

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208723Orig1s000**

**CHEMISTRY REVIEW(S)**

uploaded  
8/25/2016



QUALITY ASSESSMENT



**NDA Recommendation: Approval**

**NDA 208723  
Review #1**

<b>Strength</b>	175 mg/vial
<b>Route of Administration</b>	Injection
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Actavis LLC
<b>US agent, if applicable</b>	N/A
<b>Drug Name/Dosage Form</b>	Levoleucovorin for injection

<b>SUBMISSION(S) REVIEWED</b>	<b>DOCUMENT DATE</b>	<b>DISCIPLINE(S) AFFECTED</b>
Original NDA – 0000 (1)	01-Dec-2015	Drug Substance, Drug Product, Process, Facilities, Biopharmaceutics, and Microbiology
Amendment (revised container and carton labeling) – 0002 (3)	03-Mar-2016	Drug Substance, Drug Product, and Microbiology
Amendment (Response Agency's Information Request dated 02-Feb-2016) – 0004 (5)	23-May-2016	Microbiology
Amendment (Response Agency's Information Request dated 02-May-2016) – 0005 (6)	10-Jun-2016	Drug Substance, Drug Product, Process, and Microbiology
Amendment (Response Agency's Information Request dated 13-Jul-2016) - 0006 (7)	20-Jul-2016	Drug Product
Amendment (Response Agency's Information Request dated 22-Jul-2016 & 27-Jul-2016) – 0007 (8)	05-Aug-2016	Drug Product, Process, and Microbiology



## CHEMISTRY REVIEW



### Quality Review Team

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
Drug Substance	Haripada Sarker	OPQ/ONDP/DNDPAPI/BI
Drug Product	William Adams	OPQ/ONDP/DNDPI/BII
Process	Kumar Janoria	OPQ/OPF/DPAIII/BVII
Microbiology	Elizabeth Berr	OPQ/OPF/DMA/BI
Facility	Rose Xu	OPQ/OPF/DIA/BII
Biopharmaceutics	Jing Li/Okpo Eradiri	OPQ/ONDP/DB/BI
Regulatory Business Process Manager	Steve Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Joyce Crich	OPQ/ONDP/DNDPI/BII
Laboratory (OTR)	N/A	
Environmental Assessment (EA)	William Adams	OPQ/ONDP/DNDPI/BII

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## 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)	Drug substance manufacturing and testing	Adequate	07/05/2016	LoA provided Dated 11/3/2015. DMF was reviewed by Dr. Anjali Bain
	Type III	(b) (4)	(b) (4)	N/A	---	LOA dated 09/11/15. Adequate information in the NDA
	Type III	(b) (4)	(b) (4)	Adequate	04/06/2016	LOA dated 09/07/15. DMF was reviewed by Dr. Elizabeth Bearr
	Type V	(b) (4)	(b) (4)	Adequate	08/02/2016	LOA dated 11/13/15. DMF was Reviewed by Dr. Elizabeth Bearr

**B. Other Documents: IND, RLD, or sister applications**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20140	RD, FUSILEV® (levoleucovorin) for injection, 50 mg/vial (Spectrum Pharmaceuticals, Inc)

(b) (4)

**2. CONSULTS:**

<b>DISCIPLINE</b>	<b>STATUS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Pharmacology /Toxicology	Conducted separate review	Approval	12-Aug-2016	Emily Wearne
Clinical	Conducted separate review	Approval	29-Jul-2016	Shan Pradhan
Clinical Pharmacology	Completed review note	No clinical pharmacology issues are to be addressed	15-Mar-2016	Safaa Burns
Medication Error	Conducted separate review	Labeling Comments for Carton, Container Closure and Package Insert were conveyed	10-Mar-2016	Otto Townsend
Biostatistics	N/A			
CDRH	N/A			

## Executive Summary

### I. Recommendations

#### A. Recommendation 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.

Include the following language in the approval letter:

Based on the provided stability data, a 18-month expiration dating period is granted for Levoleucovorin for injection (175 mg/vial) in the proposed commercial container closure system when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

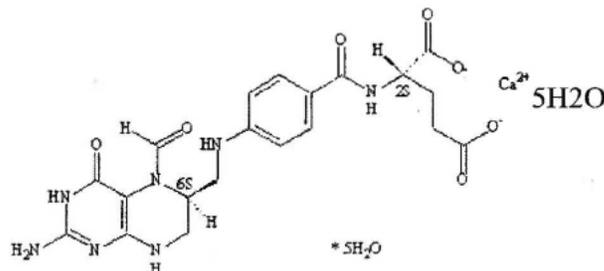
### II. Summary of Quality Assessments

#### A. Drug Substance [Levoleucovorin Calcium] Quality Summary

##### 1. Chemical Name or IUPAC Name/Structure

International Non-proprietary Name (INN): Levoleucovorin Calcium (the free acid is designated as (6S)-Folinic acid or (6S)-Leucovorin)

Chemical Name: Calcium (2S)-2-[[4[[[(6S)-2-amino-5-formyl-4-oxo-1,4,5,6,7,8-hexahydropteridin-6-yl]methyl]amino]benzoyl]amino]-pentanedioate.



Molecular Formula:  $C_{20}H_{21}CaN_7O_7 \cdot 5H_2O$

Molecular Weight: 601.6 (b) (4)

## 2. Properties/CQAs Relevant to Drug Product Quality

Levoleucovorin, a folate analog, is the levo isomeric form of racemic *d,l*-leucovorin. The active pharmaceutical ingredient (API) is (b) (4) levoleucovorin calcium salt.

The API has the following properties:

- (b) (4) Powder
- Slightly soluble in water, practically insoluble in acetone and in alcohol
- Optical Rotation: -15.1
- (b) (4)

## 3. List of starting materials

Cross-referred to DMF (b) (4)

## 4. Suppliers of starting materials (site)

Cross-referred to DMF (b) (4)

## 5. Summary of Synthesis

Cross-referred to DMF (b) (4)

## 6. Process

- a. Sterilization processes of the sterile bulk, as applicable: Cross-referred to DMF (b) (4)
- b. Critical equipment: Cross-referred to DMF (b) (4)

## 7. Container Closure

Cross-referred to DMF (b) (4). Also following information is included: Levoleucovorin Calcium, manufactured by (b) (4) is packaged in high-density polyethylene containers (b) (4). The container is closed with a (b) (4) cap (b) (4).

## 8. Retest Period & Storage Conditions

(b) (4) month retest period if stored between (b) (4) in the tightly closed container-closure system used for storage and distribution. Also cross-referred to DMF (b) (4).

(b) (4) (FEI No. (b) (4)) in (b) (4) is the drug substance manufacturer for manufacture, release testing, stability testing and packaging. The overall recommendation by Office of Process and Facilities (OPF/OPQ/CDER) for this manufacture site is "Acceptable" based on Pre-Approval Inspection.

**B. Drug Product [Levoleucovorin for injection] Quality Summary****1. Strength**

Each vial contains 175 mg levoleucovorin (formulated with levoleucovorin calcium pentahydrate)

**2. Description/Commercial Image**

The proposed product is a sterile lyophilized off-white to yellowish lyophilized powder presented in the proposed container closure, refer to # 6.

**3. Summary of Product Design**

The proposed product is a lyophilized powder intended to be reconstituted with 17.7 mL of 0.9% Sodium Chloride Injection, USP to yield a solution in concentration of 10 mg/mL. The reconstituted Levoleucovorin for injection solution is to 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. Diluted solution is to be administered by intravenous infusion.

**4. List of Excipients:**

Mannitol, USP  
Sodium Hydroxide/Hydrochloric Acid, NF  
Water for Injection, USP

**5. Process Selection (Unit Operations Summary)**

a. The manufacturing process for Levoleucovorin for injection consists of

(b) (4)  
[Redacted]

b. Critical equipment: Lyophilizer.

**6. Container Closure**

(b) (4) glass vial (Type I) with (b) (4)  
stopper and aluminum overseal with (b) (4) disc.

**7. Expiration Date & Storage Conditions**

18 months in the vial carton (b) (4) at US CRT.

**8. List of co-packaged components**

None

Actavis Italy SPA (FEI 3001116953) in Nerviano, Italy is the drug product manufacturer for drug product manufacturing, release testing, stability testing,

packaging, and labeling. The overall recommendation by OPF/OPQ/CDER for this manufacture site is “Acceptable” based on profile review.

**C. Summary of Drug Product Intended Use**

<b>Proprietary Name of the Drug Product</b>	None
<b>Non Proprietary Name of the Drug Product</b>	Levoleucovorin for injection
<b>Non Proprietary Name of the Drug Substance</b>	Levoleucovorin calcium
<b>Proposed Indication(s) including Intended Patient Population</b>	<ul style="list-style-type: none"> <li>• Rescue after high-dose methotrexate therapy in osteosarcoma.</li> <li>• Diminishing the toxicity (b) (4) methotrexate elimination (b) (4)</li> </ul> <p><u>Limitations of Use</u>                      Levoleucovorin for injection is not (b) (4) for pernicious anemia (b) (4) megaloblastic anemias. (b) (4) hematologic remission (b) (4)</p>
<b>Duration of Treatment</b>	Treatment is based on patient serum methotrexate levels. Although the reference drug (b) (4) state that “Levoleucovorin for injection rescue at a dose of 7.5 mg (approximately 5 mg/m <sup>2</sup> ) every 6 hours for 10 doses starts 24 hours after the beginning of the methotrexate infusion”, the labels also include instructions for treatment extension until the methotrexate level is below 5 x 10 <sup>-8</sup> M (0.05 micromolar), as well as statements that the dose may need to be adjusted.
<b>Maximum Daily Dose</b>	Multiple dosing regimens intended for various clinical scenarios (e.g., based on patient serum methotrexate levels) (b) (4)
<b>Alternative Methods of Administration</b>	None

**D. Biopharmaceutics Considerations**

1. BCS Classification:

- Drug Substance: Not established.

- Drug Product: N/A. The drug product is a lyophilized powder for injection.

## 2. Biowaivers/Biostudies

- Biowaiver Requests: A biowaiver request was submitted in accordance with 21 CFR 320.22 (b)(1)(i)&(ii). The request is granted on the basis of the nature of the reconstituted drug product for injection (solution), that is, the comparable physical and chemical characteristics of the proposed drug product to the listed drug.

A waiver of the *in vivo* bioequivalence study requirement is granted. From a Biopharmaceutics perspective, NDA 208723 for Levoleucovorin for Injection 175 mg/vial is recommended for approval.

**E. Novel Approaches:** None

## F. Any Special Product Quality Labeling Recommendations

- Reconstituted solution should be used immediately, but may be stored for not more than 24 hours at room temperature.
- Reconstituted solution diluted with 0.9% sodium chloride injection, USP may be stored not more than 24 hours at room temperature.
- Reconstituted solution diluted with 5% dextrose injection, USP may be stored not more than 6 hours at room temperature.

## G. Life Cycle Knowledge Information

See Section III Attachment A

## OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

**Application Technical Lead Signature:** From the chemistry, manufacturing and controls standpoint, this NDA is recommended for approval.

Joyce Z Crich, PhD

Application Technical Lead (Acting) OPQ/ONDP/DNDP-I/Branch II

Date: August 25, 2016

Joyce  
Crich -S

Digitally signed by Joyce Crich -S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
cn=Joyce Crich -S,  
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**ASSESSMENT OF THE BIOPHARMACEUTICS**

12. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

The drug product is a solution for injection; therefore dissolution testing is not applicable.

The Applicant requests a waiver of the bioequivalence requirement for Levoleucovorin Calcium for Injection 175 mg/vial, in accordance with 21 CFR 320.22 (b)(1)(i)&(ii). This Biopharmaceutics review will be focused on evaluating the biowaiver request.

Table 38-1 shows a side-by-side comparison of the proposed drug product and the listed drug FUSILEV (NDA 020140).

Table 38-1. Comparison between the proposed drug product and the listed drug

	<b>Listed Drug</b>	<b>Proposed Drug</b>
	<b>FUSILEV® (levoleucovorin) for injection</b>	<b>Levoleucovorin Calcium for Injection</b>
<i>Conditions of use</i>	<p>Fusilev® is a folate analog indicated for:</p> <ul style="list-style-type: none"> <li>Rescue after high-dose methotrexate therapy in osteosarcoma.</li> <li>Diminishing the toxicity and counteracting the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists.</li> <li>Use in combination chemotherapy with 5-fluorouracil in the palliative treatment of patients with advanced metastatic colorectal cancer.</li> </ul> <p><u>Limitations of Use</u> Fusilev is not approved for pernicious anemia and megaloblastic anemias. Improper use may cause a hematologic remission while neurologic manifestations continue to progress. Levoleucovorin Calcium</p>	<p>Levoleucovorin Calcium for Injection is a folate analog indicated for:</p> <ul style="list-style-type: none"> <li>Rescue after high-dose methotrexate therapy in osteosarcoma.</li> <li>Diminishing the toxicity (b) (4)</li> <li>methotrexate elimination (b) (4)</li> </ul> <p><u>Limitations of Use</u> (b) (4) pernicious anemia (b) (4) megaloblastic anemias. (b) (4) hematologic remission (b) (4)</p>
<i>Active Ingredient</i>	Levoleucovorin Calcium	Levoleucovorin Calcium
<i>Inactive Ingredients</i>	Mannitol Sodium Hydroxide Hydrochloric Acid	Mannitol Sodium Hydroxide Hydrochloric Acid
<i>Route of administration</i>	Intravenous use	Intravenous use
<i>Strength(s)</i>	50 mg/vial	175 mg/vial
<i>Dosage form</i>	POWDER;IV	POWDER;IV
<i>Labeling comparison<sup>a</sup></i>	See Module 1, Subsection 1.14	See Module 1, Subsection 1.14

The quantitative and qualitative composition of the proposed drug product and the listed drug are shown in Table 38-2. Both products are formulated as a lyophilized powder for injection and they have qualitatively the same composition; both contain the same

(b) (4) (mannitol), and the same pH adjusting agents (hydrochloric acid and sodium hydroxide) as the inactive ingredients. The only difference is the total amount of the lyophilized powder in the vial. However, (b) (4) 10 mg/mL upon reconstitution, because the proposed 175 mg/vial product is reconstituted with 17.7 mL of 0.9% sodium chloride while the listed drug (50 mg/vial) is reconstituted with 5.3 mL of 0.9% sodium chloride.

Table 38-2. Formulations of the proposed drug product and the listed drug

Actavis Levoleucovorin Powder for Injection 175 mg/vial (NDA/505(b)2)			Listed Drug Fusilev <sup>®</sup> for Injection 50 mg/vial		
Component	mg/Vial	Concentration after reconstitution	Component	mg/Vial	Concentration after reconstitution
(b) (4) Calcium Folate Pentahydrate	222 mg (equivalent to 175 mg of Levoleucovorin)	10 mg/mL	(b) (4) Calcium Folate Pentahydrate	64 mg (equivalent to 50 mg of Levoleucovorin)	10 mg/mL
Mannitol Ph.Eur./USP	175 mg	10 mg/mL	Mannitol	50 mg	10 mg/mL
Hydrochloric Acid Ph.Eur./USP	q.s. to target pH	NA	Hydrochloric Acid	q.s. to adjust the pH	NA
Sodium Hydroxide (b) (4) Ph.Eur./USP	q.s. to target pH	NA	Sodium Hydroxide	q.s. to adjust the pH	NA
Reconstituted with 17.7 mL of 0.9% Sodium Chloride Injection			Reconstituted with 5.3 mL of 0.9% Sodium Chloride Injection		

(b) (4) drug product and the listed drug have a target (b) (4). The pharmaceutical development data showed that both drug products have comparable osmolality values in the reconstituted solution as shown in Table 38-3.

**Table 38-3. Osmolality of the reconstituted solutions**

Tested product	Osmolality (mOsm/Kg)				
	After reconstitution with 5.3 ml of 0.9% NaCl solution	After reconstitution with 5.3 ml of 0.9% NaCl solution and further dilution to 0.5 mg/mL in 0.9% NaCl solution	After reconstitution with 5.3 ml of 0.9% NaCl solution and further dilution to 5 mg/mL in 5% NaCl solution	After reconstitution with 5.3 ml of 0.9% NaCl solution and further dilution to 0.5 mg/mL in 5% Dextrose solution	After reconstitution with 5.3 ml of 0.9% NaCl solution and further dilution to 5 mg/mL in 5% Dextrose solution
Levoleucovorin powder for Injection Batch # 3HK001	357	285	323	291	329
Fusilev® Batch 237922	357	286	321	292	325

**Reviewer's Assessment:**

According to 21 CFR 320.22(b), the in vivo bioavailability (BA) or bioequivalence (BE) of certain drug products may be self-evident and the Agency can waive the requirement for the submission of in vivo BA/BE data for such drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident if the drug product meets the following:

- Is a parenteral solution intended solely for administration by injection, and
- Contains the same active and inactive ingredients (b)(4) as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

Based on the information provided in NDA 208723, Levoleucovorin Calcium for Injection 175 mg/vial meets the above requirements for granting the biowaiver request, because:

- The proposed product is a lyophilized powder to be reconstituted to a solution for injection.
- The proposed drug product is qualitatively the same as the listed drug. Though the absolute quantity of the active and inactive ingredient in each vial is different from the listed drug (175 mg versus 50 mg), the final concentration in the reconstituted solution (b)(4) use of different volumes of the reconstitution liquid (17.7 mL versus 5.3 mL). The volume needed for reconstitution was selected (b)(4). The development data are submitted in section 3.2.P.2, and are evaluated by the Drug Product Quality Reviewer.
- The pH and osmolality of the proposed reconstituted product are comparable to that of the listed drug.

Therefore the biowaiver request submitted in NDA 208723, Levoleucovorin Calcium for Injection 175 mg/vial is granted.



13. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

The same formulation was used for development and the proposed commercial product. No bridging is needed.

**OVERALL ASSESSMENT AND SIGNATURES:  
BIOPHARMACEUTICS**

**Reviewer's Assessment and Signature:**

**A waiver of the in vivo bioequivalence study requirement is granted. From a Biopharmaceutics perspective, NDA 208723 for Levoleucovorin Calcium for Injection 175 mg/vial is recommended for APPROVAL.**

Jing Li, Ph.D.      3/21/2016  
Biopharmaceutics Reviewer  
Division of Biopharmaceutics  
Office of New Drug Products  
Office of Pharmaceutical Quality

**Secondary Review Comments and Concurrence:**

**I concur with Dr. Li's assessment and approval recommendation for NDA 208723.**

Okpo Eradiri, Ph.D.      4/11/2016  
Biopharmaceutics Lead (acting)  
Division of Biopharmaceutics  
Office of New Drug Products  
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

14. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response: N/A

Reviewer's Assessment: N/A

2.3.P.7 Container/Closure System

15. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: Please refer to question 34.

Reviewer's Assessment: Please refer to question 34.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

16. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: N/A

Reviewer's Assessment: N/A

17. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

**Applicant's Response:** N/A

**Reviewer's Assessment:** N/A

**OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY**

**Reviewer's Assessment and Signature:**

The submission is recommended for approval on the basis of sterility assurance.

Elizabeth Berr, Ph.D. 08/12/2016  
Branch I  
Division of Microbiology Assessment/OPF

**Secondary Review Comments and Concurrence:**

I concur.  
Erika Pfeiler, Ph.D.  
8/12/2016

**ASSESSMENT OF ENVIRONMENTAL ANALYSIS**

(b) (4) and Actavis (Italy) have each provided a signed/dated statement that the manufacture of bulk drug substance and drug product, respectively, meets applicable environmental laws.

Actavis has provided a signed/dated 11/23/15 statement which claims categorical exclusion for environmental assessment requirements under 21 CFR 2.31(a) in that the proposed drug product will not be administered at higher dosage levels or at different indications than currently approved. Also, no substances with environmental or extraordinary toxicity are in the proposed drug product.

- 18. Is the applicant's claim for categorical exclusion acceptable?
- 19. Is the applicant's Environmental Assessment adequate for approval of the application?

**Reviewer's Assessment:**

Acceptable: The request for categorical exclusion is justified in that both the DS and DP manufacturers certify to meet local environmental laws and the proposed NDA meets the requirements for a 505(b)(2) application.

**OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL****Reviewer's Assessment and Signature:**

Categorical exclusion is granted based on the submitted CMC – DP information.

**William M. Adams, ONDP/DNDP-I/Branch II**

**Date: August 16, 2016**

**Secondary Review Comments and Concurrence:**

**I concur**

**Anamitro Banerjee, PhD**

**Branch Chief (Acting) OPQ/ONDP/DNDP-I/Branch II**

**Date: August 16, 2016**

**I. Review of Common Technical Document-Quality (Ctd-Q) Module 1**

**Labeling & Package Insert - NDA**

**1. Package Insert**

**(a) "Highlights" Section (21CFR 201.57(a))**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use LEVOLEUCOVORIN FOR INJECTION safely and effectively. See full prescribing information for LEVOLEUCOVORIN FOR INJECTION.

LEVOLEUCOVORIN for injection, intravenous use

Initial U.S. Approval: 1952

**---DOSAGE AND ADMINISTRATION---**

Intravenous administration only. Do not administer intrathecally. (2.1)

Levoleucovorin injection is dosed at one-half the usual dose of racemic d,l-leucovorin. (2.1)

**---DOSAGE FORMS AND STRENGTHS---**

For Injection: 175 mg (b) (4) in single-dose vial for reconstitution. (3)

Item	Information Provided in NDA	Reviewer's Assessment
<b>Product title, Drug name (201.57(a)(2))</b>		
Proprietary name and established name	LEVOLEUCOVORIN for injection, intravenous use	Acceptable
Dosage form, route of administration	Lyophilized powder for injection	Acceptable
Controlled drug substance symbol (if applicable)	N/A	N/A
<b>Dosage Forms and Strengths (201.57(a)(8))</b>		
A concise summary of dosage forms and strengths	175 mg/vial of levoleucovorin (formulated as the calcium pentahydrate salt)	Acceptable

**Conclusion:**

The package insert dated 05/05/16 was edited by CMC on 07/07/16; labeling review is continuing.

CMC conclusions below are based on the proposed revisions made by the review team. Acceptable based on the CMC information provided in module 3.2.P.1.

(b) “Full Prescribing Information” Section

Dosage Forms and Strengths (21CFR 201.57(c)(4))

2.6 Preparation and Administration

Preparation

- Reconstitute (b) (4) vial with 17.7 mL of 0.9% Sodium Chloride Injection, USP (b) (4) 10 mg (b) (4) mL. Reconstitution with a sodium chloride solution with preservatives (e.g. benzyl alcohol) has not been studied.
- (b) (4)
- Discard vial if particulate matter or discoloration is observed.
- (b) (4) dilute (b) (4) immediately, to concentrations of 0.5 mg/mL to 5 mg/mL in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.

Storage

(b) (4)

Administration

- Do not co-administer (b) (4) with other agents in the same admixture, due to the risk of precipitation.
- (b) (4) 16 mL (b) (4) (160 mg of levoleucovorin) (b) (4)

3 DOSAGE FORMS AND STRENGTHS

For injection: 175 mg (b) (4) sterile, lyophilized powder in single-dose vial for reconstitution.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	175 mg/vial	Acceptable
Strengths: in metric system	175 mg/vial of levoleucovorin	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	30cc clear, colorless glass vial with stopper and aluminum overseal with (b) (4) disc	Acceptable

**Conclusion:**

Acceptable based on CMC information in modules 3.2.P.1; 3.2.P.2 and 3.2.P.8. Microbiology Reviewer concurs with hold time/conditions for reconstituted and admixture solutions.

**#11: Description (21CFR 201.57(c)(12))**

Levoleucovorin, a folate analog, (b) (4) pharmaceutical active (b) (4)

the chemical (b) (4) calcium (6S)-N- {4-[[2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl] amino]benzoyl}-L-glutamate pentahydrate. The molecular formula is C<sub>20</sub>H<sub>21</sub>CaN<sub>7</sub>O<sub>7</sub> • 5 H<sub>2</sub>O with molecular weight 601.6 amu. The molecular structural is:

[molecular structure]

Levoleucovorin for injection is (b) (4) a sterile lyophilized powder consisting of 175 mg levoleucovorin (equivalent to 222 mg levoleucovorin calcium pentahydrate) and 175 mg mannitol per vial. Sodium hydroxide and/or hydrochloric acid are used to adjust the pH during manufacture. It is (b) (4) intravenous infusion after reconstitution with 17.7 mL of sterile 0.9% sodium chloride injection, USP [see Dosage and Administration (2.6)].

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	None is proposed.	Acceptable
Dosage form and route of administration	Lyophilized powder of injection for IV administration	Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)	175 mg levoleucovorin (formulated with 222 mg levoleucovorin calcium pentahydrate)	Acceptable
Inactive ingredient information	175 mg Mannitol, USP; Sodium Hydroxide, NF/Hydrochloric Acid, NF to adjust pH (b) (4)	Acceptable
Statement of being sterile (if applicable)	Sterile	Acceptable
Pharmacological/ therapeutic class	Folate analog	Acceptable
Chemical name, structural formula, molecular weight	Calcium (6S)-N- {4-[[2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl] amino]benzoyl}-L-glutamate pentahydrate C <sub>20</sub> H <sub>21</sub> CaN <sub>7</sub> O <sub>7</sub> • 5 H <sub>2</sub> O 601.6 amu	Acceptable
If radioactive, statement of important nuclear characteristics.	N/A	Acceptable
Other important chemical or physical properties (such as pKa, solubility, or pH)	None	Acceptable

**Conclusion:**  
Acceptable based on the CMC information provided in modules 3.2.P.1 and 3.2.P.2.1.



# QUALITY ASSESSMENT



### #16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Single-dose vial containing 175 mg of Levoleucovorin formulated as a sterile, preservative-free, off-white to yellowish lyophilized powder. The vial stopper is not made with natural rubber latex.

NDC 0591-4130-54

Store at 25°C (77°F); excursions permitted from 15° to 30° C (59° to 86°F). [See USP Controlled Room Temperature]. Protect from light.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	175 mg levoleucovorin	Acceptable
Available units (e.g., bottles of 100 tablets)	Single dose vial	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	30cc clear, colorless glass vial NDC 0591-4130-54	Acceptable
Special handling (e.g., protect from light, do not freeze)	Protect from light	Acceptable
Storage conditions	USP CRT	Acceptable

### Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name	Made in Italy Distributed by: Actavis Pharma, Inc. Parsippany, NJ 07054 USA [logo] Actavis	Acceptable

### **Conclusion:**

Acceptable based on the CMC information provided in modules 3.2.P.7 and 3.2.P.8.

**2. Container and Carton Labeling**

**1) Immediate Container Label**



*Reviewer's Assessment:*

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence)	None	Acceptable
Strength	None	Acceptable
Route of administration	None	Acceptable
Net contents*	None	Acceptable
Name of all inactive ingredients	None	Acceptable
Lot number	None	Acceptable
Expiration date	None	Acceptable
"Rx only" statement	None	Acceptable
Storage	None	Acceptable
NDC number	None	Acceptable
Bar Code	None	Acceptable
Name of manufacturer/distributor	None	Acceptable
Others	None	Acceptable

**Conclusion:**  
 Acceptable. The Actavis vial label is shown to be comparable to the reference drug (Spectrum Pharmaceutical's Fusilev) vial label and the required information is present. DMEPA made no comments in their review.

**2) Carton Labeling**



(b) (4)

<b>Item</b>	<b>Comments on the Information Provided in NDA</b>	<b>Conclusions</b>
Proprietary name, established name (font size and prominence)	None	Acceptable
Strength	None	Acceptable
Net contents	None	Acceptable
Lot number	None	Acceptable
Expiration date	None	Acceptable
Name of all inactive ingredients	None	Acceptable
Sterility Information	None	Acceptable
"Rx only" statement	None	Acceptable
Storage Conditions	None	Acceptable
NDC number	None	Acceptable
Bar Code	None	Acceptable
Name of manufacturer/distributor	None	Acceptable
"See package insert for dosage information"	Text edit recommended in initial DMEPA review. None for CMC.	Acceptable
"Keep out of reach of children"	None	Acceptable
Route of Administration	None	Acceptable



**Conclusion:**

Acceptable. The Actavis vial label is shown to be comparable to the reference drug (Spectrum Pharmaceuticals's Fusilev) vial label and the required information is present. DMEPA had only 1 comment in their review.

**OVERALL ASSESSMENT AND SIGNATURES: LABELING**

**Reviewer's Assessment and Signature:**

CMC information in the edited versions of the submitted labels and labeling is Adequate to support approval of the NDA.

**William M. Adams, OPQ/ONDP/DNDP-I/Branch II**

**Date: 16 August 2016**

**Secondary Review Comments and Concurrence:**

I concur

**Anamitro Banerjee, PhD**

**Branch Chief (Acting) OPQ/ONDP/DNDP-I/Branch II**

**Date: August 16, 2016**

**II. List of Deficiencies To Be Communicated**

Drug Substance - None

Drug Product - None

Process - None

Facility - None

Biopharmaceutics - None

Microbiology - None

Environmental - None

Label/Labeling - None

### III. Attachments

#### A. Lifecycle Knowledge Management

##### a) Drug Substance

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
Appearance – solid	Synthesis process	Low	Acceptance specification	Acceptable	None
Appearance - solution	Synthesis process	Low	Acceptance specification	Acceptable	None
pH, solution	Synthesis process	Low	Acceptance specification	Acceptable	None
Identity for * calcium salt * levo-enantiomer * leucovorin	Synthesis process	Low	Acceptance specification	Acceptable	None
Assay	Synthesis process	Low	Acceptance specification	Acceptable	None
Related Substances/ Degradants	Synthesis process and material storage	Low	Acceptance specification	Acceptable	None
Inorganic Impurities (b) (4)	Synthesis process	Low	Acceptance specification	Acceptable	None
Moisture Content	Synthesis process	High	Acceptance specification	Acceptable	None
Residual Solvents	Synthesis process	High	Acceptance specification	Acceptable	None
Endotoxins	Synthesis process	Low	Acceptance specification	Acceptable	None
Retest Period/ Storage Condition	Synthesis process	High	Supplier type II DMF (b) (4)	Acceptable	(b) (4) month retest period* if stored between (b) (4) (b) (4) closed container-closure system used for storage and distribution. *DMF was granted (b) (4) months at (b) (4) with (b) (4)

b) Process, Drug Product, Microbiology

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
Sterility	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container/closure</li> <li>• Process parameter</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	High	Sterile filtration process	Acceptable	Continue stability monitoring post approval
Endotoxin Pyrogen	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container/closure</li> <li>• Process parameter</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	Medium	Control of components, (b) (4)	Acceptable	Continue stability monitoring post approval
Appearance - lyophilized powder	Purity of drug substance, excipients (b) (4)	High	Raw materials specifications	Acceptable	None
Identity, Leucovorin	Drug substance quality	High	Drug product specifications	Acceptable	Enantiomeric identity is based on drug substance release testing
Assay, mg/vial	Manufacturing process	High	Raw materials weigh-out	Acceptable	None
Related Substances/ Degradants	Drug substance quality, manufacturing process and drug product storage	High	Raw material specifications; manufacturing process parameters; and long term stability studies	Acceptable	Initial studies reported only largest impurity
Moisture Content	Manufacturing process	High	Lyophilization process development and process controls	Acceptable	None
Reconstitution Time	Manufacturing process	Low	Lyophilization process development and process controls	Acceptable	None
Visible Particles	Manufacturing process	Low	Lyophilization process development and process controls	Acceptable	None
Appearance - Reconstituted Solution	Manufacturing process	Low	Lyophilization process development and process controls	Acceptable	None

Particulate Matter	Manufacturing process	Low	Lyophilization process controls	Acceptable	None
pH	Manufacturing process	Low	Manufacturing process controls	Acceptable	None
Analytical methods and criteria	Method changes	High	Method validation studies	Acceptable	Method and criteria for related substances were revised during NDA development
Enantiomeric Identity	Drug substance quality	High	Product development studies and drug substance specification	Acceptable	Enantiomeric identity is based on drug substance release testing
Osmolality	Formulation	Low	Product development studies	Acceptable	None
In-Use Stability	Formulation	High	Product development studies	Acceptable	None
Drug Product Shelf life	Formulation and manufacturing process	High	Product development and long term stability studies	Acceptable	Applicant requested (b) (4) months to match RLD, but was granted 18 months based on submitted studies
Label Storage Conditions	Formulation, manufacturing process	High	Product development and long term stability studies	Acceptable	None

From: Steven Kinsley  
To: RegulatoryAffairsUS@actavis.com  
Cc: Rebecca Cohen  
Subject: NDA 208723 CMC Information Request 7-27-16  
Date: July 27, 2016

Dear Joann,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA Wednesday, August 10, 2016

We note that your response (dated 06/10/2016) to IR#16 did not include discussion of any other rejects (and total rejects) that were found during the manufacturing process. Please include relevant discussion on overall rejects other than those found during integrity test.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,

Steve

Steven Kinsley, Ph.D.  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
CDER/FDA  
240-402-2773



Steven  
Kinsley

Digitally signed by Steven Kinsley  
Date: 7/27/2016 09:20:28AM  
GUID: 555cc3bc000836e194b17e8bf695ce5f



From: Steven Kinsley  
To: RegulatoryAffairsUS@actavis.com  
Cc: Rebecca Cohen  
Subject: NDA 208723 CMC Information Request 7-22-16  
Date: July 22, 2016

Dear Joann,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA Wednesday, August 10, 2016

The justification for bioburden sampling following the (b) (4)  
provided in the applicant's submission dated June 10, 2016 is acknowledged.

Although (b) (4)

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,

Steve

Steven Kinsley, Ph.D.  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
CDER/FDA  
240-402-2773

This document is a PDF copy of an e-mail sent to the e-mail address and on the date given above.

**Steven Kinsley -A**

Digitally signed by Steven Kinsley -A  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Steven Kinsley -A,  
0.9.2342.19200300.100.1.1=2001720189  
Date: 2016.07.22 09:54:25 -04'00'

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

**Application #: 208723      Submission Type: NDA**

**Established/Proper Name:**  
**Levoleucovorin for injection**  
 (non Proprietary Name of the drug product)

**Applicant: Actavis LLC      Letter Date: 12/1/2015**

**Dosage Form: Powder for Injection.**

**Chemical Type:                      Stamp Date: 12/1/2015**

**Strength: 175 mg base/vial**

PLEASE PROVIDE YOUR INPUT AS NEEDED. IF NO COMMENTS, DELETE THE "INPUT NEED" COMMENT FOR YOUR SECTION. LEAVE A COMMENT WHERE APPROPRIATE.

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	<b>DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?</b>	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Not Applicable
3.	Are there any <b>potential review</b> issues to be forwarded to the Applicant, not including any filing comments stated above?			Not identified at the filing review stage

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
2.	Botanical <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
3.	Naturally-derived Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.	PET Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
6.	PEPFAR Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.	Sterile Drug Product	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
8.	Transdermal <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.	Pediatric form/dose <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.	Locally acting drug <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
11.	Lyophilized product <sup>1</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
12.	First generic <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Solid dispersion product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
14.	Oral disintegrating tablet <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
15.	Modified release product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
16.	Liposome product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Biosimilar product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
18.	Combination Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
19.	Other	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Regulatory Considerations</b>				
20.	USAN Name Assigned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
21.	End of Phase II/Pre-NDA Agreements	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
22.	SPOTS (Special Products On-line Tracking System)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
24.	Comparability Protocol(s) <sup>2</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
25.	Other	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Quality Considerations</b>				
26.	Drug Substance Overage	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
27.	Design Space	Formulation	<input type="checkbox"/>	<input checked="" type="checkbox"/>
28.		Process	<input type="checkbox"/>	<input checked="" type="checkbox"/>
29.		Analytical Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>
30.		Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>
31.	Real Time Release Testing (RTRT)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
32.	Parametric Release in lieu of Sterility Testing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
33.	Alternative Microbiological Test Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
34.	Process Analytical Technology <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	<input checked="" type="checkbox"/>	<input type="checkbox"/>
36.		Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>
37.		Microbial	<input type="checkbox"/>	<input checked="" type="checkbox"/>
38.	Unique analytical methodology <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
39.	Excipients of Human or Animal Origin	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
40.	Novel Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
41.	Nanomaterials <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
42.	Hold Times Exceeding 30 Days	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
43.	Genotoxic Impurities or Structural Alerts	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
44.	Continuous Manufacturing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
45.	Other unique manufacturing process <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
47.	New delivery system or dosage form <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
48.	Novel BE study designs	<input type="checkbox"/>	<input checked="" type="checkbox"/>	A biowaiver request is submitted
49.	New product design <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
50.	Other	<input type="checkbox"/>	<input type="checkbox"/>	

<sup>1</sup>Contact Office of Testing and Research for review team considerations

<sup>2</sup>Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
<b>GENERAL/ADMINISTRATIVE</b>					
1.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

**OFFICE OF PHARMACEUTICAL QUALITY  
FILING REVIEW**

<b>C. FILING CONSIDERATIONS</b>				
	review? <input type="checkbox"/> Drug Substance <input type="checkbox"/> Drug Product <input type="checkbox"/> Appendices <ul style="list-style-type: none"> <li><input type="checkbox"/> Facilities and Equipment</li> <li><input type="checkbox"/> Adventitious Agents Safety Evaluation</li> <li><input type="checkbox"/> Novel Excipients</li> </ul> <input type="checkbox"/> Regional Information <ul style="list-style-type: none"> <li><input type="checkbox"/> Executed Batch Records</li> <li><input type="checkbox"/> Method Validation Package</li> <li><input type="checkbox"/> Comparability Protocols</li> </ul>			
<b>FACILITY INFORMATION</b>				
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: <ul style="list-style-type: none"> <li><input type="checkbox"/> Name of facility,</li> <li><input type="checkbox"/> Full address of facility including street, city, state, country</li> <li><input type="checkbox"/> FEI number for facility (if previously registered with FDA)</li> <li><input type="checkbox"/> Full name and title, telephone, fax number and email for on-site contact person.</li> <li><input type="checkbox"/> Is the manufacturing responsibility and function identified for each facility, and</li> <li><input type="checkbox"/> DMF number (if applicable)</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: <ul style="list-style-type: none"> <li><input type="checkbox"/> Is a manufacturing schedule provided?</li> <li><input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle?</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>DRUG SUBSTANCE INFORMATION</b>				
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

C. FILING CONSIDERATIONS				
	<ul style="list-style-type: none"> <li><input type="checkbox"/> general information</li> <li><input type="checkbox"/> manufacture                             <ul style="list-style-type: none"> <li>○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)</li> <li>○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only</li> <li>○ Includes complete description of product lots and their uses during development – BLA only</li> </ul> </li> <li><input type="checkbox"/> characterization of drug substance</li> <li><input type="checkbox"/> control of drug substance                             <ul style="list-style-type: none"> <li>○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred)</li> <li>○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only</li> </ul> </li> <li><input type="checkbox"/> reference standards or materials</li> <li><input type="checkbox"/> container closure system</li> <li><input type="checkbox"/> stability                             <ul style="list-style-type: none"> <li>○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment</li> </ul> </li> </ul>			
DRUG PRODUCT INFORMATION				
7.	<p>Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Description and Composition of the Drug Product</li> <li><input type="checkbox"/> Pharmaceutical Development                             <ul style="list-style-type: none"> <li>○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots</li> <li>○ Includes complete description of product lots and their uses during development</li> </ul> </li> <li><input type="checkbox"/> Manufacture                             <ul style="list-style-type: none"> <li>○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter?</li> </ul> </li> <li><input type="checkbox"/> Control of Excipients</li> </ul>	☒	<input type="checkbox"/>	<input type="checkbox"/>

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

C. FILING CONSIDERATIONS					
	<input type="checkbox"/> <b>Control of Drug Product</b> <ul style="list-style-type: none"> <li>○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)</li> <li>○ Includes data to demonstrate process consistency (i.e. data on process validation lots)</li> <li>○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred)</li> <li>○ Analytical validation package for release test procedures, including dissolution</li> </ul> <input type="checkbox"/> <b>Reference Standards or Materials</b> <input type="checkbox"/> <b>Container Closure System</b> <ul style="list-style-type: none"> <li>○ Include data outlined in container closure guidance document</li> </ul> <input type="checkbox"/> <b>Stability</b> <ul style="list-style-type: none"> <li>○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment</li> </ul> <input type="checkbox"/> <b>APPENDICES</b> <input type="checkbox"/> <b>REGIONAL INFORMATION</b>				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: <ul style="list-style-type: none"> <li>• Does the application contain the complete BA/BE data?</li> <li>• Are the PK files in the correct format?</li> <li>• Is an inspection request needed for the BE study(ies) and complete clinical site information provided?</li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Division of Biopharmaceutics is not responsible for reviewing the BA/BE studies per current MOU.  The Applicant submitted a biowaiver request.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The formulation was developed based on characterization of the listed drug, and there was no formulation change during development.
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	A biowaiver request was submitted in accordance with 21 CFR 320.22(b)(1)(i). The comparisons in formulation, pH and osmolality between the proposed and the listed drug products are provided.
11.	For a modified release dosage form, does the application include information/data on the in-vitro	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

C. FILING CONSIDERATIONS				
	alcohol dose-dumping potential?			
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
REGIONAL INFORMATION AND APPENDICES				
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? <ul style="list-style-type: none"> <li><input type="checkbox"/> facilities and equipment                             <ul style="list-style-type: none"> <li>○ manufacturing flow; adjacent areas</li> <li>○ other products in facility</li> <li>○ equipment dedication, preparation, sterilization and storage</li> <li>○ procedures and design features to prevent contamination and cross-contamination</li> </ul> </li> <li><input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.:                             <ul style="list-style-type: none"> <li>○ avoidance and control procedures</li> <li>○ cell line qualification</li> <li>○ other materials of biological origin</li> <li>○ viral testing of unprocessed bulk</li> <li>○ viral clearance studies</li> <li>○ testing at appropriate stages of production</li> </ul> </li> <li><input type="checkbox"/> novel excipients</li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
17.	Are the following information available for Biotech Products: <ul style="list-style-type: none"> <li><input type="checkbox"/> Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example:                             <ul style="list-style-type: none"> <li>○ LAL instead of rabbit pyrogen</li> <li>○ Mycoplasma</li> </ul> </li> </ul> Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples			

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PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN
<b>Sterility</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	<ul style="list-style-type: none"> <li>• Non-sterile unit(s)</li> </ul>	4	Others (5)	5	100
<b>Endotoxin Pyrogen</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	<ul style="list-style-type: none"> <li>• Excessive Endotoxin Levels</li> </ul>	Others (2)	4	4	32
<b>Assay (API), stability</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	<ul style="list-style-type: none"> <li>• Impurity formation due to excipient reactions or unspecified reactions</li> <li>• (b) (4)</li> <li>• (b) (4)</li> <li>• Organic solvents</li> </ul>	Highly stable drug (1)	2	1	2
<b>Physical stability (solid state) lyophilized small molecule products</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	<ul style="list-style-type: none"> <li>• (b) (4)</li> <li>Lower solubility/inaccurate dosing or degradation</li> </ul>	Amorphous (4)	2	4	32
<b>Uniformity of Dose (Fill Volume/deliverable volume)</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	<ul style="list-style-type: none"> <li>• Insufficient dose</li> </ul>	2	(b) (4) (2)	2	8
<b>Osmolality</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	<ul style="list-style-type: none"> <li>• Irritation</li> <li>• Edema</li> </ul>	2	(b) (4) (3)	3	12

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<b>Particulate matter (non aggregate for solution only)</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	<ul style="list-style-type: none"> <li>• Irritation</li> <li>• Embolism</li> </ul>	3	IV (5)	3	45
<b>Leachable extractables</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	<ul style="list-style-type: none"> <li>• Generation of impurities</li> </ul>	2	4	3	24
<b>Re-dispersability /reconstitution time</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	(b) (4)	4	(b) (4) 3)	(b) (4)	(b) (4)
<b>Moisture content (lyophilized)</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment's</li> <li>• Site</li> </ul>	(b) (4)	3	4	2	24
<b>Appearance</b> (b) (4)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	(b) (4)	3	4	(b) (4)	(b) (4)
		<ul style="list-style-type: none"> <li>• Degradation</li> </ul>			Stability (4)	48
<b>Appearance (Color/turbidity)</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	<ul style="list-style-type: none"> <li>• Degradation</li> </ul>	3	3	1	9

**1D: Product Design FMECA – Parenteral Drug Products**

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Joyce Crich, Ph.D.

Acting QAL, ONDP, Division I, Branch II

Completed on Feb 2, 2106\*

\*This filling review was completed on Feb 2, 2016. However, it was not placed in Panorama by then.

Joyce  
Crich -S

Digitally signed by Joyce Crich -S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
cn=Joyce Crich -S,  
0.9.2342.19200300.100.1.1=2000  
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