CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211226Orig1s000

PRODUCT QUALITY REVIEW(S)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 17, 2018
FROM: Nina Ni, Ph.D., Application Team Lead, ONDP/DNDPI
THROUGH: Anamitro Banerjee, Ph.D., Brach Chief, ONDP/DNDPI
SUBJECT: Addendum to CMC Labeling Review #1 for NDA 211226
TO: NDA 211226

During this review cycle, the applicant has proposed the following proprietary names of (b) (4) which were all denied by DMEPA. In the CMC Labeling Review #1, dated 08/30/2018, the proposed container and carton labels (without a proprietary name) found acceptable. The applicant, Spectrum proposed an alternate proprietary name of Khapzory which was received on September 18, 2018 and the team found Khapzory was acceptable on October 11, 2018. Thus, Spectrum submitted the updated carton and container labels in the Amendment SDN 26, dated 11/17/2018, which are duplicated in the Attachment below. The updated labels include the following changes:

- Replaced "Brand Name (levoleucovorin) for injection" with the Khapzory logo on the vial and carton labeling for the 175 mg/vial and 300 mg/vial strengths;
- Changed the color of the "175 mg/vial" text on the vial and carton labeling from (b) (4) to green;
- Changed the color of the "300 mg/vial" text on the vial and carton labeling from (b) (4) to gold;
- Deleted (b) (4) on the carton labeling for the 175 mg/vial and 300 mg/vial strengths.

Evaluation: The updated carton and container labels are acceptable from a CMC perspective.

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

Nina Ni

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Date: 10/18/2018 08:14:10AM
GUID: 502d1ab500002afbbe642f8f37136920

Recommendation: Approval

NDA 211226

Review 1

Drug Name/Dosage Form	Levoleucovorin for Injection
Strength	175 mg/vial, 300 mg/vial
Route of Administration	Intravenous administration
Rx/OTC Dispensed	Rx
Applicant	Spectrum Pharmaceuticals, Inc.
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA- 0001 (1)	*12/22/2017*	*Drug Substance, Drug Product, Process, Facilities, Biopharmaceutics, and Microbiology*
Amendment – 0003 (3), quality response to IR dated 02/02/2018, quality update Module 3 (P.3.3)	*02/08/2018*	*Drug Product*
Amendment – 0010 (10), quality response to IR dated 04/24/2018, quality update Module 3 (S.5 and P.1, P.5, P.6, P.7, and P.8)	*05/08/2018*	*Drug Substance and Drug Product*
Amendment – 0011 (11), quality response to IR dated 04/30/2018	*05/14/2018*	*Microbiology*
Amendment – 0013 (13), quality response to IR dated 05/14/2018, quality update	*06/01/2018*	*Process*

Module 3 (P.3.4)		
Amendment – 0014 (14), quality response to IR dated 06/13/2018	*06/18/2018*	*Drug Product*
Amendment – 00015 (15), quality response to IRs dated 05/08/2018 and 05/14/2018, quality update Module 3 (P.2, P.5, and P.7)	*06/29/2018*	*Drug Product*
Amendment – 0018 (18), quality response to IR dated 08/16/2018	*08/24/2018*	*Microbiology*
Amendment – 0019 (19), quality response to IR dated 09/06/2018	*09/07/2018*	*Microbiology*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Gaetan Ladouceur	Charles Jewell
Drug Product	William (Mike) Adams	Anamitro Banerjee
Process	David Anderson	Rakhi Shah
Microbiology	Hemlata Tamta	Nandini Bhattacharya
Facility	David Anderson	Derek Smith
Biopharmaceutics	Akm Khairuzzaman	Banu Zolnik
Regulatory Business Process Manager	Steven Kinsley	NA
Application Technical Lead	Nina Ni	NA
Laboratory (OTR)	NA	NA
ORA Lead	Caryn McNab	NA
Environmental	William (Mike) Adams	Anamitro Banerjee

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

DMFs:

	Type			Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Adequate	NA	Adequate information provided in the NDA
	Type V			Adequate	09/21/2018	
	Type V			Adequate	09/21/2018	
	III			Adequate	NA	Adequate information provided in the NDA
	II			Adequate	04/28/2018	
	II			Adequate	06/13/2018	

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DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20140	RLD
NDA	8107	RLD

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

From the chemistry, manufacturing, and controls standpoint, this NDA is recommended for approval. There are no outstanding CMC issues that impact approvability of this NDA.

Based on the provided stability data, a 24-month expiration dating period is granted for levoleucovorin for injection, 175 mg/vial and 300 mg/vial when stored at USP controlled room temperature 20 - 25ºC (68 - 77ºF); with excursions permitted to 15 - 30ºC (59 - 86ºF).

II. Summary of Quality Assessments

A. Product Overview

Spectrum submitted NDA 211226 on 12/22/2017 to pursue approval of (b) (4) levoleucovorin for injection, 175 mg/vial and 300 mg/vial, under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) as this product (b) (4) (b) (4) (b) (4) includes the addition of a new strength, 300 mg/vial. Spectrum is referencing two listed drugs (LDs): Spectrum's Fusilev® (levoleucovorin) lyophilized and ready-to-use drug products approved under NDA 020140, and Hospira Inc.'s leucovorin calcium for injection approved under NDA 008107 (which was withdrawn not due to safety or efficacy concerns). Spectrum's drug products and Hospira's drug product are the calcium salt of leucovorin. Upon reconstitution, Spectrum's proposed drug is claimed to contain (b) (4) levoleucovorin for injection which is composed of the active moiety l-isomer of folinic acid; the same active moiety in Spectrum's approved Fusilev. (b) (4) (b) (4) The applicant provided a bio-waiver request of in-vivo bioavailability/bioequivalence studies to support the equivalence of the LDs and the proposed drug product in Module 1.12.5. No clinical data was submitted in the application. The Biopharmaceutics reviewer has found adequate of the overall information/data provided supporting biowaiver request and bridging.

The drug substance, levoleucovorin is a folate analog and the pharmacologically active levo-stereoisomer of leucovorin free acid. Labeling and strength designation is based on the levoleucovorin free acid which is consistent with the listed drug product, Fusilev, and the FDA salt nomenclature policy adopted for labeling purpose. The applicant has referred to (b) (4) DMFs (b) (4) for all pertinent drug substance CMC information in the

NDA. DMF (b) (4) is for (b) (4) then DMF (b) (4) is for the (b) (4) was last reviewed and found adequate on 04/28/2018. DMF (b) (4) was last reviewed and found adequate on 06/13/2018.

The proposed drug substance is crystalline powder of levoleucovorin free acid. The proposed drug product is claimed to be levoleucovorin (b) (4) (b) (4)

Please refer to review on drug product section for a detailed evaluation.

The drug product, levoleucovorin for injection is a lyophilized product containing 175 mg or 300 mg of levofolinic acid per vial. The lyophilized cake has a white to pale yellow appearance. The drug product is reconstituted with sterile 0.9% saline to 50 mg/mL. The reconstituted colorless to slightly yellow solution is either injected or further admixed prior to injection. The 300 mg/vial strength is supplied in a 20-mL (b) (4) clear glass vial closed with a 20-mm (b) (4) (b) (4) stopper. The 175 mg/vial strength is supplied in 10-cc (b) (4) (b) (4) clear glass vial closed with a same stopper. The recommended storage condition for drug product is controlled room temperature. (b) (4) (b) (4)

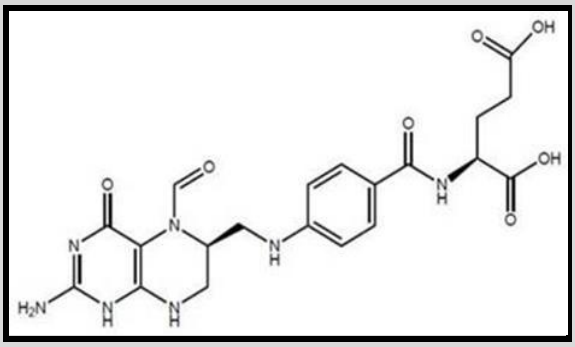
Proposed Indication(s) including Intended Patient Population	• Rescue after high-dose methotrexate therapy in patients with osteosarcoma. • Diminishing the toxicity associated with over-dosage of folic acid antagonists or impaired methotrexate elimination. • Treatment of patients with metastatic colorectal cancer in combination with fluorouracil.
Duration of Treatment	Continue treatment until disease progression or unacceptable toxicity
Maximum Daily Dose	100 mg/m^2 for 5 consecutive days
Alternative Methods of Administration	NA

B. Quality Assessment Overview

1. Drug Substance [Levoleucovorin]

The drug substance levoleucovorin has the following chemical name, structural formula, molecular formula, and molecular weight:

International Non-proprietary Name (INN): Levofolinic acid
Chemical Name: (2S)-2-((4-((((6S)-2-amino-5-formyl-4-oxo-1,4,5,6,7,8-hexahydropteridin-6-yl) methyl) amino) benzoyl) amino) pentanedioic acid
(CAS) Registry Number: 68538-85-2
Mol. Formula: $C_{20}H_{23}N_7O_7$
Mol. Wt.: 473.5 g/mole
Structural Formula:



Levofolinic acid possesses the (6S) absolute configuration at carbon 6 of the

(b) (4)

(b) (4)

(b) (4)

endotoxins, microbial limits testing, residual solvent, assay, related substances (specified, unspecified, and total) and (b) (4) limit. Batch analysis data is provided for two drug substance lots used in the NDA registration drug product batches. Both lots meet the proposed specification. Stability protocols and study data in (b) (4) concludes that bulk drug substance stored at (b) (4) °C in (b) (4) is stable for (b) (4)

The drug substance reviewer has recommended approval for application. Please see his review for detailed evaluation.

Office of Process and Facilities (OPF/OPQ/CDER) has recommended "Acceptable" for the following drug substance manufacturers (for manufacture, release testing, stability testing, packaging, and storage) based on Profile.

- (b) (4)
-

2. Drug Product [Levoleucovorin for Injection, 175 mg/vial and 300 mg/vial]

The proposed drug product is a white to pale yellow lyophilized powder formulated to contain 175 mg or 300 mg levofolinic acid in a single-dose vial which is to be stored at USP controlled room temperature. The commercial presentations are a 10-mL (175 mg) or 20-mL (300 mg) (b) (4) clear glass vial closed with a 20-mm grey (b) (4) stopper and a (b) (4) aluminum over seal. The primary container is enclosed in a single vial carton.

The proposed drug product is intended to be reconstituted with 3.6 mL or 6.2 mL sterile normal saline (0.9% sodium chloride for injection, USP) to obtain a colorless to slightly yellow solution containing 50 mg/mL levoleucovorin. Reconstituted solution is either injected directly or further diluted with sterile normal saline or sterile D5W (5% dextrose for injection, USP) for intravenous (IV) infusion as a solution containing 0.5 - 5.0 mg/mL levoleucovorin.

Unit formulation is levoleucovorin (b) (4) with mannitol, USP and sodium hydroxide, USP formulated with water for injection, USP which is removed during lyophilization. Sodium hydroxide and hydrochloric acid are used to adjust pH in the (b) (4)

Pharmaceutical development studies are provided to support the proposed bulk (b) (4) formulation; the manufacturing process, process parameters and equipment materials; chemical stability of the reconstituted vial solutions and IV dosing solutions; volume, pH, and osmolality of the reconstituted solutions; and physical stability of the IV dosing solutions (b) (4) (b) (4)

Drug product is manufactured at (b) (4) release and stability tested at (b) (4) labeled and secondary packaged at (b) (4) (b) (4) (b) (4) (b) (4)

(b) (4) (b) (4)

(b) (4)

lyophilization process. Commercial bulk (b) (4) batch size is (b) (4) Both process reviewer and micro reviewer from OPF have recommended approval for this application. Please see their reviews for detailed evaluations.

Excipients are shown to be BSE/TSE/melamine-free and none are of human or animal origin. No excipient is novel. All excipients meet USP/NF monograph requirements for acceptance. Certificates of analysis are provided from the proposed suppliers and the recipient.

The drug product release specification includes testing for appearance, reconstitution time (per the package insert), endotoxin, sterility, content uniformity by weight variation, and water content on the lyophilized powder; and appearance, identity, pH, assay, (b) (4) limit, related substances (specified, unspecified, total), visible particles, and seal integrity on the vial solution. Drug product is certified to meet the USP <232> and ICH Q1D requirement for Elemental Impurities. The proposed criteria are justified by USP expectations and available batch analysis and stability data. A risk assessment study for Elemental Impurities submitted during the review showed the risk to be low, thus the proposed test is not needed to be included in the release specification.

Analytical methods are described in sufficient detail and validated for their intended use in a series of reports. The validation report for the identity/assay/related substances HPLC method includes forced degradation for acid, base, neutral, oxidation, and thermal stress. Calculations for identity, assay, related substances, and stereoisomer limit are made relative to peak area for levoleucovorin (b) (4) obtained by the HPLC analysis of USP reference standard of calcium levoleucovorin which is (b) (4) levo- and dextro-leucovorin. This reference standard and identity standards for the specified related substances are characterized for identity and purity.

Batch analysis data is provided for four NDA registration/process validation batches, two batches of each vial strength, made with two drug substance lots at the proposed commercial manufacturing site using the proposed excipients, and packaging components, but at about half of commercial-scale. The submission of four NDA registration batches was accepted as adequate to support NDA approval based on the use of a (b) (4) and lyophilization process.

Components for the primary and secondary packages are described in sufficient detail and acceptance specifications are provided. Also provided are certificates of analysis and conformance from the component suppliers along with letters authorizing reference to their type III DMFs. DMFs are not reviewed as adequate information was provided in the NDA submission.

The primary stability study protocol is for the four NDA registration batches stored at ICH long condition (25°C) for up to 48 months; ICH accelerated conditions

(40°C) for up to 6 months; and an ICH Q1B photo-stability study. Submitted data is for each of the four NDA registration batch stored at 25°C for 12 months and at 40°C for 6 months with a 175-mg vial batch in the ICH Q1B photo-stability study. Sample testing includes all the release specification except identity. All batches remained within the proposed criteria at all sample points and storage conditions with no consistent trends. The photo-stability study showed no degradation. The applicant proposed a 24-month initial shelf life with storage at USP controlled room temperature, which is granted (see memo from Anamitro Banerjee, dated 09/06/2018).

The applicant includes a commitment to place the first three commercial-scale batches on stability using the primary stability study protocol; and to place at least one batch of each vial strength on the post approval protocol, then submit the study results in the annual reports. The post approval stability protocol is for storage at ICH long term conditions up to 48 months using the approved release specification.

The applicant claims a categorical exclusion from the environmental assessment requirement based on a calculation of expected EIC-aquatic for the active moiety and the formation of biologically inactive metabolites, which is granted.

The drug product reviewer has recommended approval for this application. Please refer to his review for a detailed evaluation.

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stability testing, packaging, and labeling) based on PAI conducted on (b) (4)

- (b) (4)

C. Special Product Quality Labeling Recommendations (NDA only)

NA

D. Final Risk Assessment (see Attachment)

Attachment - Final Risk Assessment for Levoleucovorin for Injection, 175 mg/vial and 300 mg/vial

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations / Comments**
Assay/ Stability	• Formulation • Raw materials • Process parameters • Scale/equipments • Site • Container closure	Low	Both the assay and impurities of the drug product are quantitated using an HPLC method and controlled to the same acceptance criteria as the LDs. Isomeric purity is controlled in DP specification. Elemental impurities are controlled in drug product per USP <232>. Water content is controlled per USP <921>.	Acceptable	Controls are in place. Continue stability monitoring post approval.
Appearance/ Visible particles	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Container closure	Low	Appearances for both lyophilized cake and reconstituted solution are controlled per USP <1> and USP <641>. Visible particles are controlled per USP <790>.	Acceptable	Controls are in place. Continue stability monitoring post approval.
Uniformity of dosage units	• Formulation • Process parameters • Scale/equipments	Low	The proposed product is (b) (4) (b) (4) (b) (4) lyophilized (b) (4) It is controlled per USP <905>.	Acceptable	Control is in place.

Deliverable/ Minimal fill volume	• Formulation • Process parameters • Scale/equipment	Medium	Overfill and deliverable volume are determined to ensure correct amount of drug is	Acceptable	None
Sterility/Endotoxin	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Medium	(b) (4) USP.	Acceptable	Controls are in place. Continue stability monitoring post approval.
Particulate Matter	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	(b) (4)	Acceptable	Control is in place. Continue stability monitoring post approval.
pH/Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	pH is controlled per USP <791>. Osmolality is controlled by (b) (4)	Acceptable	Control is in place. Continue stability monitoring post approval.

Leachable/Extractable	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	The proposed product is lyophilized cake.	Acceptable	None
CCIT	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	Seal integrity of the final drug product vial is confirmed via a standard dye ingress test and controlled in DP specification.	Acceptable	Control is in place.

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LABELING

NDA 211226 Review #1

Drug Product: (Brand Name) Levoleucovorin for Injection
Strength: 175 mg/vial and 300 mg/vial
Route of Administration: injection or IV infusion
Applicant Name: Spectrum Pharmaceuticals, Inc. (Irvine, CA)

(b) (4)

[redacted]

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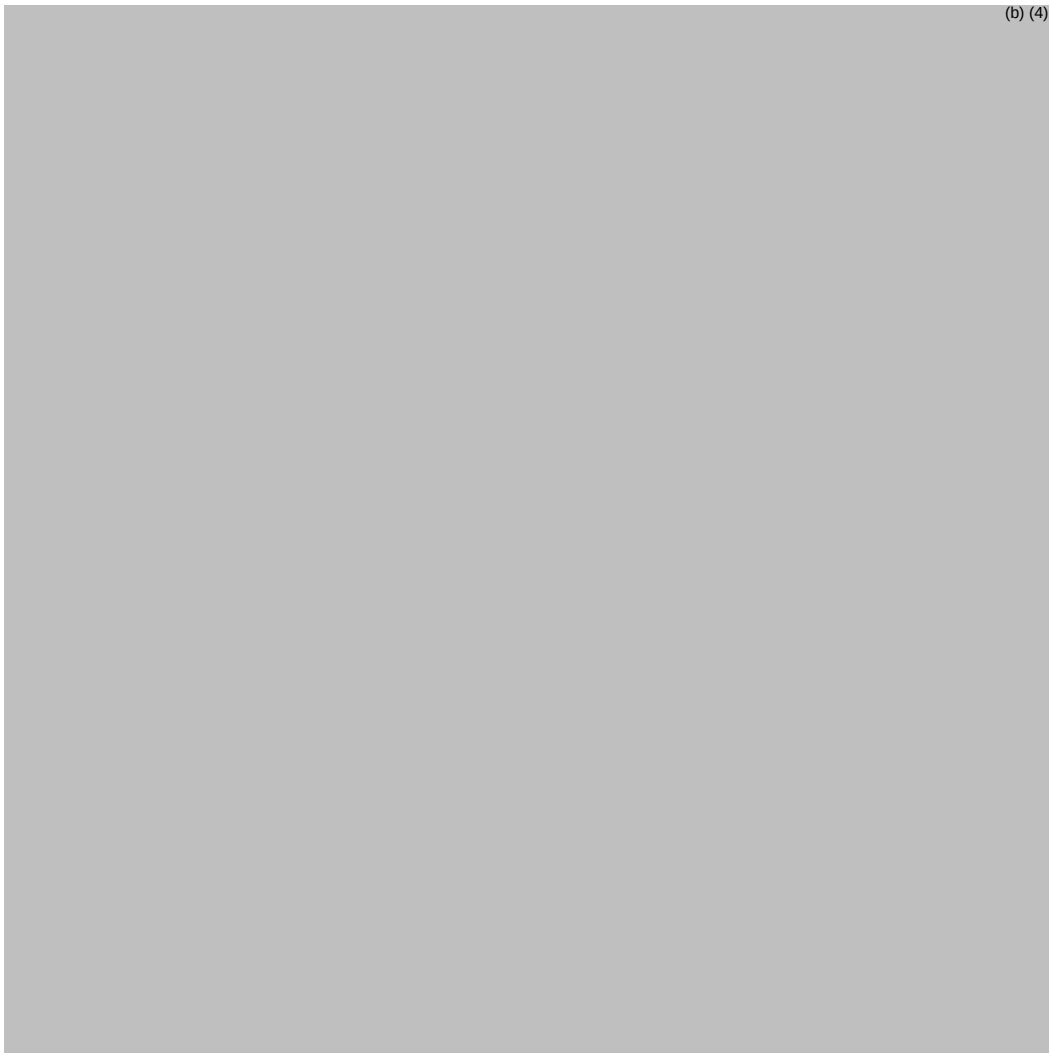

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BRAND NAME safely and effectively. See full prescribing information for BRAND NAME.

BRAND NAME (levoleucovorin) for injection, for intravenous use
Initial U.S. Approval: 1952 (d,l-leucovorin)

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Brand Name is indicated for:

- rescue after high-dose methotrexate therapy in patients with osteosarcoma.
- diminishing the toxicity associated with overdosage of folic acid antagonists or impaired methotrexate elimination.
- the treatment of patients with metastatic colorectal cancer in combination with fluorouracil.

Limitations of Use

Brand Name is not indicated for the treatment of pernicious anemia and megaloblastic anemia secondary to lack of vitamin B12 because of the risk of progression of neurologic manifestations despite hematologic remission.

2 DOSAGE AND ADMINISTRATION

2.1 Important Use Information

(b) (4)

Brand Name is indicated for intravenous administration only. Do not administer intrathecally.

2.5 Preparation

Reconstitute the 175 mg and 300 mg vial contents with 3.6 mL and 6.2 mL of 0.9% Sodium Chloride Injection, USP, respectively to obtain a clear, colorless to yellowish solution (resultant concentration 50 mg per mL levoleucovorin). Reconstitution with a sodium chloride solution with preservatives (e.g., benzyl alcohol) has not been studied. Do not store reconstituted solution for more than 12 hours at room temperature. Protect from light.

Dilute reconstituted solution immediately (if possible), to concentrations of 0.5 mg/mL to 5 mg/mL in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Do not store diluted reconstituted solution for more than 12 hours at room temperature. Protect from light.

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration. Discard if particulate matter or discoloration is observed.

3 DOSAGE FORMS AND STRENGTHS

For Injection: 175 mg and 300 mg of levoleucovorin as a sterile, white to yellowish lyophilized powder in a single-dose vial for reconstitution.

11 DESCRIPTION

Brand Name (b) (4) is a folate analog and the pharmacologically active levo-isomer of d,l-leucovorin. The chemical name is (2S)-2-[[4-[[(6S)-2-amino-5-formyl-4-oxo-1,6,7,8-tetrahydropteridin-6-yl] methylamino]benzoyl]amino] pentanedioate. The molecular formula is $C_{20}H_{23}N_7O_7$ and the molecular weight is 473.45. The chemical structure is:

[molecular structure]

- Levoleucovorin is a slightly hygroscopic, crystalline, yellow powder which is soluble in water when pH is at or above 8.

Brand Name 175 mg is a sterile lyophilized powder consisting of 175 mg levoleucovorin, 29.6 mg sodium hydroxide, and 105 mg mannitol in each vial. Additional sodium hydroxide and/or hydrochloric acid may be used to adjust the pH during manufacture. It is intended for intravenous administration after reconstitution with 3.6 mL of sterile 0.9% Sodium Chloride Injection, USP [See Dosage and Administration (2.5)].

Brand Name 300 mg is a sterile lyophilized powder consisting of 300 mg levoleucovorin, 50.7 mg sodium hydroxide, and 180 mg mannitol in each vial. Additional sodium hydroxide and/or hydrochloric acid may be used to adjust the pH during manufacture. It is intended for intravenous administration after reconstitution with 6.2 mL of sterile 0.9% Sodium Chloride Injection, USP [See Dosage and Administration (2.5)].

16 HOW SUPPLIED/STORAGE AND HANDLING

Brand Name (levoleucovorin) for Injection is a sterile, preservative-free, white to yellowish lyophilized powder in a single-dose vial. It is available as:

175 mg vial – NDC 68152-112-01.
300 mg vial – NDC 68152-114-01.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Store vial in original carton until contents are used. Protect solutions from light.

Distributed by:
Spectrum Pharmaceuticals, Inc.
Irvine, CA 92618

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

SN-016 – Carton and Vial Labels: Acceptable. Established name/strength and composition have been revised to reflect levoleucovorin, NaOH and mannitol. A proposed Brand Name has yet to be accepted. Hold time for reconstituted solution and storage statement for drug product are supported by the stability information in modules 3.2.P.2.6 and 3.2.P.8. Noted that the storage statement is not exactly the same as in the package insert, but is acceptable. The bar code, exp date and lot# are present and easily found. Noted as product of (b) (4) and drug product is made in and distributed (b) (4) (b) (4) statement is correct.

SN-016 – Package Insert: Acceptable. Title reflects 'levoleucovorin' not (b) (4) (b) (4) Section 1 - Indications are as presented in the NDA. Section 2.5 – Preparation diluents/volumes and concentrations are supported by information in module 3.2.P.2.6 and the Fusilev labeling. Section 3 – Dosage Forms reflects amount (mg) of levoleucovorin per vial and accurately describes the lyo-powder. Section 11 – Description information is complete and correct; composition statement reflects API, NaOH and mannitol and appropriate reconstitution volumes. Section 16 – How Supplied information reflects an acceptable established name and the storage statement is supported by information in module 3.2.P.8. 'Distributed by' and 'Brand Name' statements are correct.

Trade (Brand) Name: To date (b) (4) have been denied by DMEPA; proposed name (b) (4) is pending.

SN-016 – Medication Guide: None submitted

List of Deficiencies: None

Primary Labeling Reviewer Name and Date:

William M. Adams, ONDP, 08/29/18

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

Anamiro Banerjee, Ph.D., Branch Chief, 08/29/18

William Adams

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Anamitro Banerjee

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BIOPHARMACEUTICS

Application No: NDA 211226
Applicant Name: Spectrum Pharmaceuticals, Inc.
Drug Product Name/Strength: (b) (4) levoleucovorin for injection, 175 mg/vial and 300 mg/vial
Route of Administration: Intravenous infusion

List of Reviewed Submissions:
eCTD 0000 (SND#1) dated 12/22/2017
eCTD 0003 (SND #3) dated 2/08/2018
eCTD 0014 (SND #15) dated 4/19/2017

Biopharmaceutics Review Team:
Primary Reviewer: Akm Khairuzzaman, Ph.D.
Secondary Reviewer: Banu Zolnik, Ph.D.

RECOMMENDATION: ADEQUATE

REVIEW SUMMARY

Submission: Spectrum Pharmaceuticals, Inc. is seeking approval for (b) (4) levoleucovorin for injection, 175 mg/vial and 300 mg/vial, under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The proposed drug product is a sterile lyophilized powder in a vial to be reconstituted with 0.9% Sodium Chloride prior to administration. Spectrum is referencing Spectrum's Fusilev® (levoleucovorin) lyophilized drug products approved under NDA 020140. The Listed Product contains calcium salt whereas the proposed drug product is (b) (4) levoleucovorin. This submission includes the addition of a new strength, 300 mg/vial.

Review Objective: The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting; **1)** dissolution method and acceptance criterion, 2**)** biowaiver request, and 3) bridging throughout product development.

1) ***Dissolution Method:*** The drug product is a lyophilized powder in a vial to be reconstituted with 0.9% sodium chloride prior to administer in to patient as either bolus shot or into the infusion line. The reconstituted drug product is a solution, confirmed with the drug product and therefore, dissolution testing is not applicable for this drug product.

2) ***Biowaiver Request/Assessment of the Bridge:*** Applicant requested a biowaiver for the submission of in vivo bioavailability/bioequivalence studies of the proposed drug product. Although biowaiver under 21 CFR 320.22 (b) (1) regulation is not feasible, the **"bridge"** between the proposed drug product and listed drug product(s) is established under 21 CFR 320.24 (b)(6) based on the following information/data: *i)* qualitative and quantitative composition similarity before and after reconstitution and dilution, *ii)* the comparative physicochemical data for the proposed drug product and listed drug product, and *iii)* the

comparative bioavailability (b) (4) of levofolinate cited from published literature.

3) ***Bridging of Formulations:*** The formulation of the drug product used in the pharmaceutical development, registration batches and to-be-marketed batches are the same. The manufacturing site of the drug product batches used in the registration-stability studies is the proposed commercial site. Therefore, bridging between registration and to-be-marketed-products is not needed.

OVERALL RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 211226 for (b) (4) levoleucovorin for injection, 175 mg/vial and 300 mg/vial, is recommended for **APPROVAL**.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

Akm Khairuzzaman, PhD ***7/5/2018***
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Secondary Biopharmaceutics Reviewer Name and Date:

Banu Zolnik, PhD ***7/5/2018***
Division of Biopharmaceutics
Office of New Drug Products, OPQ

BIOPHARMACEUTICS ASSESSMENT

- **DRUG PRODUCT:**

The proposed drug product, (b) (4) Levoleucovorin for Injection, 175 mg/vial and 300 mg/vial, is a sterile lyophilized powder in vial containing (b) (4) (b) (4) Levoleucovorin.

- ***BCS DESIGNATION***

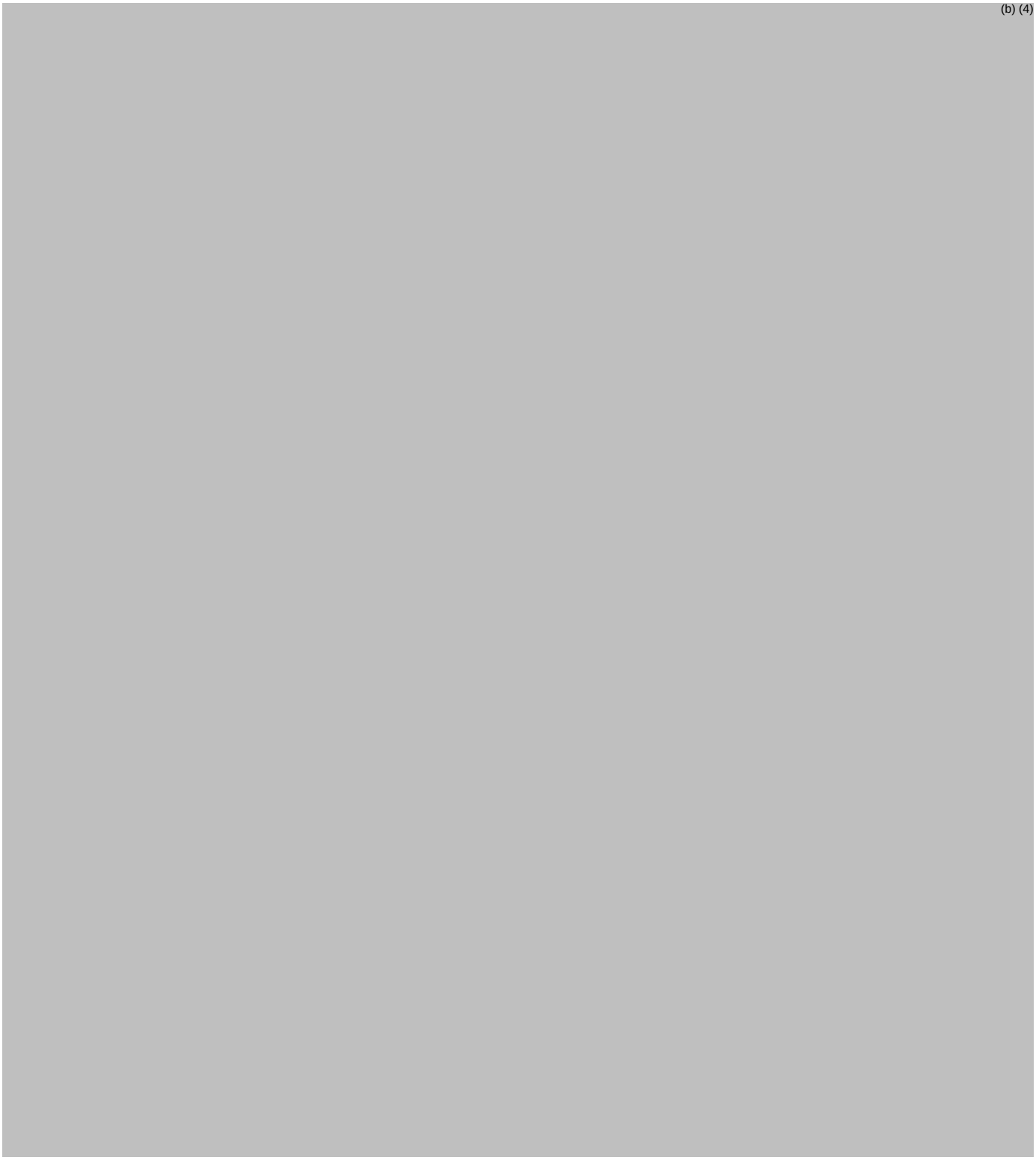
There is no official BCS designation request nor it is applicable for this application. (b) (4)

- ***BIOWAIVER REQUEST/ASSESSMENT OF BRIDGE***

Based on the Agency's feedback during the Pre-NDA meeting (dated 28 Jun 2017), the Applicant provided a "bridge" between the proposed drug product and the Listed Drug in Module 1.12.5 under 21 CFR 320.24 (b)(6). The following bridging information of the (b) (4) Levoleucovorin compared with the listed drug Fusilev® is provided:

- Qualitative and quantitative composition before and after reconstitution and dilution
- Comparative physicochemical data for the proposed drug product and listed drug product
- Published literature on pharmacokinetics studies (Study conducted by Applicant's partner (b) (4)

The difference between the test product and the listed drug product (b) (4) The listed drug product has calcium salt (b) (4) (b) (4)



(b) (4)

A (b) (4) disodium folinate and to calcium levofolinate. This study is designed as single-dose, three-treatment (b1-b3), three-period (a1-a3) and six sequence (c1-c6) cross-over bioequivalence study in 24 healthy volunteers. This study was conducted by the Applicant partner, (b) (4) The result of the BE study is shown in the Table 4. It should be noted as stated under the Reviewer's assessment section of this review below, the purpose of this supporting literature data is solely to show as an example from the literature that (b) (4) did not result in PK differences.

Table 4: Comparative physicochemical data Statistical Comparison of Pharmacokinetic Parameters for 1-CHO-THF and CH3-THF Observed in the Administrated Treatments b1/b2 and b1/b3

Pharmacokinetic parameter [Unit]	ANOVA CV [%]		Point estimate Test/Ref.	90% Confidence interval
l-CHO-THF				
C_{max} [mg/L]	8.92	b_1 / b_3	103.95	99.34 - 108.77
AUC_{0-t} [mg*h/L]	5.24	b_1 / b_3	103.21	100.50 - 106.00
$AUC_{0-\infty}$ [mg*h/L]	5.23	b_1 / b_3	102.58	99.89 - 105.35
$t_{1/2\lambda z}$ [h]	11.89	b_1 / b_3	99.00	93.20 - 105.15
MRT [h]	6.06	b_1 / b_3	99.24	96.23 - 102.35
CH_3-THF				
C_{max} [mg/L]	6.67	b_1 / b_3	100.01	96.67 - 103.46
AUC_{0-t} [mg*h/L]	7.05	b_1 / b_3	98.42	94.96 - 102.02
$AUC_{0-\infty}$ [mg*h/L]	6.25	b_1 / b_3	97.34	94.29 - 100.48
$t_{1/2\lambda z}$ [h]	20.78	b_1 / b_3	93.08	83.83 - 103.36
MRT [h]	11.74	b_1 / b_3	94.98	89.48 - 100.81

b_1: (b) (4) levofolinate, solution for i.v. administration, 100 mg levofolinic acid/m² body surface (test)
b_3: Calcium levofolinate, solution for i.v. administration, 100 mg levofolinic acid/m² body surface (reference)

Reviewer's Assessment:

1) This Reviewer confirmed with the Drug Product Reviewer that the proposed drug product following reconstitution forms a solution which is similar to the listed product. Similarly, the 300 mg strength also forms a solution following reconstitution.
2) The composition between the proposed drug product and the LD is (b) (4) (b) (4)
3) The comparative physicochemical data shows that both products show similar osmolality and pH.
4) The supporting literature PK data showed that (b) (4) levofolinate was bioequivalent to calcium levofolinate indicating that differences (b) (4) did not result in PK differences. It should be noted, however; this is a supporting example since this study was not conducted with (b) (4) levoleucovorin nor calcium levoleucovorin.

OVERALL RECOMMENDATION:
From a Biopharmaceutics perspective, NDA 211226 for (b) (4) levoleucovorin for injection, 175 mg/vial and 300 mg/vial, is recommended for **APPROVAL**.

Akm Khairuzzaman

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Banu Zolnik

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QUALITY ASSESSMENT

MICROBIOLOGY

Product Background:

NDA:211226

Drug Product Name / Strength: (b) (4) Levoleucovorin Injection, Powder for Solution/ 175mg/vial, 300mg/vial

Route of Administration: Intravenous

Applicant Name: Spectrum Pharmaceuticals, Inc.

Manufacturing Site: (b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Review Summary: The submission is **recommended** for approval on the basis of sterility assurance.

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
12/22/2017	12/22/2017	N/A	01/10/2017
02/08/2018	02/08/2018	N/A	N/A
03/19/2018	03/19/2018	N/A	N/A
05/14/2018	05/14/2018	N/A	N/A
08/27/2018	08/27/2018	N/A	N/A

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: This is an eCTD submission. IR1 was conveyed to the applicant on 04/30/2018 and the response received on 05/10/2018. IR2 was conveyed to the applicant on 08/15/2018 and the response received on 08/27/2018. The response to IRs was incorporated in the review.

Concise Description Outstanding Issues Remaining: None

Supporting Documents: Type V DMF (b) (4) by (b) (4) (b) (4) and associated microbiology review (b) (4) .doc dated 3/07/2017 (adequate). Type V DMF# (b) (4) (b) (4) review (b) (4) .doc dated (b) (4) (adequate). Microbiology review (b) (4) .pdf dated 7/25/2011 (adequate).

List Number of Comparability Protocols (ANDA only): None

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2496-101, 2496-102- 30L (300mg/ vial; 10 mL vial)

Proposed Commercial Batch Size: (b) (4) (300mg/vial; 20 mL vial); (b) (4) vials)
(175mg/vial; 10 mL vial); vials)

Reviewer's Assessment: ***Adequate***

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility. The (b) (4) stopper is referenced to Type V DMF (b) (4)

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

(3.2.P.5.2. CM278.R02 Container/Closure Integrity Testing by Dye Immersion.pdf; Section 3.2.P.2 Pharmaceutical Development.pdf)

Report#: 944964; Dated 07/06/2016

Lot No. LFA-Na-1511, and LFA-Na-1603

Test method: Dye ingress was used for the container closure integrity testing. The test was performed by (b) (4)

Test units:

- 6 test vials (intact sample vials of the drug product).
- 3 positive control vials
- Preparation of positive control vials: Flip-off cap was removed and the (b) (4) stopper was pierced with a 21-gauge needle or equivalent. The needle was embedded in the stoppers.
- 3 vials not subjected to dye immersion or vacuum pulses were used as negative controls.

Note to the reviewer: Description of the primary container/closure us integrity testing could not be located. Information is requested below.

(b) (4)

Brief description: Test vials and positive controls were completely su containing 300-700 mL of 0.1 % w/v methylene blue dye solution. Th a vacuum chamber and subjected to vacuum pressure of 15 psi for 30 restored to 1 atmospheric pressure and remained submerged for an ad vials were rinsed thoroughly with DI water and wiped with isopropyl negative controls and sample vials was equilibrated by briefly insertin the septum of each vial. Test vials, positive control and negative contr with appropriate volume of DI water (6 mL and 3.8 mL for 300mg/mL respectively) to obtain a concentration of 50 mg/mL. The vials were a UV-Visible spectrophotometer at 664 nm.

Validation acceptance criteria:

- All samples and negative controls must show no spectrophotometric evidence of dye ingression through the vial stopper system. The absorbance difference of samples measurements compared to the average of the negative controls must be less than (b) (4) in the case of Calcium Leucovorin DP and less than (b) (4) for (b) (4) (b) (4) DP
- All positive controls must contain detectable levels of methylene blue, spectrophotometrically. The absorbance difference of positive controls compared to the average of the negative controls must be greater than (b) (4) in the case of Calcium Leucovorin DP and less than (b) (4) for (b) (4) DP

Results:

Solution	Absorbance at 664 nm	Difference
Negative control-1	0.0481	
Negative control-2	0.0423	
Negative control-3	0.0425	
Average	0.0443	
Sample-1	0.0443	-0.0010
Sample-2	0.0451	0.0008
Sample-3	0.0446	0.0003
Sample-4	0.0441	-0.0002
Sample-5	0.0444	0.0001
Sample-6	0.0437	-0.0006
Positive control-1	4.5000	4.4557
Positive control-2	4.5000	4.4557
Positive control-3	4.5000	4.4557

- Samples and negative controls show no spectrophotometric evidence of dye ingression through the vial stopper system.
- Positive controls show detectable levels of methylene blue.
- The applicant states that the limit of detection (LOD) of the instrument with respect to the concentration of methylene solution in the reconstituted sample has been established at (b) (4) ppm.

Note to the reviewer: The reconstituted volume of the sample was not provided. Information is requested below.

The following information request was conveyed to the applicant on 04/30/2018 and the response was received on 05/10/2018.

IR:

Regarding container closure integrity testing using dye ingress:

1. *Please provide additional details of the container closure used for the container closure integrity testing. Also, clarify if container closure integrity testing was performed using container closure proposed for commercial production and provide justification in case routine production container closure is not used for the studies.*

Applicant's response: The applicant stated that the container closure integrity test method was developed using developmental batches of the drug product prepared in 10 and 20 mL (b) (4) vials with an alternate (b) (4) stopper.

The applicant also stated that this method is routinely used to test seal integrity for the drug product in commercial production at the time of release and as a part of routine stability testing. The results for batch release of product in the production container closure are summarized below.

Parameter	Acceptance criteria	Lot Numbers (strength)			
		2475-101 (175mg/vial)	2475-102 (175mg/vial)	2496-101 (300mg/vial)	2496-102 (300mg/vial)
Seal Integrity	Meets test	Conforms	Conforms	Conforms	Conforms

Note to the reviewer: The vials used for the CCIT is identical to the vial proposed for routine production. However, an alternate stopper from a different supplier was used in the CCIT. Comparison of dimensions and formulation between (b) (4) stoppers (used for CCIT) and (b) (4) stoppers (proposed for production) to justify that the two stoppers are equivalent was not provided. Information is requested below.

IR:

2. *Please provided the volume of DI water used to reconstitute the test vials, positive controls, and negative controls to confirm that the test is sensitive enough to allow the detection of the entry and subsequent dilution of approximately 1-5 µL of the dye into the solution in the vials.*

Applicant's response: The applicant states that 300 mg/vial and 175 mg/vial are reconstituted with 6.0 mL and 3.8 mL of water respectively. These volumes for samples and negative controls were used during test validation and are currently used for product testing. The volume is reduced in positive controls to account for the volume uptake of dye solution. The positive controls are reconstituted to the same approximate solution volumes as the reconstituted samples and negative controls. The cutoff for absorbance of methylene blue in product vials (0.0074AU) corresponds to a concentration of 100 ppb, which corresponds to less than 1 µL of 0.1% dye solution in 6 mL of reconstituted product at 300 mg strength or 3.8mL of reconstituted product at 175mg strength.

The reviewer calculates the sensitivity as follows:
The absorbance difference of 6 mL test solution compared to the average of the negative controls is less than 0.0074 AU (or 1 ppb).
Therefore, 6 mL solution has less than 1 ppb of Methylene blue.
1 ppb is equivalent to 1 µg/L or 0.006 µg/6 mL

Concentration of Methylene blue solution prepared for immersion = 0.1 % w/v.
100 mg of Methylene blue intruded should result in 100 mL of intrusion volume.
1µg of Methylene blue intruded should result in 1 µL of intrusion volume.
Therefore, intrusion volume for 0.006µg of Methylene blue = 0.006 µL per 6 mL of drug product solution.

The following information request was conveyed to the applicant on 8/15/2018 and the response was received on 08/27/2018.

IR:

1. *Container closure integrity testing (CCIT) needs to be conducted using the proposed stopper and vial for commercial product. CCIT was performed using the vial proposed for routine production and an alternate (b) (4) stopper. To support the included CCIT study results, provide a comparison of the dimensions and (b) (4) formulations for the (b) (4) alternate stoppers (used for CCIT) and the 20 mm, (b) (4) stopper supplied by (b) (4) (proposed for routine production) used for commercial product. If the two stoppers are not equivalent in terms of dimensions and formulation, conduct and provide results for CCIT studies using the proposed stoppers and vials for the commercial drug product.*

Applicant's response: The applicant states that CCIT using the container closure proposed for the subject drug product was validated by Spectrum for Fusilev (levoleucovorin for Injection). The CCIT data was reviewed and found adequate in N020140S013R1.pdf (dated 7/25/2011). The Applicant also committed to supplement the validation study of the CCIT procedure with additional validation studies to confirm that acceptable limits of detection are achieved with the product in container/closure proposed for routine production in NDA 211226. The study will be completed prior to marketing and submitted in the first annual report.

Reviewer's Assessment: ***Adequate***

The applicant provided adequate information regarding container closure integrity testing.

Antimicrobial Effectiveness Testing-

Reviewer's Assessment: N/A
The sterile drug product is a single dose. Antimicrobial testing is not required.

P.3 Manufacture

P.3.1 Manufacturers

(b) (4)

This facility is responsible for drug product manufacturing, release testing on final drug product for sterility and bacterial endotoxins

(b) (4)

This facility is responsible for drug product release and stability testing

Reviewer's Assessment: ***Adequate***

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P.7 Container Closure

Summary table of the container closure system proposed

Reviewer's Assessment: Please refer to P.1.

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(3.2.P.8.1. Stability Summary and Conclusion.pdf, p2/2)

Proposed Expiry: 24 months

Reviewer's Assessment: ***Adequate***

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

The product stability specification includes the following microbiological tests:

Test	Test method	Acceptance criteria
Bacterial Endotoxins	USP<85>	NMT (b) (4) EU/mg
Sterility	USP<71>	Sterile
Seal Integrity	(b) (4)*	Meets Test

*Container closure seal integrity testing of the subject drug product, by dye immersion test.

Note to the reviewer: The seal integrity testing method ((b) (4)) is same as that used for container closure integrity testing (Dye immersion test).

The testing schedule in the post-approval protocol is as follows:
Stability storage conditions: 25° ± 2°C/60% ± 5% RH

Test	Initial	Time (months)							
		3	6	9	12	18	24	36	48
Bacterial Endotoxins	X				X		X	X	X
Sterility	X				X		X	X	X
Seal Integrity	X								X

Post Approval Stability Commitment

Stability on two validation/registration batches of each strength, 175 mg/vial and 300 mg/vial, manufactured by (b) (4) is ongoing. Spectrum commits to continue testing these validation batches as indicated in protocol above. The applicant commits to placing one commercial batch of each strength on a yearly basis, on long-term stability (if manufactured).

Reviewer's Assessment: ***Adequate***

The post approval protocol and stability commitment is adequate.

P.8.3 Stability Data

(3.2.P.8.3. Stability Data.pdf)

Stability data generated for the following registration batches of 300mg/vial and 175 mg/vial under accelerated conditions (40° ± 2°C/75% ± 5% RH) until 6-month time point, and long term conditions (25° ± 2°C/60% ± 5% RH) until 12-month time point has been tested per the stability schedule. The report was included in the submission. Bacterial endotoxins testing and sterility met the specifications at 0,1,3,6,9 and 12-month time point for long term stability studies, and 0,1,3, and 6-month time point for accelerated stability studies. The applicant states that long term stability studies are ongoing.

Note to the reviewer: The applicant submitted stability data from two batches for each strength. The CMC review team sent an Information Request (dated 02/01/2018) requesting the applicant to submit stability data on the third batch for each strength as per ICH Q1A (R2). The applicant submitted an amendment (dated 02/08/2018) stating that, Spectrum has utilized a reduced design for generating primary stability data in support of the proposed shelf-life per ICH Q1D. A total of four drug product registration batches were manufactured comprising two batches each at 175mg/vial and 300mg/vial. The drug product strengths (b) (4) (b) (4) (b) (4) Therefore, the applicant stated that data from these four primary registration batches supports the proposed shelf-life for the two product strengths. The applicant's response was discussed with the process review team and deemed adequate.

Product	Primary Registration Batches		
	1st Batch	2nd Batch	3rd Batch
175mg/vial 40L commercial scale	2475-101 DS Lot No. B00004	2475-102 DS Lot No. B00003	Two batches of 300mg/vial batches provide sufficient data to support the shelf-life for 175mg/vial product
300mg/vial 30L commercial scale	2496-101 DS Lot No. B00003	2496-102 DS Lot No. B00004	Two batches of 175mg/vial batches provide sufficient data to support the shelf-life for 300mg/vial product

Reviewer's Assessment: ***Adequate***

The stability data provided for accelerated, intermediate, and long term storage conditions up to 6 months support the expiration dating of the drug product as proposed.

R Regional Information

Executed Batch Records

Executed lot #(s): 2475-101 (175 mg/vial), 2475-102 (175 mg/vial), 2496-101 (300 mg/vial), and 2496-102 (300 mg/vial)

The batch records confirm that validated sterilization/depyrogenation process were used for manufacture of the exhibit batches. (b) (4) (b) (4)

(b) (4)

Reviewer's Assessment: ***Adequate***

Comparability Protocols

Reviewer's Assessment: No CP was included in the application

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

(1.14.1.3)

Storage temperature: (b) (4) excursions permitted from 15-30ºC (59-86ºF)
Route of administration: Intravenous
Container: 300mg/ 20mL vial; 175mg/ 10mL vial; single-dose vials for reconstitution

- **Reconstitution and further dilution of drug product**

Reconstitution: 175mg/mL and 300mg/mL lyophilized drug product vials are reconstituted with 3.6 mL and 6.2 mL of 0.9% Sodium Chloride Injection, USP, respectively to yield a levoleucovorin concentration of 50 mg/mL. The storage period for reconstituted product is NMT 12 hours at room temperature.

Dilution: Saline reconstituted drug product may be further diluted, immediately, to concentrations of 0.5 mg/mL to 5 mg/mL in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. The storage period of diluted product is NMT 12 hours at room temperature.

Microbial Hold Time Study:

A microbial assessment for reconstituted drug product to evaluate adventitious microbial growth during the post-dilution hold times was provided. The study evaluated the growth potential of Sodium Levofolinate drug product reconstituted with 0.9% Saline to a final concentration of 50 mg/mL, drug product diluted to 0.5mg/mL with 0.9% Saline, and drug product diluted to 0.5mg/mL with Dextrose 5% in Water and subsequently held at 20-25ºC storage temperature.

Report # 077712-01-01, dated 09/06/2017; P27202.00 Microbial Hold Time Study.pdf
Lot Number: 2496-102 (300 mg/vial)

Method verification: Direct plate method used for enumeration of surviving microbial population was verified per modified USP <51> and performed for each product strength and diluent combination (described in table below).

Sample	Storage Condition	Number of preparations (one preparation per microorganism)	Container Type
Sodium Levofolinate Drug Product for Injection, 50mg/mL (Saline)	20-25ºC	6 containers	Sterile 150mL Bottle
Sodium Levofolinate Drug Product for Injection in 0.9% Saline, 0.5 mg/mL		6 containers	100mL IV Flexible Containers
Sodium Levofolinate Drug Product for Injection in D5W, 0.5 mg/mL		6 containers	
0.9% Saline Control		6 containers	
D5W Control		6 containers	

Six sterile tubes (one for each microorganism) containing 10mL of the sample solution or control solution (described in the table above) was inoculated with 100 µL suspension of each microorganism (*E. coli, B. subtilis, A. brasiliensis, P. aeruginosa*, *S. aureus* and *C. albicans*) to achieve a final concentration NMT (b) (4) CFU/mL. 1mL aliquots from the inoculated sample and control solution tubes for each microorganism was plated and overlaid with media and incubated at the required temperature for ≤ 3 days (Max. 66 hours).

Organism	Overlay Media/Temperature	Incubation temperature/Time
E. coli	TSA media at ≤ 45ºC	30-35ºC for ≤ 3days (Max. 66 hours)
S. aureus		
P. aeruginosa		
B. subtilis		
Candida albicans	SDA media at ≤ 45ºC	20-25ºC for ≤ 3days (Max. 66 hours)
A. brasiliensis		

Method verification acceptance criteria:

- The method is acceptable if the % recovery for the sample/control and dilution control plates show not less than (b) (4)%.
- Population verification results for each microorganism is < (b) (4) CFU.

Method verification Results: The method verification met the % recovery acceptance criteria for each of the sample formulations and controls. Direct transfer method was acceptable with undiluted as the lowest valid reportable dilution for each microorganism. The results are summarized below.

Sample		*E. coli*	*S. aureus*	*P. aeruginosa*	*B. subtilis*	*C. albicans*	*A. brasiliensis*
Drug Product in 0.9% Saline, 50mg/mL	Average Sample CFU	36	22	25	30	89	34
	% recovery	84	122	100	135	103	92
Drug Product in 0.9% Saline, 0.5 mg/mL	Average Sample CFU	42	17	33	26	91	29
	% recovery	98	94	132	113	106	78
Drug Product in D5W, 0.5 mg/mL	Average Sample CFU	36	17	29	26	93	38
	% recovery	84	94	116	113	108	103
0.9% Saline Control	Average Sample CFU	37	18	36	21	78	37
	% recovery	86	100	144	91	91	100
D5W Control	Average Sample CFU	36	22	23	21	93	33

	% recovery	84	122	92	91	108	89

Microbial Hold Time Study: 100 mL of each solution for each study replicate for product strength/diluent/control/storage condition/organism combination was prepared. Each 100mL sample was inoculated with 0.1mL aliquot of the microorganism suspension and stored at 20-25ºC. Time of inoculation was considered as initial time point (0 hour). The samples were tested according to the testing conditions and time points described in the table below. At each time point, the samples were removed and serial diluted in phosphate buffer. 1 mL of the undiluted inoculated solution and the prepared dilutions were plated in separate sterile petri plates. The plates were overlaid with media and incubated at the required temperature. The media, incubation time, and temperature are summarized below.

Sample	**Storage Condition**	**Time points for testing**	**Number of preparations (one preparation per microorganism)**
Sodium Levofolinate Drug Product for Injection, 50mg/mL (Saline)	20-25ºC	0 (initial), 12 hour, 24 hour	6 containers
Sodium Levofolinate Drug Product for Injection in 0.9% Saline, 0.5 mg/mL			6 containers
Sodium Levofolinate Drug Product for Injection in D5W, 0.5 mg/mL			6 containers
0.9% Saline Control			6 containers
D5W Control			6 containers

Organism	**Overlay Media/Temperature**	**Incubation temperature/Time**
E. coli	TSA media at ≤ 45ºC	30-35ºC for 3-5 days
S. aureus		
P. aeruginosa		
B. subtilis		
Candida albicans	SDA media at ≤ 45ºC	20-25ºC for 3-5 days
A. brasiliensis		20-25ºC for 3-7 days

Acceptance criteria:

- Population verification results must yield a level of < (b) (4) CFU/mL in the 100mL sample container.

Result: There was no growth (defined as less than 0.5 log increase in count) observed for any organisms over the course of the study and the drug solution is not growth promoting. The proposed acceptance criteria were met. Results are summarized in the table below.

Sodium Levofolinate drug product for injection, 50 mg/mL (0.9% Saline)

Organism	*E. coli*	*S. aureus*	*P. aeruginosa*	*B. subtilis*	*C. albicans*	*A. brasiliensis*
0 hr. CFU/mL	1.7×10^1	2.4×10^1	7×10^0	2.5×10^1	7.4×10^1	1.6×10^1
12 hr. CFU/mL	1×10^1	2×10^1	< 1	1.7×10^1	3.1×10^1	2.0×10^1
24 hr. CFU/mL	< 1	6×10^0	1×10^0	1.6×10^1	3.9×10^1	1.7×10^1*

Organism	*E. coli*	*S. aureus*	*P. aeruginosa*	*B. subtilis*	*C. albicans*	*A. brasiliensis*
0 hr. Log of CFU/mL	1.23	1.38	0.85	1.40	1.87	1.20

12 hr. Log of CFU/mL	0	0.30	0	1.23	1.49	1.30
24 hr. Log of CFU/mL	0	0.78	0	0.20	1.59	1.23*

Sodium Levofolinate drug product for injection, 0.5 mg/mL (0.9% Saline)

Organism	*E. coli*	*S. aureus*	*P. aeruginosa*	*B. subtilis*	*C. albicans*	*A. brasiliensis*
0 hr. CFU/mL	3.1×10^1	3.4×10^1	2.8×10^1	2.7×10^1	6.9×10^1	1.8×10^1
12 hr. CFU/mL	1.6×10^1	1.4×10^1	1.3×10^1	1.9×10^1	7.0×10^1	1.2×10^1
24 hr. CFU/mL	1.3×10^1	2.1×10^1	1.4×10^1	2.1×10^1	6.2×10^1	1.5×10^1
Organism	*E. coli*	*S. aureus*	*P. aeruginosa*	*B. subtilis*	*C. albicans*	*A. brasiliensis*
0 hr. Log of CFU/mL	1.49	1.53	1.45	1.43	1.84	1.26
12 hr. Log of CFU/mL	1.20	1.15	1.11	1.28	1.85	1.08
24 hr. Log of CFU/mL	1.11	1.32	1.15	1.32	1.79	1.18

Sodium Levofolinate drug product for injection, 0.5 mg/mL (D5W)

Organism	*E. coli*	*S. aureus*	*P. aeruginosa*	*B. subtilis*	*C. albicans*	*A. brasiliensis*
0 hr. CFU/mL	2.8×10^1	2.8×10^1	2.4×10^1	2.0×10^1	8.3×10^1	1.7×10^1
12 hr. CFU/mL	2.1×10^1	1.2×10^1	1.9×10^1	1.4×10^1	5.5×10^1	1.4×10^1
24 hr. CFU/mL	1.8×10^1	8.0×10^0	1.4×10^1	1.2×10^1	5.7×10^1	1.7×10^1*

Organism	*E. coli*	*S. aureus*	*P. aeruginosa*	*B. subtilis*	*C. albicans*	*A. brasiliensis*
0 hr. Log of CFU/mL	1.45	1.45	1.38	1.30	1.92	1.23
12 hr. Log of CFU/mL	1.32	1.08	1.28	1.15	1.74	1.15
24 hr. Log of CFU/mL	1.26	0.90	1.15	1.08	1.76	1.23

0.9% Saline control

Organism	*E. coli*	*S. aureus*	*P. aeruginosa*	*B. subtilis*	*C. albicans*	*A. brasiliensis*
0 hr. CFU/mL	3.0×10^1	3.4×10^1	2.2×10^1	2.4×10^1	8.5×10^1	1.6×10^1
12 hr. CFU/mL	2.7×10^1	2.6×10^1	2.2×10^1	1.6×10^1	7.3×10^1	1.1×10^1
24 hr. CFU/mL	2.9×10^1	1.5×10^1	1.1×10^1	1.3×10^1	5.0×10^1	1.2×10^1

Organism	*E. coli*	*S. aureus*	*P. aeruginosa*	*B. subtilis*	*C. albicans*	*A. brasiliensis*
0 hr. Log of CFU/mL	1.48	1.53	1.34	1.38	1.93	1.20
12 hr. Log of CFU/mL	1.43	1.41	1.34	1.20	1.86	1.04
24 hr. Log of CFU/mL	1.46	1.18	1.04	1.11	1.70	1.08

D5W Control

Organism	*E. coli*	*S. aureus*	*P. aeruginosa*	*B. subtilis*	*C. albicans*	*A. brasiliensis*
0 hr. CFU/mL	2.4×10^1	3.4×10^1	1.7×10^1	1.7×10^1	6.8×10^1	2.3×10^1
12 hr. CFU/mL	9×10^0	2×10^0	2×10^0	1.1×10^1	4.3×10^1	1.7×10^1
24 hr. CFU/mL	3×10^0	< 1	< 1	1.2×10^1	5.1×10^1	1.6×10^1

Organism	*E. coli*	*S. aureus*	*P. aeruginosa*	*B. subtilis*	*C. albicans*	*A. brasiliensis*
0 hr. Log of CFU/mL	1.38	1.53	1.23	1.23	1.83	1.36
12 hr. Log of CFU/mL	0.95	0.30	0.30	1.04	1.63	1.23
24 hr. Log of CFU/mL	0.48	0	0	1.08	1.71	1.20

*Less than 0.5 log increase in count

Reviewer's Assessment: ***Adequate***

Post-Approval Commitments: NA

List of Deficiencies:

NDA: 211226APPLICANT: Spectrum Pharmaceuticals, Inc.

DRUG PRODUCT: Disodium Levoleucovorin Injection, Powder for Solution/ 175mg/vial, 300mg/vial

The Division of Microbiology Assessment has no comments at this time.

Primary Microbiology Reviewer Name and Date:
Hemlata Tamta, Ph.D.
Microbiologist
CDER/OPQ/OPF/DMA/BII
Date: 09/26/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Nandini Bhattacharya, Ph.D.
Microbiologist
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Date: 09/26/2018

Hemlata Tamta

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Nandini Bhattacharya

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