CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210737Orig1s000
210737Orig2s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 210737
Review #1

Drug Name/Dosage Form	methotrexate injection
Strength	25 mg/mL, with multiple doses from 7.5 to 25.0 mg
Route of Administration	subcutaneous injection (into thigh or abdomen)
Rx/OTC Dispensed	Rx
Applicant	Cumberland Pharmaceuticals Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	*05-NOV-2018*	*All*
Amendment	*10-DEC-2018*	*Biopharmaceutics*
Amendment	*18-DEC-2018*	*Biopharmaceutics*
Amendment	*08-JAN-2019*	*Biopharmaceutics and microbiology*
Amendment	*13-MAR-2019*	*Microbiology*
Amendment	*10-MAY-2019*	*Drug product, microbiology, process/facilities*
Amendment	*12-JUN-2019*	*Microbiology*
Amendment	*26-JUN-2019*	*Drug product*
Amendment	*28-JUN-2019*	*Microbiology*
Amendment	*05-JUL-2019*	*Drug product, microbiology*
Amendment	*08-JUL-2019*	*Process/facilities*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Larry Perez	Donna Christner
Drug Product	Jizhou Wang	Julia Pinto
Process	Ted Chang	Yong Hu
Microbiology	Catherine Gilbert	Paul Dexter
Facility	Ted Chang	Yong Hu
Biopharmaceutics	Bryan Ericksen	Haritha Mandula
Regulatory Business	Florence Aisida/	

Process Manager	Grace Gnall	
Application Technical Lead	Craig M. Bertha	
Laboratory (OTR)	N/A	
ORA Lead		
Environmental	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Adequate	04-APR-2019	
	Type II			Adequate	26-NOV-2018	
	Type III			Adequate	19-MAY-2014	Via DMF (b) (4)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

2. CONSULTS

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

Executive Summary

I. Recommendations and Conclusion on Approvability

The application is recommended for **approval**; however, the following labeling changes will be recommended during labeling negotiations:

1. The DOSAGE FORMS AND STRENGTHS section should be revised to include a more complete description of the identifying characteristics of the dosage form (e.g., as is currently in the DESCRIPTION section).[1]

2. The DESCRIPTION section should be revised to include the quantity or proportion of each active ingredient (e.g., as is currently in the DOSAGE FORMS AND STRENGTHS section) and list the target pH.[1]

3. The cartons should be revised to list the inactive ingredients of the formulation and indicate that it is sterile, as stated in the DESCRIPTION section.

II. Summary of Quality Assessments

A. Product Overview

The combination product methotrexate injection is indicated for the management of patients with severe, active rheumatoid arthritis (RA) and polyarticular juvenile idiopathic arthritis (pJIA), who are intolerant of or had an inadequate response to first-line therapy. The sterile injection drug product is formulated with a concentration of 25.00 mg/mL (b) (4) in water adjusted to pH 8.2. There are 8 strengths (determined by fill) in unit dose pre-filled glass syringes with staked needles, (b) (4) a plunger rod and passage safety cover for the needle which is removed prior to use. The formulation is sterilized (b) (4) Based on the type of syringe being used, a consult to CDRH is unnecessary for this combination product.

	⇦ Total Number of Comparability Protocols (ANDA only)

Proposed Indication(s) including Intended Patient Population	indicated for the management of patients with severe, active rheumatoid arthritis (RA) and polyarticular juvenile idiopathic arthritis (pJIA), who are intolerant of or had an inadequate response to first-line therapy
Duration of Treatment	chronic

[1] Note, however that the applicant has formatted the DOSAGE FORMS AND STRENGTHS AND DESCRIPTION sections as per the already approved methotrexate injections (b) (4) Otrexup). This will be discussed during labeling negotiations with the clinical Division and DMEPA, with regard to consistency.

Maximum Daily Dose	doses adjusted gradually to achieve optimal response; no maximum doses listed in labeling
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

The drug substance is Methotrexate, is an established and characterized molecule containing a single chiral center (a single enantiomer) at the (b) (4) with the (2*S*)-configuration. As per the USP monograph, the applicant includes a test to assure sufficient enantiomeric purity of the drug substance (b) (4) The drug substance for this NDA is manufactured by (b) ( ) Information supporting the CMC for the drug substance was included by reference to (b) (4) DMF (b) (4) which has been recently reviewed and found to be acceptable for injection drug products. Methotrexate is a compendial drug substance and the release specification listed by the NDA applicant complies with the current USP monograph. The retest period of (b) (4) months is supported by data in the DMF, when the drug substance is stored at (b) (4)

The drug product consists of a (b) (4) prefilled syringe (PFS) injection composed of drug substance Methotrexate USP dissolved in an isotonic aqueous solution of sodium chloride, adjusted to a mildly basic pH target (8.2) with sodium hydroxide. There had initially been some concern for the potential of the basic pH formulation to promote racemization of the single chiral center of methotrexate. However, from a chemical perspective, this is unlikely. Once both carboxylic acid moieties of methotrexate are depronated in the mildly basic pH, the proton on the chiral carbon would have no propensity to deprotonate allowing racemization. In addition, the USP monograph standard for methotrexate injections does not include a test and acceptance criteria to monitor enantiomeric purity and the Agency has not required such a test be included for the multiple methotrexate injection applications approved thus far.

The sterile clear yellow solution is packaged in a 1 mL glass syringe with a staked needle and a plunger rod with a (b) (4) stopper (b) (4) plunger) as the primary container and Needle Safety Device w/finger flange as a secondary packaging system. The entire drug product system is packaged in an individual carton that protects the product from exposure to light. The Sponsor has manufactured a number of batches of Methotrexate Injection 25 mg/mL, at various scales throughout development including registration batches and batches at the intended commercial scale. The quality of the drug product is adequately controlled as per official USP monograph, USP General Chapters, Eur. Ph. General Chapters, and ICH guidelines. The long term stability data **justified a drug product shelf-life or expiry period of 30 months.**

With regard to extractables (E) and leachables (L), the applicant's study conditions were vigorous enough to extract all the possible E/L in the drug product. The screening methods had the sensitivity to be able to detect organic E/L that might give a patient exposure at a proposed safety concern threshold (SCT) of 1.5 µg/day, which is the limit recommended in the current PQRI draft guideline for E/L for parenteral drug products.[2] The SCT is used to calculate the necessary E/L method sensitivity, which is defined as the analytical evaluation threshold (AET). With these methods no leachables were detected that would have lead to an exposure above this quantity and no "special case" compounds were identified (*vide infra*).

Initially, there had been some concern with regard to the applicant's use of an SCT of 1.5 mcg/day and the corresponding AET for evaluation of the leachables for the drug product. Currently, the Agency has a final Guidance for Industry entitled *Container Closure Systems for Packaging Human Drugs and Biologics; Chemistry, Manufacturing, and Controls Documentation* (May 1999). Section E.1 provides recommendations for injectable drug products and states that for elastomeric components, such as a syringe plunger, "data showing that a component meets the requirements of USP Elastomeric Closures for Injections will typically be considered sufficient evidence of safety." Note that the plunger used for NDA 210737 does comply with that USP chapter (see review of DMF (b) (4) dated 29-MAY-2014).

More recently, the USP proposed three general information chapters in the Pharmacopeial Forum 39(5) that covered <1663> *Assessment of Extractable Associated with Pharmaceutical Packaging Delivery Systems,* <1664> *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging Delivery Systems*, and <1664.1> *Orally Inhaled and Nasal Drug Products (OINDPs)*. The Agency provided input into the content and recommendations of these informational chapters. These informational chapters were finalized and appear in the current USP. Note that for OINDPs the SCT is set at 0.15 mcg/day to calculate AET, as a lower threshold (than for other liquid/solution drug products) was considered appropriate regarding the direct delivery of some of these products to diseased organs of a sensitive patient population. The approach to the assessment of extractables/leachables (E/L) outlined in these USP informational chapters follows the principles put forth in the final PQRI document of August 2006 entitled *Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products.* The recommendations in this document outlined a safety concern threshold, or SCT, which is defined as the threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effects. The SCT is then used to calculate the AET specific for a drug product and its dosing regimen. The AET is defined as the threshold at or above which a chemist should begin to identify a particular leachable and/or extractable and report it for

[2] Product Quality Research Institute (PQRI) is a non-profit collaboration of pharmaceutical industry, academia and the FDA with the goal of creating best practice and conducting joint research in support of pharmaceutical regulation; see draft E/L recommendations of 2019 document entitled *Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products*.

potential toxicological assessment. This PQRI document and USP <1664> and <1664.1> refer to "special case" compounds of concern specifically with respect to OINDPs: these include polynuclear aromatic hydrocarbons (PAHs or PNAs), N-nitrosamines, and 2-mercaptobenzothiazole, which were of concern historically as they were found in previously approved inhalation aerosol (metered dose inhaler) drug products that had chlorofluorocarbon propellant-based formulations. The common SCT of 0.15 mcg/day (and corresponding calculated AETs) are *not* appropriate for these special case compounds for OINDPs, and more sensitive analytical methods are needed to characterize and control their quantities as E/Ls.

The current application for an injection of methotrexate in a pre-filled syringe (PFS) uses a (b) (4) syringe fitted with a (b) (4) plunger, a PFS that has been approved for use in other aqueous based injection products currently marketed for chronic use. The applicant has followed the approach to E/L outlined in the latest PQRI document for parenteral drug products of 2019,[2] which recommends an SCT of 1.5 mcg/day for organic leachables to calculate AETs. For OINDPs, PQRI and the USP informational chapters recommend it be required to characterize and routinely control drug products for special case E/L with methods of sufficient sensitivity below the typical AET (i.e., with SCT lower than 0.15 mcg/day). However, for parenteral products, additional characterization with more sensitive methods would only be warranted if a leachable was identified as a special case compound with methods having AETs calculated from the recommended SCT of 1.5 mcg/day. The E/L studies reported in this NDA have *not* identified any special case compounds as extractables or leachables with AETs based on that SCT. Thus, from a quality perspective, the control of E/L for this drug product is considered to be adequate. In addition, the pharmacology/toxicology team in DPARP has also confirmed that they have no concerns with respect to the E/L for this application and completely agree with the above assessment.

From a biopharmaceutical perspective, the drug product is a parenteral solution that has the same active and inactive ingredients as compared to the listed drug (Otrexup), but with two differences. Specifically, the applicant's drug product contains (b) (4) mg/mL of sodium chloride and the listed drug contains (b) (4) mg/mL. Also, the target pH of the applicant's product formulation is 8.2 whereas the listed drug is 8.0. (b) (4) The osmolality difference between this product and the listed drug product are not expected to impact bioavailability. The pH difference is considered to be of no consequence when considering the pKa's of the methotrexate molecule. In summary, a bridge between the proposed drug product and the listed drug has been established in accordance with 21 CFR 320.24(b)(6).

The drug product is (b) (4) sterilized (b) (4) filled into syringes. (b) (4)

(b) (4) The syringes are purchased already (b) (4) The batch size for manufacture ranges from (b) (4) which will be adjusted to produce (b) (4) syringes per batch, depending on the strength. The information describing the microbiological-related controls and processes was initially found to be quite deficient and resulted in multiple information requests and responses from the applicant to be evaluated. In fact, some of the development work was found to still be in progress, e.g., the container closure integrity (CCI) method development and validation. Once the CCI information was provided, it was found to be adequate, however. The applicant may use multiple drug substance batches to prepare drug product, but nevertheless, the (b) (4) validation studies will support the range of processing time being proposed. The information provided regarding the floorplans, manufacturing area design, and personnel/material movement were found to be adequate in order to reduce the risk of microbial contamination. Additional information provided during the review supported the adequacy of the applicant's microbial monitoring of the manufacturing area. The applicant is using the (b) (4) manufacturer's recommendation for the (b) (4) integrity test for their batch size range, and have validated the capability of the (b) (4) microbial challenge, which is acceptable. The maximum holding periods for (b) (4) solution are also found to be adequate to support the microbiological quality of the drug product. Note that the DMF (b) (4) was found to be adequate. The endotoxin exposure of patients receiving the maximum dose was found to be within the USP <85> recommendation of 100 endotoxin units/m^2/hr, and the sterility testing performed as per USP <71> was found to be acceptable. A review of the executed batch records has confirmed that validated (b) (4) manufacturing processes were used to prepare the registration batches supporting the application. Labeling also includes instructions to assure microbiological quality of the drug product when used. Finally, the applicant has agreed to modify the routine stability protocol to test the drug product for microbiological quality at the expiry, currently at 30 months.

The manufacturing process of this drug-device combination product includes (b) (4)

(b) (4)

The drug product is contract-manufactured at (b) (4) The drug substance (DMF (b) (4) is manufactured by (b) (4) functions as the alternate site for API release and stability testing. All three facilities are recommended "Approve Facility." In addition, an assessment by the CDRH Division of Health Technology 3C has concluded that the application can be approved, with respect to compliance with the 21 CFR 820 regulations for combination products.

In conclusion, the application is recommended for approval by OPQ, from a quality perspective. However, there are several labeling changes that are recommended (see section I above).

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

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Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: (b) (4) Established Name: methotrexate	Acceptable
Dosage form, route of administration	Dosage: Solution Route: subcutaneous injection	Acceptable Acceptable
Controlled drug substance symbol (if applicable)	N/A	Acceptable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Single-dose pre-filled syringe (in a needle safety device) delivering methotrexate in the following dosage strengths: 7.5mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg and 25 mg	Acceptable

Conclusion: Acceptable with the required data elements as summarized above

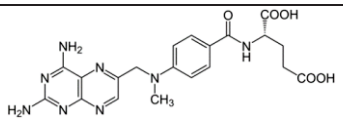
(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	prefilled syringe (in a needle safety device) to administer methotrexate solution	Acceptable
Strengths: in metric system	7.5 mg, 10 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg and 25 mg	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Not provided *Clear yellow solution, essentially free of visible foreign matter*	Not Acceptable

Conclusion: Not Acceptable with the required data elements as summarized above

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

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	(b) (4) methotrexate	Acceptable
Dosage form and route of administration	sterile, preservative-free, solution in a pre-filled syringe	Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)	Not provided *7.5 mg, 10 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg and 25 mg*	Not Acceptable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	sodium chloride, sodium hydroxide and water for injection, USP	Acceptable
Statement of being sterile (if applicable)	Yes	Acceptable
Pharmacological/ therapeutic class	a folate analog metabolic inhibitor	
Chemical name, structural formula, molecular weight	 [N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-Lglutamic acid Molecular Formula: C22H25NO6 Molecular weight: 454.45	Acceptable
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	N/A	N/A

Conclusion: Acceptable with the required data elements as summarized above

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

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	7.5mg/0.3mL, 10mg/0.4mL, 12.5 mg/0.5 mL, 15mg/0.6mL, 17.5mg/0.7mL, 20mg/0.8mL, 22.5mg/0.9 mL and 25 mg/mL	Acceptable
Available units (e.g., bottles of 100 tablets)	Pre-filled syringe with 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 or 1.0 mL	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC number provide for Carton of 1 and Carton of (b) (4) for each strength	Acceptable
Special handling (e.g., protect from light, do not freeze)	PROTECT FROM LIGHT (keep in carton until the time of use)	Acceptable
Storage conditions	Store between 20˚C to 25˚C (68˚F to 77˚F); excursions permitted to 15˚C to 30˚C (59˚F to 86˚F).	Acceptable

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

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	**Manufactured for:** Cumberland Pharmaceuticals Inc. Nashville, TN 37203 (b) (4) is a trademark of Cumberland Pharmaceuticals Inc.	Acceptable

Conclusion: Acceptable with the required data elements as summarized above

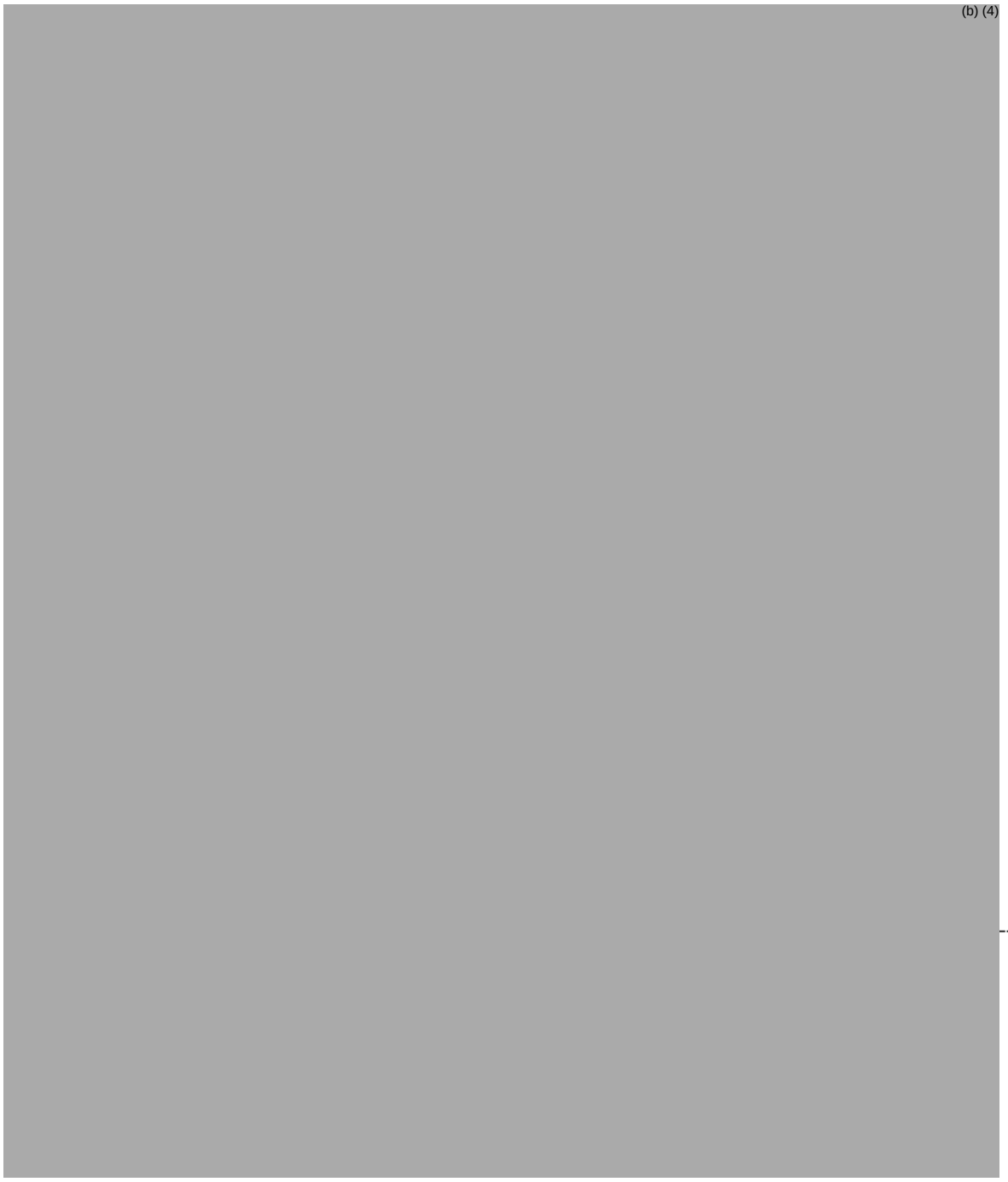
2. Labels

1) Immediate Container Label

Syringe label for all Doses

(b) (4)

(b) (4)



Reviewer's Assessment: Acceptable. See summary in the table below.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	(b) (4) (methotrexate)	Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	7.5mg/0.3mL, 10mg/0.4mL, 12.5 mg/0.5 mL, 15mg/0.6mL, 17.5mg/0.7mL, 20mg/0.8mL, 22.5mg/0.9 mL and 25 mg/mL	Acceptable
Net contents (21 CFR 201.51(a))	See above	Acceptable
Lot number per 21 CFR 201.18	Yes	Acceptable
Expiration date per 21 CFR 201.17	Yes	Acceptable
"Rx only" statement per 21 CFR 201.100(b)(1)	Yes	Acceptable
Storage (not required)	No	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	Yes	Acceptable
Name of manufacturer/distributor	Cumberland Pharmaceuticals Inc.	Acceptable
Others	N/A	N/A

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Acceptable

2) Cartons

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

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	(b) (4) (methotrexate)	Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	7.5mg/0.3mL, 10mg/0.4mL, 12.5 mg/0.5 mL, 15mg/0.6mL, 17.5mg/0.7mL, 20mg/0.8mL, 22.5mg/0.9 mL and 25 mg/mL	Acceptable
Net contents (21 CFR 201.51(a))	See above	Acceptable
Lot number per 21 CFR 201.18	Yes	Acceptable
Expiration date per 21 CFR 201.17	Yes	Acceptable
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Not provided	Not Acceptable
Sterility Information (if applicable)	Not provided	Not Acceptable
"Rx only" statement per 21 CFR 201.100(b)(1)	Yes	Acceptable
Storage Conditions	Store between 20°C and 25°C (68°F - 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) **Protect from light.**	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	Yes	Acceptable
Name of manufacturer/distributor	Cumberland Pharmaceuticals Inc	Acceptable
"See package insert for dosage information" (21 CFR 201.55)	Yes	Acceptable
"Keep out of reach of children" (optional for Rx, required for OTC)	Not applicable for Rx drugs	Acceptable
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	For subcutaneous use only	Acceptable

Conclusion: Not acceptable

II. List of Deficiencies To Be Communicated

A. Drug Substance
B. Drug Product
C. Process/Facility
D. Biopharmaceutics
E. Microbiology
F. Label/Labeling

Jizhou Wang

Digitally signed by Jizhou Wang
Date: 7/24/2019 11:25:27AM
GUID: 53160853000083c4052c25f3a3cf964a

Julia Pinto

Digitally signed by Julia Pinto
Date: 7/24/2019 11:26:33AM
GUID: 5050dbcb00001294a888a4bdc20a3a58

BIOPHARMACEUTICS

Product Background:
This Section 505(b)(2) submission is for Methotrexate for Injection in a (b) (4) prefilled syringe for subcutaneous use in the treatment of severe, active rheumatoid arthritis (RA) and polyarticular juvenile idiopathic arthritis (PJIA), who are intolerant of or had an inadequate response to first-line therapy and symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy. The prefilled syringe will be available in doses ranging from 7.5 mg to 25 mg.

NDA: 210737

Drug Product Name / Strength: Methotrexate for Injection / 7.5 mg, 10 mg, 12.5 mg, 15 mg, (b) (4) 20 mg, (b) (4) 25 mg

Route of Administration: Subcutaneous Injection

Applicant Name: Cumberland Pharmaceuticals Inc.

Review Summary:

List Submissions being reviewed (table):

11/05/2018	ANDA 210737/Sequence 0008/Original Submission
12/10/2018	ANDA 210737/Sequence 0009/Waiver Request
12/18/2018	ANDA 210737/Sequence 0010/Response to Information Request
01/08/2019	ANDA 210737/Sequence 0011/Response to Information Request

Highlight Key Outstanding Issues from Last Cycle:

In an information request dated December 17, 2018, the Agency communicated the following comment:

> Provide osmolality values in triplicate for both the proposed drug and listed drug to demonstrate that the products are isosmotic.

Concise Description Outstanding Issues Remaining:

None

Bridging of Formulations

Reviewer's Assessment:

Only one formulation was mentioned in the Application; therefore, no formulations need to be bridged.

Biowaiver Request

The original submission in Sequence 0008 included neither a biowaiver request nor a summary of biopharmaceutics in Module 2.7.

In an information request communicated on December 3, 2018, the Agency asked the Applicant to submit a biowaiver request. On December 10, 2018, the Applicant submitted the biowaiver request in Sequence 0009, Module 1.12. The request is based on 21 CFR 320.24(b)(6). The product is a parenteral solution with the same active and inactive ingredients as the Listed Drug (LD) with one quantitative difference. The Applicant's product contains (b) (4) mg/mL of sodium chloride and the LD contains (b) (4) mg/mL. The pH of the Applicant's product is 8.2, compared to the LD, with a pH of 8.0. The two products are compared in the following table.

Table 1.12.13-1 Comparison of MTX Injection and Otrexup PFS Characteristics

Characteristic	MTX SC Injection								Otrexup Injection PFS					
Description	Sterile, preservative-free, (b) (4) solution								Sterile, preservative-free, (b) (4) solution					
Composition														
Volume (mL)	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1	0.4	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
MTX, USP (mg)	(b) (4)								10	15		20		25
Sodium Chloride, USP (mg)									1.96	(b) (4)				
Sodium Hydroxide, USP	q.s. to pH 8.2 (b) (4)								q.s. to pH 8.0 (pH adjust)					
Hydrochloric acid	--								q.s. to pH 8.0 (pH adjust)					
pH	8.2								8					
Osmolarity	Isosmotic								Isosmotic					
Drug concentration (mg/mL)	25	25	25	25	25	25	25	25	25	25	25	25	25	25

MTX= methotrexate; SC= subcutaneous; PFS= prefilled syringe; mL= milliliter; USP= United States Pharmacopeia; mg= milligram; q.s.= quantity sufficient

The Applicant did not provide data to support the designation of "isosmotic" in the above table.

On December 12, 2018, an information request was communicated to the Applicant to submit the Summary of Biopharmaceutic Studies and Associated Analytical Methods in Module 2.7.1 to the NDA. On December 18, 2018, the Applicant submitted the file summary-biopharm.pdf in

Sequence 0010, Module 2.7.1, which is materially identical to the biowaiver request, including the same table shown above.

In an information request dated December 17, 2018, the Agency communicated the following comment:

> Provide osmolality values in triplicate for both the proposed drug and listed drug to demonstrate that the products are isosmotic.

On January 8, 2019, the Applicant responded:

Osmolality values of 10 batches of the proposed drug product were presented:

Table 1.11.1–2 Osmolality of Cumberland's Proposed Drug Product

Batch	Manufacture Date	Osmolality (mOsm/kg)		
		Value 1	Value 2	Average
C29244	29 SEP 2015	(b) (4)		
C29245/B	09 OCT 2015			
C29543	08 MAY 2018			
C29544	09 MAY 2018			
C29545	09 MAY 2018			

Batch	Manufacture Date	Osmolality (mOsm/kg)		
		Value 1	Value 2	Average
C29546	17 MAY 2018	(b) (4)		
C29547	17 MAY 2018			
C29548	17 MAY 2018			
C29197/B	27 SEP 2013			
C29195/A	29 SEP 2013			

Abbreviations: kg = kilogram; mOsm = milliosmol

Mean osmolality of the proposed product was (b) (4) mOsm/kg. The Applicant claimed that this value is comparable to normal saline, which is considered to be isosmotic.

Since the listed drug is not commercially available, the Applicant formulated a batch using the formulation listed in the package insert, yielding the following results:

Table 1.11.1-3 Osmolality of Reference Listed Drug

Batch	Manufacture Date	Osmolality (mOsm/kg)			
		Value 1	Value 2	Value 3	Average
NBII - 5	21 DEC 2018	(b) (4)			

Abbreviations: kg = kilogram; mOsm = milliosmol

Mean osmolality of the LD was (b) (4) mOsm/kg. The Applicant claimed that this value is comparable to other solutions considered to be isosmotic, such as 5% dextrose.

> According to *Adv Physiol Educ* 40: 499 –500, 2016, both normal saline and 5% dextrose have an osmolality of 278 mOsm/kg.

Reviewer's Assessment:

In general, the range of (b) (4) mOsm/kg is considered isosmotic. (b) (4) The difference between (b) (4) is not considered significant, and so this product can be considered isosmotic. pH of the test product is comparable to that of the LD.

The only differences between the proposed product and the LD is difference in sodium chloride concentration. This difference is not expected to affect bioavailability. Moreover based on the totality of the provided information (comparative pH and osmolality data), a bridge between the proposed drug product and the LD has been established in accordance with 21 CFR 320.24(b)(6) regulation. .

Primary Biopharmaceutics Reviewer Name: Bryan Ericksen, Ph.D.

Secondary Reviewer Name (and Secondary Summary, as needed): Haritha Mandula, Ph.D.

Bryan Ericksen

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Date: 4/25/2019 02:51:47PM
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Haritha Mandula

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Date: 4/25/2019 04:19:40PM
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MICROBIOLOGY

IQA Review Guide Reference

Product Background:

NDA: 210737

Drug Product Name / Strength: Methotrexate Injection, 25 mg/mL

Route of Administration: Subcutaneous Injection

Applicant Name: Cumberland Pharmaceuticals, Inc.

Manufacturing Site: (b) (4)

Method of Sterilization: (b)

Review Recommendation: **Adequate**

Review Summary: **The drug product i** (b) (4)

List Submissions Being Reviewed:

Document(s) Assessed	Date Received
Original Submission (SN 0008)	11/05/2018
Filing Review IR Response (SN 0011)	01/08/2019
IR Response (SN 0014)	03/13/2019
Labeling IR Response (SN 0015)	05/02/2019
IR Response (SN 0017)	05/10/2019
IR Response (SN 0018)	06/12/2019
IR Response (SN 0020)	06/28/2019
IR Response (SN 0021)	07/05/2019

Highlight Key Outstanding Issues from Last Cycle: Issues regarding (b) (4) **and the environmental monitoring program were identified in the Microbiology Filing Review for this NDA.**

Remarks: This is an eCTD submission. An original IR response with incomplete information was submitted on 03/06/2019, a more complete response was available

by eCTD on 03/13/2019 (SN 0014). Relevant dosage information from the 05/02/2019 labeling IR response (SN 0015) was also reviewed.

Concise Description Outstanding Issues Remaining: None

Supporting Documents:

- **DMF** (b) (4)

(b) (4)

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** Methotrexate Injection (25 mg/mL) is a sterile, pyrogen-free, clear yellow solution indicated for the treatment of severe, active rheumatoid arthritis in adults and polyarticular juvenile idiopathic arthritis in pediatric patients who are intolerant of or have an inadequate response to first-line therapy, and for control of severe, recalcitrant, and disabling psoriasis in adults who are not responsive to other forms of therapy. It is provided in eight different fill volumes: 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, and 1.0 mL.
- **Drug product composition –**

Ingredient	Content per mL	Function
Methotrexate, USP	25.00 mg	API
Sodium Chloride, USP	(b) (4)	Isotonic Agent
Sodium Hydroxide, USP	q.s.to pH 8.2 (b) (4)	pH Adjustment
WFI, USP	q.s. to 1 mL	Diluent

- **Description of container closure system –**

Component	Packaging	Description (Gland material code)	Manufacturer
Syringe Barrel	Primary	(b) (4)	
Stopper	Primary		
Needle Safety Device w/ finger flange	Secondary		

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(b) (4)

Reviewer's Assessment: The applicant appropriately demonstrated the method suitability of the sterility test using the proposed drug product for the sterility specification.

Adequate

P.7 Container Closure – See P.1

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(Section 3.2.P.8.1: Stability Summary and Conclusion; Section 3.2.P.8.3: Stability Data)

The stability protocol includes 36 months of testing under long-term (25ºC/60% RH) storage conditions on (b) (4) exhibit batches C29195, C29196, and C29197, as well as for the (b) (4) commercial scale batches C29459, C29472, and C29458. The analytical testing includes the same tests and acceptance criteria as at release.

Test	Time (Months)										
	0	1	2	3	6	9	12	18	24	30	36
Sterility	X						X	X	X	X	X
Bacterial Endotoxins	X						X	X	X	X	X
Container Closure Integrity	X			X*	X*	X	X	X	X	X	X

* These time points were only tested with the (b) (4) exhibit batches. They were not included in the 6 months of data provided for the commercial scale batches.

Note to Reviewer: The applicant did not describe the frequency of microbiological testing of stability batches. The frequency was inferred based on the 36 months of stability data provided for the (b) (4) exhibit batches in Section 3.2.P.8.3: Stability Data. Only 6 months of data were provided for the (b) (4) batches, and there were differences observed in the frequency of CCI testing of the two batch types. While these differences indicate that the commercial batches may not be tested on the same schedule as the

exhibit batches, the data provided from the exhibit batches support an adequate stability testing program.

The proposed expiry is 30 months.

Reviewer's Assessment: The frequency of microbiological testing of stability batches is adequate.

Adequate

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(Section 3.2.P.8.2: Post Approval Stability Protocol and Stability Commitment)

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Sterility	USP <71>, membrane filtration	Must comply with USP
Bacterial Endotoxins	USP <85>, chromogenic kinetic method	NMT (b)(4) EU/mg
Container Closure Integrity	USP <1207>, dye ingress	No dye ingress

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: 25°C/60% RH

Test	Time (Months)									
	0	3	6	9	12	15	18	24	30	36
Sterility	X				X			X		X
Bacterial Endotoxins	X				X			X		X

The applicant does not state why testing is not performed on the drug product at expiry (30 months).

Post Approval Stability Commitment

A post approval stability commitment was provided by Cumberland Pharmaceuticals, Inc. The NDA applicant committed to placing the first three commercial production batches of the subject drug product into their stability program, which will include one lot each of the 0.3 mL, 0.6 mL, and 1 mL fill presentation. Thereafter, on an annual basis, at least one commercial batch of the highest and lowest strength manufactured that year will be added to the stability program.

The following information request was provided to the applicant on 02/08/2019:

Regarding the post-approval stability protocol, the Agency recommends that sterility testing be performed at expiry (30 months). Please revise the stability protocol.

In their response dated 03/13/2019, the applicant stated that sterility has been added to the 30 month time point. (b) (4)

Reviewer's Assessment: The applicant has provided an adequate post-approval stability protocol and stability commitment to assure the microbiological quality of the drug product over the proposed shelf-life.

Adequate

P.8.3 Stability Data

(Section 3.2.P.8.3: Stability Data)

The applicant provided 36 months of stability data on batches C29195, C29196, and C29197 ((b) (4) exhibit batches) and 6 months of stability data on batches C29459, C29472, and C29458 ((b) (4) commercial scale batches). All batches met specification for bacterial endotoxins, sterility, and CCI at the applicable timepoints.

Reviewer's Assessment: The applicant has provided up to 36 months of long term stability data that support the maintenance of microbiological quality for the subject drug at 25°C.

Adequate

R Regional Information

Executed Batch Records

(Section 3.2.R: Regional Information, AP-R-1-2 – Batch Master Record – C29195 (1.0mL, (b) (4)) – English, AP-R-1-4 – Batch Master Record – C29197 (0.3mL, (b) (4)) – English, AP-R-1-6 – Batch Master Record – C29458 (1.0mL, (b) (4)) – English, AP-R-1-8 – Batch Master Record – C29459 (0.3mL, (b) (4)) – English)

Exhibit batch records were provided for multiple batches. The batches used are summarized in the table below.

Batch Size (L)	Batch #	Volume (mL)	# of Syringes
(b) (4)	C29458	1.0	(b) (4)
	C29459	0.3	
	C29195	1.0	
	C29197	0.3	

The batch records confirm that validated (b) (4) manufacturing processes were used for the manufacture of the exhibit batches. While multiple deviations relating to the

microbiological quality of the product were identified (b) (4) they were investigated and the deviations closed.

Reviewer's Assessment: The batch records confirm that validated (b) (4) manufacturing processes were used for the manufacture of the exhibit batches.

Adequate

Comparability Protocols

No comparability protocol was provided.

Reviewer's Assessment: N/A

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

2.A. Package Insert

(1.14.1.3: Draft Labeling Text – Reditrex; Instruction For Use Draft, Patient Information Draft)

- Storage temperature: 20-25ºC, excursions permitted to 15-30ºC
- Route of administration: Subcutaneous injection
- Container: Single dose. It is noted that the solution is for a single subcutaneous injection.

The drug product is not further diluted prior to use.

Reviewer's Assessment: The package insert provides adequate instructions for storage of the subject drug product to assure microbiological quality of the drug product during administration.

Adequate

Post-Approval Commitments: N/A

Lifecycle Management Considerations

Reviewer's Assessment: Changes to the container closure system, equipment and component (b) (4) process, and syringe filling line could affect microbiological quality of the subject drug product.

List of Deficiencies: **N/A**

Primary Microbiology Reviewer Name and Date: **Catherine Gilbert, Ph.D., 07/09/2019**

Secondary Reviewer Name and Date (and Secondary Summary, as needed): **CAPT Paul Dexter, M.S., 07/09/2019**

Catherine Gilbert

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Date: 7/09/2019 02:51:14PM
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Paul Dexter

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ICCR QUALITY SYSTEM REVIEW MEMO

Date:	February 25, 2019
To:	Keith Marin, OPEQ/OHT3/DHT3C, CDRH, keith.marin@fda.hhs.gov
From:	Nikhil Thakur, OPEQ/OHT3/DHT3C, CDRH, Nikhil.thakur@fda.gov
Applicant/Licensure:	Cumberland Pharmaceuticals 2525 West End Avenue 3012597673
Submission (Type & Number):	NDA 210737
Combination Product Name:	Methotrexate Prefilled Syringe
Combination Product Indications for Use:	treatment of severe, active rheumatoid arthritis and polyarticular juvenile idiopathic arthritis who are intolerant of or had an inadequate response to first-line therapy and [cont'd]
Device Constituent (Type):	Prefilled Syringe
ICCR Sharepoint Tracking Number:	ICCR2018-04003
ICCR CTS Tracking Number:	ICC1800983
Pre-Approval Facility Inspection:	Yes, Post-Approval Inspections Also Requested
Documentation Review (Status):	**Complete**

CDRH/OC Recommendation: **Approvable**

CDRH received a consult from CDER requesting the identification of the device manufacturing sites for NDA 210737 which will require a device inspection.

PRODUCT DESCRIPTION

Provide a brief description of the combination product including proposed intended use. A picture of the combination product, interesting information may be added here for clarity.

REGULATORY HISTORY

The following facility was identified as being involved in the manufacturing and/or development of the combination product, Methotrexate Prefilled Syringe, in NDA 210737.

Combination Product Applicant

Fill out the following for the applicant. Note: The applicant has overall responsibility for all manufacturing sites and will be issued any deficiencies.

Firm Name: Cumberland Pharmaceuticals

Address: 2525 West End Avenue

FEI: 3012597673

Responsibility – Applicant for the listed combination product.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected. There are no manufacturing operations at this facility.

Inspection Recommendation:

An inspection is not required because the manufacturing site does not require an inspection at this time given the risk of the combination product.

Finished Combination Product Manufacturer

(Fill out the following for the finished combination product manufacturer. This site typically finishes manufacturing of the product, for example, the site fills the syringe with the drug substance.)

(b) (4)

Responsibility – • Manufacture of Drug Product; • Sterilization of Drug Product; • Packaging and Labeling of Drug Product; • Release Testing of Drug Product; • Stability Testing of Drug Product; • Batch Release of Drug Product

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted (b) (4). The inspection covered drug CGMP and was classified VAI. It is noteworthy that the firm has never been inspected per the Medical Device PAC Code (7382.845).

Inspection Recommendation:

An inspection is not required because the manufacturing site does not require an inspection at this time given the risk of the combination product.

DOCUMENTATION REVIEW

Device Consituent Part Type: Prefilled Syringe

Device Consituent Part Class Class II: E.g. Prefilled Syringe, Auto Injector, Inhaler, Vaginal Ring, IUD

Combination Product NDA 210737 Proposed Indication for Use: treatment of severe, active rheumatoid arthritis and polyarticular juvenile idiopathic arthritis who are intolerant of or had an inadequate response to first-line therapy and [cont'd]

CDRH conducted a risk-based assessment of the device constituent part and has determined that does not need to conduct a compliance evaluation of the application unless changes to the delivery system are made that need a re-evaluation of our decision.

This assessment pertains exclusively to the Compliance Review:

- Desk review of 21 CFR 820 call-outs, and
- Evaluation of manufacturing facilities to determine the need for inspections associated with this application.

The decision for not conducting a device compliance review for this application is independent from the technical review of the device constituent part done by our pre-market colleagues.

However, the applicant is still responsible to ensure their product is compliant with all applicable regulatory requirements and is ready to provide proof of compliance during inspection if requested. Thus, we recommend the applicant follows FDA's guidance for the current good manufacturing practice requirements under 21 CFR part 820 for combination products.

Reviewer: _____

Branch Chief or Lead CSO: _____

OFFICE OF PHARMACEUTICAL QUALITY

Final Risk Assessment for NDA 210737 – Methotrexate Injection

DP attribute/ CQA	Factors that may impact the CQA	O[1]	S[1, 2]	D[1]	Initial RA FMECA RPN #	Comment & considerations for risk assessment	Final RA	Lifecycle considerations or comments
Sterility[3]	•					•		
Endotoxins[3]	•					•		
Assay (API)	(b) (4)	2	3	3	18	(b) (4)		
Purity (API-related)	• Purity of input API • Racemization of API • Increase in API-related impurities during manufacturing of MDM injection • Increase in API-related degradants with time (stability)	1	3	5	45		1x3x5 = 15	• (b) (4)

[1] O = Probability of Occurrence; S = Severity of Effect; D = Detectability

[2] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs (thus a median value of "3" was used throughout)

[3] To be evaluated by the microbiology team

[4] See H-K Chan and I. Gonda *Int. J. Pharmaceutics* **68** (1991), pp. 179-190.

						(b) (4)		
Osmolality	• Incorrect formulation (API and/or NaCl)	3	3	2	18			
pH	• Incorrect pH adjustment	3	3	2	18			
Particulate matter	• Particulates in formulation components • Particulates in or from CCS components • Particulates from manufacturing process	2	3	3	18			
Content Uniformity	• Variability in filling of pre-filled syringes	2	3	4	24			

Craig
Bertha

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Memo:

Environmental Analysis was not included in the original review of NDA210737. Upon review now, we found the Environmental Analysis is acceptable.

Jizhou Wang

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Date: 9/25/2019 12:32:57PM
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Julia Pinto

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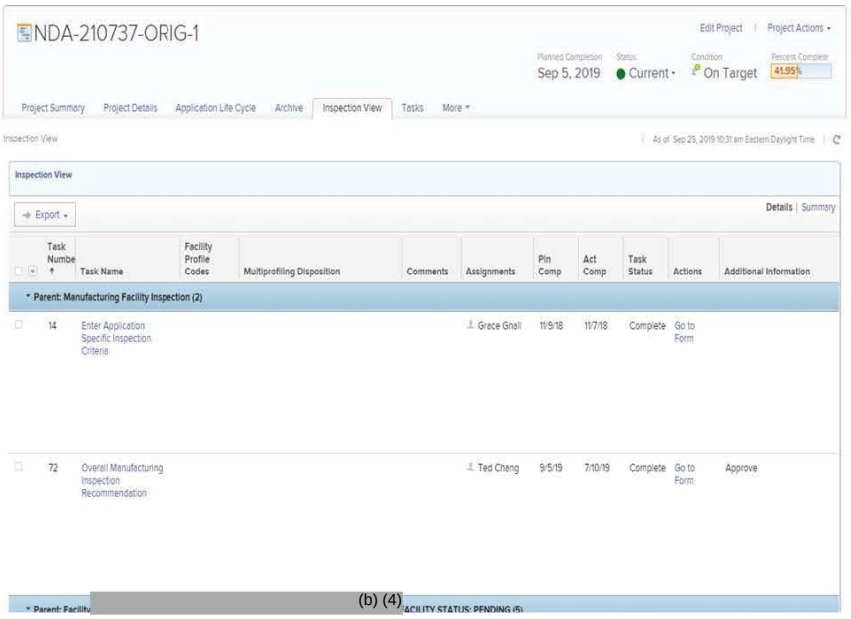
Facilities Inspection Recommendation


NDA-210737-ORIG-1
Edit Project | Project Actions
Planned Completion Sep 5, 2019
Status Current
Condition On Target
Percent Complete 41.95%
Project Summary
Project Details
Application Life Cycle
Archive
Inspection View
Tasks
More
Inspection View
As of Sep 25, 2019 10:31 am Eastern Daylight Time
Inspection View
Export
Details | Summary
Task Numbe
Task Name
Facility Profile Codes
Multiprofiling Disposition
Comments
Assignments
Pln Comp
Act Comp
Task Status
Actions
Additional Information
Parent: Manufacturing Facility Inspection (2)
14
Enter Application Specific Inspection Criteria
Grace Gnall
11/9/18
11/7/18
Complete
Go to Form
72
Overall Manufacturing Inspection Recommendation
Ted Chang
9/5/19
7/10/19
Complete
Go to Form
Approve
(b) (4)

Other Product Quality Documents

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JESSICA K LEE
11/27/2019 11:02:58 AM