CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211415Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 211415
Review #1

Drug Name/Dosage Form	cetirizine hydrochloride
Strength	10.00 mg/mL
Route of Administration	intravenous injection
Rx/OTC Dispensed	Rx
Applicant	JDP Therapeutics Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	*30-NOV-2018*	*All*
Amendment	*13-DEC-2018*	*Drug product*
Amendment	*02-JAN-2019*	*Drug product*
Amendment	*14-JAN-2019*	*Microbiology, process/facilities*
Amendment	*21-FEB-2019*	*Drug product, facilities*
Amendment	*26-MAR-2019*	*Microbiology*
Amendment	*26-JUN-2019*	*Drug substance*
Amendment	*09-JUL-2019*	*Drug product*
Amendment	*25-JUL-2019*	*Process/facilities*
Amendment	*29-JUL-2019*	*Drug product*
Amendment	*05-AUG-2019*	*Process/facilities*
Amendment	*09-AUG-2019*	*Drug product*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Paresma Patel	Donna Christner
Drug Product	Venkat Pavuluri	Craig M. Bertha
Process	Hang Guo	Pei-I Chu
Microbiology	Koushik Paul	Jesse Wells
Facility	Hang Guo	Pei-I Chu
Biopharmaceutics	N/A	

Regulatory Business Process Manager	Florence Aisida	
Application Technical Lead	Craig M. Bertha	
Laboratory (OTR)	N/A	
ORA Lead	N/A	No PAIs requested
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 II		(b) (4)	Adequate	14-JUN-2019	
	Type III			Adequate	18-JAN-2017 11-DEC-2018	
	Type III			Adequate	29-AUG-2017	
	Type III			Adequate	27-FEB-2019	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	107689	cetirizine injection

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

N/A – Application is recommended for **approval**

II. Summary of Quality Assessments

A. Product Overview

The drug product cetirizine injection is indicated for the treatment of acute urticaria in adults and children 6 months of age and older (not for chronic use). Cetirizine hydrochloride is an antihistamine. The drug product is formulated with a concentration of 10.00 mg/mL cetirizine hydrochloride (equivalent to 8.42 mg/mL of cetirizine in the base/zwitterion form) in water, with sodium chloride to adjust tonicity and adjusted to a target pH of (b) (4) The container closure system (CCS) for the injection consists of an amber glass vial fitted with an (b) (4) stopper and aluminum crimp seal. The most critical product review considerations include a focus on assuring the sterility (e.g., (b) (4) and other pertinent quality aspects (e.g., particulate matter, leachables, impurities/degradants) for the injection drug product.

The application was developed under IND 107689 since early 2010. At a pre-IND meeting of 19-MAR-2010, the Agency provided general guidance regarding the CMC information expected to be included in the IND. At an end-of-phase-two meeting on 18-MAR-2015, no CMC issues were discussed. Although this drug product would be the first cetirizine injection, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) did not grant a priority review for this application, which implies that the Division did not perceive the approval of this product to have a significantly greater benefit for patients, relative to standard of care, to warrant an earlier action goal date.

Proposed Indication(s) including Intended Patient Population	indicated for the treatment of acute urticaria in adults and children 6 months of age and older
Duration of Treatment	once a day as needed
Maximum Daily Dose	10 mg
Alternative Methods of Administration	there are dosage forms for oral administration of cetirizine

B. Quality Assessment Overview

The drug substance CMC information for cetirizine hydrochloride is provided by cross referenced to DMF (b) (4), which was reviewed by Paresma Patel on 17-June-2019 (Panorama) and found to be adequate to support this NDA. The applicant provides a brief description of the general properties of the drug substance, impurities, drug substance specifications, container closure, and stability data. The applicant provided specifications for retest of drug substance batches upon acceptance from the supplier.

The current retest period is (b) (4) months. The NDA is recommended for approval from the perspective of drug substance quality.

Cetirizine Hydrochloride Injection (10 mg /mL) is a sterile, clear, colorless, non-pyrogenic, preservative free, isotonic formulation of cetirizine HCl. The drug product is a simple solution containing Cetirizine HCl and sodium chloride, sterilized by a (b) (4). The single-use product doesn't contain preservatives and is packaged in to a 2mL amber color vial fitted with 13 mm (b) (4) rubber stopper and aluminum flip-off seal. Proposed regulatory drug product specifications, for release and end of shelf-life, together with the in-process controls implemented during manufacture are adequate to assure the quality of drug product through the end of assigned shelf-life.

No leachables, including (b) (4) detected as extractable, were reported to be present in drug product samples stored inverted, at controlled room temperature and accelerated storage conditions tested at the 12 month time-points. For parameters other than leachables, based on available stability data at accelerated conditions (40°C /75%RH) up to 6 months and at controlled room temperature (25°C/60 %RH) up to 18 months for two (b) (4)L registration stability batches manufactured at the intended manufacturing site with the to-be-marketed presentation, **a shelf life of 24 months is recommended for the drug product.** Note that the planned commercial scale is (b) (4) L. The applicant had proposed a (b) (4) month expiry, and provided (b) (4) month long term stability data for a third (b) (4)L batch. However, this batch was not manufactured at the intended commercial site and used vials not procured from the intended source for commercial production (and that were also used for the two (b) (4)L registration stability batches). Thus, the associated stability data were considered only as supportive. In addition, leachables data were only collected up to 12 months (long term and accelerated), and as this is an important stability parameter, a 24 month shelf life would be the maximum amount recommended by ICH Q1E. The post-approval commitment to conduct additional stability studies is acceptable from quality (CMC) perspective.

From a microbiology perspective, the application is recommended for approval on the basis of sterility assurance. The container closure system chosen is designed to maintain product sterility, and the container closure integrity testing validation study results support the (b) (4) manufacturing process. Building and facility floor plans and the description of the manufacturing operations are also consistent with what is expected for (b) (4) processing. Environmental monitoring information and amended information regarding (b) (4) validation, were found to be satisfactory for (b) (4) manufacture of the drug product. Clarification provided regarding (b) (4) was also found to be adequate for the (b) (4) process. The microbiology team had recently found the (b) (4) process and the sterilization process for the (b) (4) at the facility, to be adequate, so no further review was necessary for those aspects of the process. In addition, (b) (4) equipment and processes for the vials and stoppers, were found to be acceptable. Media fill studies were found to support the maximum filling time, and the

drug product specification includes the necessary tests and acceptance criteria for both bacterial endotoxins and sterility. Lastly, the application includes a commitment to test the first three full-scale commercial batches and annual stability batches on an annual basis for both endotoxin content and sterility.

Cetirizine HCl is a BCS class III drug substance with high solubility and low permeability. The overall manufacturing process consists of (b) (4) with a registration batch size of (b) (4) liters and a target fill volume per vial of (b) (4) mL. There were three registration batches produced, but one of these was subsequently converted to an engineering batch due to (b) (4) and (b) (4) The (b) (4) observed in the engineering batch (69-316-SB) was determined to be from the (b) (4). Investigation was performed, and mitigation measures were subsequently put in place at the API manufacturing site to address the issue for future API supply. Material compatibility studies and (b) (4) studies have been performed and the results are acceptable. The fill volume of (b) (4) mL has been explained and justified and the product is 100% visually inspected. The sponsor has also proposed a tentative yield of (b) (4)% for the commercial process based on batch size of (b) (4) L. Commercial scale batches will range between (b) (4) L and the (b) (4) will utilize a (b) (4) than used for registration batches.

drug substance ((b) (4)) manufacturing facilities are approvable based on profile. Both are currently in acceptable status for their proposed functions of (b) (4) , respectively. However, there were GMP issues at the (b) (4) stability testing facility ((b) (4)), which currently has Official Action Indicated (OAI) status as a result of an inspection that took place in the (b) (4) time-frame. This site was responsible for the testing of the registration batches of drug product for pH, assay, related substances, and osmolality. Some of the 483 observations were repeat observations, and most were facility and/or GMP in nature. Therefore data integrity issues, with respect to the testing that had been performed in support of the NDA, are not a concern. The sponsor has now withdrawn (b) (4) from the application. For the testing of commercial batches, (b) (4) (b) (4) will be used. Both of these sites have acceptable compliance status and are capable of performing the analytical testing. After amendment of the application, no further issues remain for manufacturing process and facilities.

C. Special Product Quality Labeling Recommendations (NDA only)

D. Final Risk Assessment (see Attachment)

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MICROBIOLOGY

Product Background: Acute Urticaria.

NDA: 211415

Drug Product Name / Strength: Cetirizine HCl, 10mg/ml (single use).

Route of Administration: Intravenous injection

Applicant Name: JDP Therapeutics Inc.

Manufacturing Site: Hospira, Inc. Highway 301 North Rocky Mount, NC 27801, FEI No. 1021343.

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary: (b) (4) .

List Submissions Being Reviewed: 12/07/2018, 01/16/2019 and 03/26/2019

Highlight Key Outstanding Issues from Last Cycle: N/A

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

Concise Description Outstanding Issues Remaining: None.

Supporting Documents:

> DMF (b) (4) regarding the (b) (4) is reviewed and found adequate in (b) (4).doc, dated 02/03/2017.

> Microbiology review of (b) (4).doc, dated 01/11/2018; and (b) (4).doc, dated 02/06/2018; regarding the manufacturing building and facilities and the (b) (4)

> Microbiology review of (b) (4).doc, dated 11/29/2018; regarding the (b) (4) (b) (4) (b) (4) and actions concerning product when media fills fail.

> Microbiology review of (b) (4).doc, dated 05/17/2005; regarding the (b) (4) (b) (4)

List Number of Comparability Protocols (ANDA only): None.

S Drug Substance- Not Applicable

P.1 Description of the Composition of the Drug Product

- **Description of the Composition of the Drug Product**
  (*3.2. P.1. 3.2.P Drug Product_ Cetirizine HCl Injection, 10 mg_mL.pdf)*

Cetirizine HCl, 10mg/ml is a sterile, clear, colorless, non-pyrogenic, preservative free, isotonic aqueous solution. It is filled in a 2ml clear glass vial (1ml fill volume with a concentration of 10mg/ml) with 13mm grey colored rubber stopper with a 13mm seal. The compositions are provided below:

Table 1, Qualitative and Quantitative Composition for Cetirizine HCl Injection, 10 mg/mL

Pfizer Drug Code	Ingredient	Quantity per mL	Function	Quality Standard
(b) (4)	Cetirizine HCl, USP	10.00 mg	API	USP
	Sodium Chloride, USP	6.50 mg	To adjust tonicity/ (b) (4)	USP
	Sodium Hydroxide, NF, (b) (4)	q.s.	To adjust pH	NF
	Acid, Hydrochloric, NF	q.s.	To adjust pH	NF
	Water for Injection, USP	(b) (4)		USP

- **Description of container closure system –**

(The following container-closure systems are used for the production of the drug product; (table is modified from *3.2. P.1. 3.2.P Drug Product_ Cetirizine HCl Injection, 10 mg_mL.pdf and 3.2.P.7 Container Closure System for Cetirizine Hydrochloride Injection, 10 mg_mL.pdf*):

Component details (material code)	Manufacturer /address	DMF
2ml (b) (4) amber glass vials with 13mm neck (b) (4)	(b) (4)	N/A
13mm (b) (4) Stoppers (b) (4) (b) (4)		(b) (4)
13 mm flip off seal (b) (4)		N/A

Reviewer's Assessment: Based on the above information the reviewer has concluded that the applicant has provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes:

Container/Closure and Package Integrity

(*3.2.P.2.5 Microbiological Attributes.pdf)*

Test method: microbial challenge study.

Type of container closure used for the testing: Hospira used worst case container-closure system (5ml vials with 13mm neck size with a 6ml fill volume) for the container closure integrity testing (CCIT) validation study. The worst case was determined based on an assessment of sealing surface engagement, utilizing primarily the plug seal and the vial neck dimensions. The worst-case combination was chosen based on the least dimensional interference in the stopper plug/glass neck interface and also the largest fill volume/vial. Please note that 2ml glass vial (Code# (b) (4)) using a 13mm stopper (Code# (b) (4)) were proposed as the final drug product container closure system.

A total number of container closure used for the testing: A total of 38 (b) (4) vials (30 vials used as a test and 4 vials each were used as positive and negative controls) were used for the CCIT study.

Challenge organism and concentration of culture: *Serratia marcescens* (ATCC 14041) culture with a concentration of 1.0 x 10^6 CFU/ml.

Brief description: A total of 38 vials filled with 6ml of Tryptic Soy Broth (TSB) were used for the CCIT. All 38 media filled vials were (b) (4) A total of 30 vials [used as the test samples] were randomly selected and submerged into a suspension of ~ 10^6 CFU/ml of the challenge organism

for 24 hours at room temperature. All test vials were then subjected to a vacuum of ≥ 15 inches of Hg for 10 minutes. Four positive control vials were also randomly selected, and the closure system were compromised by aseptically inserting a sterile 21-gauge needle through the closure system. Two positive control vials were exposed to the 24-hour immersion challenge at room temperature with the test samples and other two positive control vials were subjected to a vacuum of ≥ 15 inches of Hg for 10 minutes while they were inverted in the immersion solution. A total of 4 negative controls vials were also randomly selected. The closures on the negative control vials were not compromised. The negative controls vials were not exposed to the bacterial suspension. Two of the negative control vials were held at room temperature and other two negative controls vials were subjected to the vacuum of ≥ 15 inches of Hg for 10 minutes during immersion challenge for 24-hours. Upon completion of the immersion challenge, all samples were removed and incubated at 30-35°C for 7 days. The container contents were then inspected for microbial growth. Growth promotion was also performed in parallel with the CCIT.

Acceptance criteria:

- The container-closure system must maintain sterility of the container contents in response to the immersion challenge as demonstrated by the absence of the challenge microorganism *S. marcescens* in test samples.
- The concentration of the challenge organism in the immersion suspension must be equal to or greater than (b) (4) CFU/ml at the beginning and end of the study.
- The *S. marcescens* inoculum level used for the growth promotion samples must be less tha (b) (4) CFU/sample.
- The CCIT were demonstrated by the ability of a 5ml glass vial with a 13mm stopper to maintain sterility of the container contents in response to a 24-hour *S. marcescens* immersion challenge.

Results: No growth was observed for any of the test and negative control vials. Whereas growth in 4 positive control vials were observed. All test results met the CCIT acceptance criteria and the results are summarized below:

Samples	Total number of vials tested	Sterility results
Test sampels	30	No growth
Positive control	4	Growth
Negative control	4	No growth

Reviewer's Assessment: Based on the above information the reviewer has concluded that the applicant has provided an adequate CCIT validation methods and results to support the (b) (4) manufacturing process for the drug product.

Acceptable

Antimicrobial Effectiveness Testing--

Cetirizine Hydrochloride Injection is a single dose product. Hence, antimicrobial effectiveness testing is not required.

Jesse Wells

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Koushik Paul

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LABELING

IQA Review Guide Reference

{For NDA 211415}

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	TRADENAME (cetirizine hydrochloride),
Dosage form, route of administration	Solution for injection; intravenous
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Injection; 10 mg/mL single-dose vial.

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Not applicable for solution that is ready for injection.

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Injection, 1 mL
Strengths: in metric system	10 mg
Active moiety expression of strength with equivalence statement (if applicable)	cetirizine hydrochloride 10 mg
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	sterile, clear, colorless, non-pyrogenic, isotonic aqueous solution of cetirizine hydrochloride for intravenous injection in 2 mL amber glass vials for single use.

4. *Section 11 Description*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Proprietary name to be included. Established name should be 'cetirizine hydrochloride'
Dosage form and route of administration	injection, intravenous
Active moiety expression of strength with equivalence statement (if applicable)	Dose should be expressed as cetirizine hydrochloride 10 mg (equivalent to cetirizine 8.42 mg).
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	6.5 mg of sodium chloride is present for isotonicity adjustment.
Statement of being sterile (if applicable)	a sterile, clear, colorless, non-pyrogenic, isotonic solution
Pharmacological/ therapeutic class	selective histamine-1 H1-receptor antagonist
Chemical name, structural formula, molecular weight	(±) –[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperzinyl] ethoxy]acetic acid, dihydrochloride; $C_{21}H_{25}ClN_2O_3 \bullet 2HCl$; 461.82
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	white, crystalline powder and is water soluble.

5. ***Section 16 How Supplied/Storage and Handling***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	10 mg/mL
Available units (e.g., bottles of 100 tablets)	single-use vial
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	supplied as a sterile, clear, colorless, non-pyrogenic isotonic aqueous solution in 2 mL amber glass vials.
Special handling (e.g., protect from light)	Not applicable, (b) (4)
Storage conditions	stored at 20°C to 25°C (68°F to 77°F), excursions permitted to 15° - 30°C (59° - 86° F) [see USP Controlled Room Temperature]
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured by Pfizer (b) (4)

Reviewer's Assessment of Package Insert: Adequate, subject making changes proposed to the highlights, 3, 11 and 16 sections of the PI, and communicated to applicant.

Prescribing Information needs to be revised as indicated in the sharepoint document, including the above text identified in red color font, for compliance with all regulatory requirements from a CMC perspective.

Seed deficiencies communicated to applicant, as noted at the end of this document.

II. Labels:

1. ***Container and Carton Labels***

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Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Quzyttir™ Cetirizine HCl Injection	Quzyttir™ Cetirizine HCl Injection
Dosage strength	10 mg / mL	10 mg/mL
Net contents	1 mL	Carton of 25 1 mL single-dose vials
"Rx only" displayed prominently on the main panel	Rx only	Rx only
NDC number (21 CFR 207.35(b)(3)(i))	NDC 70720-100-01	NDC 70720-100-25
Lot number and expiration date (21 CFR 201.17)	##-####-AA MMYYYY	Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]
Storage conditions	Not included, space is limited	
Bar code (21CFR 201.25)	FPO /7.5 MIL RL-7673	FPO /MAG. 100% 3 70720 10025 1
Name of manufacturer/distributor	Distributed by: TerSera Therapeutics LLC	Manufactured by: Pfizer Rocky Mount, NC 27801 Distributed by: TerSera Therapeutics LLC Lake Forest, IL 60045
And others, if space is available	Each 1 mL vial contains Cetirizine Hydrochloride 10 mg (equivalent to 8.42 mg of Cetirizine) For intravenous use only	Each 1 mL vial contains Cetirizine Hydrochloride 10 mg (equivalent to 8.42 mg of Cetirizine) For Intravenous use only

Reviewer's Assessment of Labels: Adequate, subject to revising the text on vial label and printed carton per the recommendations below.

Refer deficiencies listed at the end in the "List of Deficiencies"

List of Deficiencies:

For PI:

1. *Include the full name of the drug substance, i.e. Cetirizine Hydrochloride, as established name throughout the PI.*

2. *Equivalency statement for active moiety should be included in parenthesis following of Cetirizine Hydrochloride in the description (Section 11), per the Agency Guidance to Industry on Labeling: Naming of Drug Products Containing Salt Drug Substances, June 2015 that can be accessed at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm379753.pdf*

3. *In the storage statement in section 16 of the PI and on printed carton the wording "excursions permitted to 15° - 30°C (59° - 86° F)" may be included after "Store at 20°C to 25°C (68°F to 77°F),".*

For Vial Label and Carton:

4. *On the Printed carton add the wording "and sodium chloride for tonicity adjustment" after Each 1 mL vial contains Cetirizine hydrochloride 10 mg (equivalent to cetirizine 8.42 mg). Add the same wording "and sodium chloride for tonicity adjustment" on vial label as well, if space permits.*

Overall Assessment and Recommendation: Acceptable, when above recommended changes are incorporated in the labeling (PI, vial label and printed carton)

Primary Labeling Reviewer Name and Date:

Venkateswara R. Pavuluri, Ph. D., R. Ph., 26-AUG-2019

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

Craig M. Bertha, Ph. D., 27-AUG-2019

Venkateswara Pavuluri

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Craig Bertha

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OFFICE OF PHARMACEUTICAL QUALITY

NDA 211415 Final Risk Assessment

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]	•					(b) (4)		
Endotoxins[3]	•							
Assay (API)/Purity	• Incorrect amount of cetirizine for (b) (4) (b) (4) • Loss of API to (b) (4) during (b) (4) • Loss of API due to degradation • Degradation of API during processing • Degradation of API as formulated during shelf life	3	3	3	27		2x3x3 = 18	25-JUL-2019 amendment provided data demonstrating that (b) (4)
Osmolality	• Incorrect formulation (API and/or NaCl)	3	3	2	18			
pH	• Incorrect pH adjustment	3	3	2	18			
Content Uniformity	• Variability in filling of vials • Variability of the assay of the (b) (4)	3	3	5	45			The firm has set an in-process fill volume target (b) (4) mL with a range of (b) (4) mL; the

[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

						(b) (4)		process/facility review team does note that this volume is more than the typically allowed (b) (4) overfill, but after discussion with DMEPA, the (b) (4) overfill is deemed low risk from a medication error perspective.

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/s/

SUSAN RHEE
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