injection
Dosage forms / Strength	Intravenous Injection, (infusion) 10 mg/mL (100 mg/10 mL, 500 mg/50 mL, 1 g/100 mL
Proposed Indications	The same as Alimta®: • In combination with pembrolizumab and platinum chemotherapy, in 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. • 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.
Recommendation:	**COMPLETE RESPONSE**

This CDTL review is based, on the primary reviews/memos of:

DICIPLINE	PRIMARY REVIEWER/TL	FINAL REVIEW DATE
Quality IQA	Banu Zolnik (Application Technical Lead)	06/07/2021
Drug Substance	Katherine Windsor Ali Al Hakim	03/11/2021
Drug Product	Mike (William) Adams Anamitro Banerjee	05/25/2021
OPMA/Facility	Yan Zheng/Yiwei Li	05/04/2021
Quality Microbiology	Amanda Buskirk/John Metcalfe	02/10/2021
Biopharmaceutics	Gerlie Gieser/Banu Zolnik	06/07/2021
Clinical	Nicole Drezner	06/08/2021
Non-Clinical (Pharmacology/Toxicology)	Anwar Goheer/Emily Wearne	05/18/2021
Clinical Pharmacology	Sriram Subramaniam/Hong Zhao	05/19/2021
Office of Prescription Drug Promotion (OPDP)	Nazia Fatima	06/04/2021
PREA waiver memo	Christine Lincoln	05/12/2021
Medication Error Prevention and Analysis	Janine Stewart/Ashleigh Lowery	03/16/2021 05/21/2021
505 (b) (2) Committee	Mary Ann Holovac (email memo)	05/11/2021

Cross Discipline Team Leader Review

1. Introduction

This is a 505 (b) (2) application by Shilpa Medicare LTD submitted on August 27, 2020 for Pemetrexed for Injection.

Pemetrexed Injection, 10 mg/mL is a clear, colorless to pale yellow to greenish yellow, sterile ready-to-use solution presented in a 10 mL (100 mg), 50 mL (500 mg) and 100 mL (1000 mg) single-dose glass vial.

The proposed drug product has the same route of administration and contains the same active moiety (pemetrexed) as the approved listed drug. There is no difference in dosing regimen. This application has the same indications as Alimta®.

The proposed drug product differs from the LD in terms of:

i) Pemetrexed disodium polymorphic hydrate form is in hemipentahydrate instead of heptahydrate);

ii) Formulation composition (contains L-cysteine hydrochloride (b) (4) sodium chloride as (b) (4), and water for injection (b) (4), in addition to mannitol and pH adjusting agents presented in the LD);

iii) Ready-to-use solution versus lyophilized powder.

No clinical safety or efficacy data were submitted in this NDA application.

The OPQ review team recommended for Complete Response due to:

1) **The drug product manufacturing facility is currently in** (b) (4) therefore, OPMA reviewer recommended for complete response.
2) At the time of Biopharmaceutics review's cut-off date (06/07/2021**), the Applicant was not able to provide the requested data** that would demonstrate that the difference in handling and preparation between the proposed "ready-to-use" solution injectable drug product and the LD's final infusion would not result in a significant difference in delivered dose of pemetrexed to the patient. Thus, it is concluded that the submitted comparative in vitro data and additional CMC data for the proposed drug product are not 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 complete response.

2. Background

The Applicant is relying on FDA findings of safety and efficacy for Alimta (Pemetrexed for Injection), 100 and 500 mg per vial), NDA 021462 which was approved on February 4, 2004. Alimta has the following indications:

- 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.
- 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.

3. Pharmaceutical Quality- *INADEQUATE*

Drug Substance: ADEQUATE

Pemetrexed disodium is a folate analog metabolic inhibitor. The drug substance is isolated as the hemipentahydrate, which is 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 hemipentahydrate drug substance to DMF (b) (4). DMF (b) (4) was last reviewed by Katherine Windsor, Ph.D. (final signature 11-MAR-2021) and found adequate to support NDA 215179. Specified and unspecified impurity controls are sufficient. Stability data in the referenced DMF support the drug product manufacturer's proposed retest period of (b) (4) months for pemetrexed disodium (hemipentahydrate) drug substance stored at (b) (4)

Drug Product: ADEQUATE

Pemetrexed Injection, 10 mg/mL is a clear, colorless to pale yellow to greenish yellow ready-to-use solution presented in a 10 mL (100 mg), 50 mL (500 mg) and 100 mL (1000 mg) single-dose glass vial. Product strength is based on Pemetrexed as the anhydrous, residual solvent-free freebase. The requisite volume of drug solution is transferred from the vial(s) into an IV bag and immediately administration over 10 minutes by an infusion pump.

Components: Formulation ingredients are acceptable. Forced degradation study shows acid hydrolysis and control have essentially the same degradation profile. Product is sensitive to pH and oxygen. Vial overfill is acceptable. (b) (4) All the excipients are commonly used in the manufacture of medicinal products for human consumption. None of the excipients are novel or of human origin.

Based on the stability studies, the proposed storage statement is "Store at 20-25ºC

(68-77ºF) excursions permitted to 15-30ºC (59-86ºF)."

The available stability 18-month data is sufficient to support the Shilpa requested [redacted] initial shelf life.

Process and Facilities: *INADEQUATE*
The drug product manufacturing facility is currently in withhold status.
The drug substance manufacturing facility is approved. The product manufacturing process includes [redacted] the proposed manufacturing process is acceptable

Quality 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.

Biopharmaceutics: *INADEQUATE*
At the time of this review's cut-off date, the Applicant was not able to provide the requested data that would demonstrate that the difference in handling and preparation between the proposed "ready-to-use" solution injectable drug product and the LD's final infusion would not result in a significant difference in delivered dose of pemetrexed to the patient. Thus, it is concluded that the submitted comparative in vitro data and additional CMC data for the proposed drug product are not 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).

Complete response action is recommended from Pharmaceutical Quality Review Team

4. Nonclinical Pharmacology/Toxicology-ADEQUATE

No new pharmacology/toxicology information was included in the submission and there are no novel excipients included in the current formulation. The cysteine excipient was not present in the listed drug. The Applicant justified the proposed level based on the IV administration of cysteine as a parenteral nutrition product at up to 490 mg (vs up to 100 mg in Pemetrexed Injection); thus, there is no further safety qualification necessary for cysteine.

The CMC review team requested input on the acceptability of the levels of one potential extractable [redacted] The Pharmacology and Toxicology reviewer concluded that based on current practice and a review of a test set of chemicals and on related compounds, there is no safety concern with the potential levels of [redacted] delivered with a single dose of pemetrexed using [redacted] manufacturing process and formulation.

The application is approvable from a pharmacology/toxicology perspective.

5. Clinical Pharmacology-*Adequate*

This NDA submission does not contain any clinical pharmacology information and does not involve any changes to the clinical pharmacology sections of the labeling. Thus, a clinical pharmacology review is not warranted and there are no clinical pharmacology issues if the Applicant's biowaiver request is granted.

6. Clinical-*Adequate*

No clinical studies have been conducted under the submitted NDA and no clinical issues need to be addressed related to this NDA.

The clinical team recommends approval upon satisfactory review from other FDA disciplines.

7. Pediatric Research Equity Act Waiver

According to the memo by Christine Lincoln dated 05/12/2021, The OCE PeRC concurred with the division's agreement with the sponsor's request for a full waiver of pediatric studies as these studies are impossible and highly impracticable to conduct in the pediatric population since the indication for rarely if ever exists in children and adequate study population does not exist.

8. Advisory Committee Meeting

Current submission did not go to an Advisory Committee Meeting.

9. Other Relevant Regulatory Issues

Per email by Mary Ann Holovac dated May 11, 2021, NDA 214657 is (b) (4) However, as the application will receive a CR action, **clearance from the 505(b) (2) committee will be needed again for the future submission.**

10. Labeling-*Adequate*

Labeling is aligned with the listed drug Alimta. OPDP and DMEPA evaluated proposed Prescribing Information (PI), Patient Information, container labels and carton labeling and found revised labeling is acceptable.

11. Risk Benefit Assessment

Please refer to NDA 021462 (Alimta)

12. Recommendations

The cross disciplinary team lead recommendation for NDA 214657 is **Complete Response**

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