CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210655Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 210655

Review #1

Drug Name/Dosage Form	PERSERIS (risperidone) for extended release injectable suspension
Strength	90 mg/0.6ml and 120 mg/0.8ml
Route of Administration	Subcutaneous
Rx/OTC Dispensed	Rx
Applicant	Indivior Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
N-0001	*28 SEP 2017*
N-0005	*27 OCT 2017*
N-0013	*14 DEC 2017*
N-0023	*15 MAR 2018*
N-0024	*19 MAR 2018*
N-0027	*28 MAR 2018*
N-0036	*14 MAY 2018*
N-0037	*16 MAY 2018*
N-0039	*25 MAY 2018*
N-0040	*30 MAY 2018*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Sharon Kelly	Charles Jewell
Drug Product	Andrei Ponta	Wendy Wilson-Lee
Process	Mark Johnson	Derek Smith
Microbiology	Amy McDaniel	Marla Stevens Riley
Facility	Frank Wackes	Ying Zhang
Biopharmaceutics	Gerlie Gieser	Ta-Chen Wu
PBPM	Teshara Bouie	
Laboratory (OTR)	JeffreyWoodruff/DiemNgo	Cynthia Sommers
Application Technical Lead	David Claffey	

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	06/04/2018,	CMC Review # 14, Sharon Kelly, PhD
	Type III and IV			All Adequate		

B. Other Documents:

DOCUMENT	DESCRIPTION
NDA 20272	Listed Drug
IND 105623	Referenced IND

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
CDRH ODE	Complete	Adequate	4 JUN 2018	Keith Marin
CDRH OC	Complete	Adequate	22 MAR 2018	Katelyn Bittleman

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends approval of this application from a product quality perspective.

II. Summary of Quality Assessments

A. Product Overview

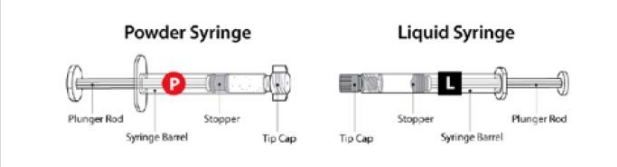
PERSERIS (risperidone) for extended release injectable suspension is a once-monthly, extended-release, subcutaneously-administered sterile depot formulation of risperidone for the treatment of schizophrenia in adults. The marketing of two strengths is proposed - 90 mg/0.6ml and 120 mg/0.8ml. This 505(b)(2) application relies on RISPERDAL® tablets, NDA 020272. It is supplied as a drug/device combination product in two separate syringes whose contents require mixing immediately prior to administration. Stability data support the labeled storage conditions, including an 18-month expiry period for the drug product when stored at refrigerated conditions (2 to 8°C).

Proposed Indication(s) including Intended Patient Population	An atypical antipsychotic indicated for the treatment of schizophrenia in adults
Duration of Treatment	Chronic
Dosage	90 mg/0.6 mL or 120 mg/0.8 mL injected subcutaneously into the abdomen once-monthly. Maximum 120 mg/month
Alternative Methods of Administration	None

B. Quality Assessment Overview

General product overview: PERSERIS (risperidone) for extended release injectable suspension is a once-monthly, extended release, subcutaneously- administered sterile depot formulation of risperidone for the treatment of schizophrenia in adults. The marketing of two strengths is proposed - 90 mg/0.6ml and 120 mg/0.8ml. This 505(b)(2) application relies on RISPERDAL® tablets, NDA 020272.

It is supplied as a drug/device combination product in two separate syringes whose contents require mixing by a Health Care Practitioner immediately prior to administration.



The drug product composition is relatively simple. One syringe contains just (b) (4) risperidone. The other syringe is filled with a liquid diluent (a.k.a. ATRIGEL). The diluent contains the extended release polymer [80:20 poly (D, L-lactide-co-glycolide)] (PLGH) (b) (4) in methyl-2-pyrrolidone (NMP), a non-aqueous (b) (4) Each syringe is packaged in a (b) (4) pouch. The pouches are packaged in a carton with an 18-gauge needle. Immediately prior to administration the syringes are coupled and the contents mixed back and forth between the syringes to form a viscous suspension of risperidone (b) (4) in the (b) (4) polymer/NMPsolution. After injection, (b) (4)

(b) (4)

Overfill: The drug product contains a (b) (4)% overfill, to account for the retention of product in each of the syringes and the needle. Delivered dose testing results demonstrated that the overfill is adequate for the higher 120 mg strength product with assay consistently near (b) (4)% of label claim. However, delivered dose release testing results for 90 mg strength product indicate that (b) (4) mg of risperidone is delivered

(b) (4)

(b) (4)

Drug product specification: The drug product release specification includes tests typical of a sterile 'for injection' product. (b) (4)

(b) (4)

(b) (4)

Stability: The stability studies contained a number of out-of-trend assay results. The Applicant attributed to a lack of details in the assay method – this was confirmed by the OPQ OTR method verification team (who found the assay method generally adequate, but lacking sufficient detail). The Applicant took corrective measures including adding more details to the methods and retraining analysts.
Stability data through 12 months on the primary stability lots support an 18-month expiry for the drug product when stored at refrigerated conditions (2 – 8°C). The label states that the product should be mixed immediately prior to administration, however data demonstrate adequate product quality for up to six hours after mixing. Data were provided to support the storage of the syringes in their original seal pouches at room temperature for up to seven days prior to administration.

Manufacturing process: The manufacturing process involves (b) (4)

(b) (4)

Microbiology: The microbiology review team found the product quality microbiology manufacturing controls and the (b) (4) sterilization process adequate from their perspective. (b) (4)

(b) (4)

Drug substance: Much of the drug substance information is referenced to (b) (4) DMF (b) (4) It was found acceptable and complies with risperidone's USP monograph.

(b) (4)

(b) (4) The DMF found a (b) (4) month retest date acceptable.

Facilities*:* An extensive review all the numerous drug substance and drug product manufacturing, testing and packaging site found them all currently acceptable from a 21 CFR 211 perspective. CDRH Office of compliance carried out a document review of the application and found it acceptable from the perspective of the applicable 21 CFR 820 Quality System Requirements (Katelyn Bittleman, 22 MAR 2018, review in Darrts).

Biopharmaceutics: The in vitro drug release (IVR) method employs USP Apparatus 4 (flow through cell, closed loop) and modified Hanks buffer medium at pH6.5 with 0.1% Triton X-100, set to a flow rate of 16 mL/min over 7 days. This method and medium were chosen because they mimic the gentle flow of subcutaneous interstitial fluid across the drug product depot. Acceptance criteria were agreed to be (b) (4)% at 24 hours, (b) (4)% at 72 hours and NLT (b) (4)% at 168 hours. The method proved discriminatory to changes in PLGH molecular weight, PLGH monomer ratio, and showed the correct rank-order relationships with respect to NMP content and risperidone particle size. In vivo and in vitro data supported the extended release claim. In vitro and in vivo animal studies showed that dose dumping was not induced by applied pressure, heat or exercise. IVIVC was not established for the proposed in vitro drug release method. Dissolution was found to be slow with (b) (4)% drug release from pivotal clinical trial lots within 10 days when using the proposed IVR method and within 28 days when using the real-time IVR method – hence the lower than usual (b) (4)% limit at the final 7-day dissolution specification time point.

Device Review: CDR Keith Marin completed a review (4 JUN 2018) of this application acceptable from a device perspective with an approval recommendation. They found syringe performance tests and controls acceptable, including syringeability, biocompatibility and shipping studies.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

David Claffey

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LABELING

(b) (4)

[redacted]

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Perseris (risperidone extended-release) injection for subcutaneous use
Dosage form, route of administration	Injection, for subcutaneous use

Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	**Injection, 90 mg/0.6 mL and 120 mg/ 0.8 mL**

Is the information accurate? ☒ Yes ☐ No

2. *Section 2 Dosage and Administration*

2 DOSAGE AND ADMINISTRATION

(b) (4)

- Allow package to come to room temperature for at least 15 minutes prior to preparation (b) (4)
- (b) (4)
- Only prepare medication when you are ready to administer the dose.
- As a universal precaution, always wear gloves.

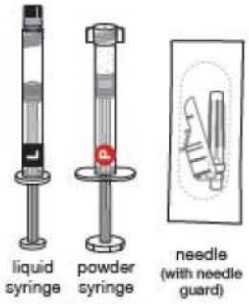
1 CHECK CONTENTS

See Figure 1

- One Liquid Syringe (L) prefilled with the (b) (4) Delivery System. Inspect liquid solution for foreign particles. This is the syringe you will use to inject the patient.
- One Powder Syringe (P) prefilled with Risperidone powder. Inspect syringe for consistency of powder color and for foreign particles.
- One sterile 18-gauge, 5/8-inch safety needle

Parenteral drug products should always be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Figure 1

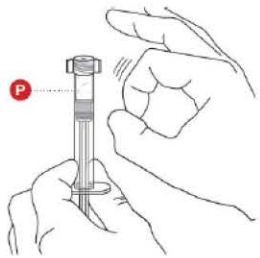


2 TAP POWDER SYRINGE

See Figure 2

Hold the Powder Syringe upright and tap the barrel of the syringe to dislodge the packed powder. NOTE Powder can become packed during shipping.

Figure 2

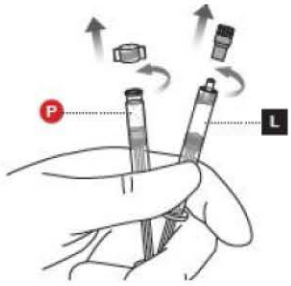


3 UNCAP LIQUID AND POWDER SYRINGES

See Figure 3

Remove the cap from the Liquid Syringe, then remove the cap from the Powder Syringe. Holding both syringes in your non-dominant hand can help with this step.

Figure 3



(b) (4)

4 CONNECT THE SYRINGES

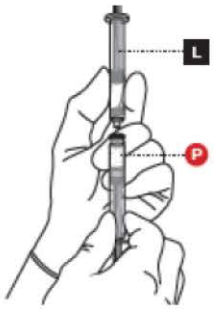
See Figure 4

Place the Liquid Syringe on top of the Powder Syringe (to prevent powder spillage) and connect the syringes by twisting approximately ¾ turn.

Do not over tighten.

Keep your fingers off the plungers during this step to avoid spillage of the medication.

Figure 4



5 MIX THE PRODUCT

See Figure 5

Failure to fully mix the medication could result in incorrect dosage.

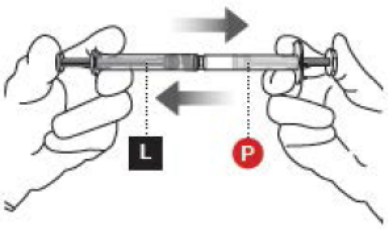
Premixing

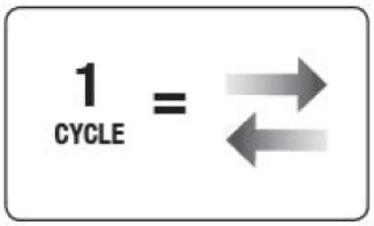
- Transfer the contents of the Liquid Syringe into the Powder Syringe.
- Gently push the Powder Syringe plunger until you feel resistance (to wet powder and avoid compacting).
- Repeat this gentle back-and-forth process for 5 cycles.

Complete mixing

- Continue mixing the syringes for an additional 55 cycles.
- This mixing can be more vigorous than when premixing.
- **Figure 5** illustrates a correct full cycle.

Figure 5





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)	Administration instruction are accurate.

Is the information accurate? ☒ Yes ☐ No

3. *Section 3 Dosage Forms and Strengths*

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

[redacted]

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Present
Strengths: in metric system	Present, needs to be updated
Active moiety expression of strength with equivalence statement (if applicable)	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Present

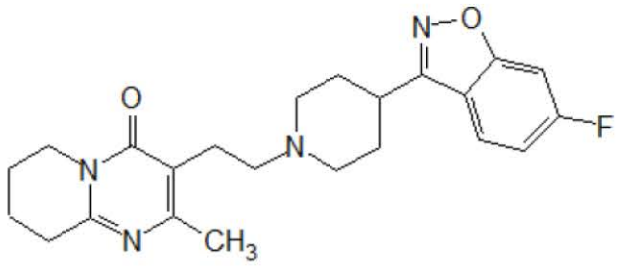
Is the information accurate? ☒ Yes ☐ No

4. *Section 11 Description*

11 DESCRIPTION

PERSERIS contains risperidone, an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives. The chemical designation 3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl) piperidin-1-yl] ethyl]-2-methyl-6,7,8,9-tetrahydropyrido[1,2-a] pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.5 g/mol.

The structural formula is:



(b) (4)

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	Does not contain established name
Dosage form and route of administration	Present
Active moiety expression of strength with equivalence statement (if applicable)	NA
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>)	Present but needs to be updated.
Statement of being sterile (if applicable)	Present
Pharmacological/ therapeutic class	Present
Chemical name, structural formula, molecular weight	Present
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	Included

Is the information accurate? ☒ Yes ☐ No

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

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	**Present, not accurate. Should state 90 mg/ 0.6 mL and 120 mg / 0.8 mL**
Available units (e.g., bottles of 100 tablets)	Present
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Present
Special handling (e.g., protect from light)	(b) (4)
Storage conditions	Store at 2° - 8°C (35.6° 46.4°F). PERSERIS may be stored in its original carton at room temperature, (b) (4) for up to 7 days prior to administration.
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Present

Reviewer's Assessment of Package Insert: ***Adequate***

Revisions identified and will be communicated to the Applicant as part of DPP labeling negotiations. The PI is adequate assuming Applicant accepts edits.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

[redacted]

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))	**Present, not accurate**	**Present, not accurate**
Dosage strength	**Present, not accurate**	**Present, not accurate**
Net contents	**Present, not accurate**	**Present, not accurate**
"Rx only" displayed prominently on the main panel	Present	Present
NDC number (21 CFR 207.35(b)(3)(i))	Present	Present
Lot number and expiration date (21 CFR 201.17)	Present	Present
Storage conditions	NA	Store at 2° - 8°C (35.6° 46.4°F). PERSERIS may be stored in its original carton at room temperature, (b) (4) [redacted] for up to 7 days prior to administration.

Bar code (21CFR 201.25)	Present	Present
Name of manufacturer/distributor	Present	Present
And others	NA	NA

Reviewer's Assessment of Labels: ***Adequate***

Revisions identified and will be communicated to the Applicant as part of DPP labeling negotiations. The Carton is adequate assuming Applicant accepts edits.

List of Deficiencies:

1. Update the strength throughout the label to 90 mg / 0.6 mL and 120 mg / 0.8 mL.
2. Remove the term (b) (4) from the label and replace it with (b) (4)
3. In the description section
    a. Include the proprietary name PERSERIS (risperidone) extended release injectable suspension, for subcutaneous use.
    b. Remove (b) (4) and replace with the following statements: (b) (4) (b) (4)
4. For the pouch, carton, and container labeling:
    a. Update the proprietary name to PERSERIS (risperidone) extended release injectable suspension, (b) (4)
    b. (b) (4)
    c. (b) (4)

Overall Assessment and Recommendation: Adequate assuming Applicant accepts edits.

Andrei Ponta

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Wendy Wilson- Lee

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BIOPHARMACEUTICS

Product Background:

NDA: 210655; 505(b)(2) NDA

Drug Product Name / Strength: PERSERIS™ (risperidone-ATRIGEL® One-month Depot) Suspension for Injection

Each kit contains a two-syringe mixing system and a sterile needle. Syringe B (labeled "P") contains 90 mg or 120 mg risperidone powder for reconstitution with the liquid in Syringe A (labeled "L") which contains (b) (4) mg or (b) (4) mg ATRIGEL® Delivery System. ATRIGEL® consists of (b) (4) 80:20 poly-D,L-lactide-co-glycolide (PLGH) polymer and (b) (4) *N*-methylpyrrolidone (NMP). Once the 90 and 120 mg powders are reconstituted in the liquid in Syringe A, the target delivered volumes of the viscous suspension are 0.6 and 0.8 mL, respectively.

Route of Administration/Dosing Frequency: For subcutaneous injection (into the abdomen); once monthly

Applicant Name: Indivior, Inc.

Review Recommendation:

From the Biopharmaceutics perspective, NDA 210655 for PERSERIS® (risperidone-ATRIGEL® Delivery System) is recommended for **APPROVAL.**

Review Summary:

In Vitro Drug Release Method and Acceptance Criteria

The proposed *in vitro* drug release (IVR) method and the revised IVR acceptance criteria (as shown in the table below) are approved for the routine QC of both strengths of PERSERIS™ (risperidone-ATRIGEL® Delivery System) at batch release and stability testing.

USP Apparatus	Flow Rate	Medium	Medium Volume	Acceptance criteria*
4 (Flow-Through Cell, closed loop)	16 mL/min	0.1% w/w Triton X-100, 9.7g/L Hanks Balanced Salt Solution without bicarbonate and phenol red (HBSS) pH 6.5, with 0.1% w/v sodium azide prepared in water, 40 °C	Added to cell to form solid depot: 8 mL Reservoir: 512 mL	(b) (4) % at 24 hours, % at 72 hours, NLT (b) (4) % at 168 hours

*per USP<711> Acceptance Table 2

Formulation Bridging
Formulation bridging data *per se* are not needed because there was no change in the formulation of risperidone – ATRIGEL Delivery System (a.k.a. RBP-7000) during clinical development. Based on the IVR profile comparisons of the clinical trial lots and bridging stability lots, the changes in the packaging, manufacturing scale and other process improvements after the conduct of the pivotal clinical trials are not anticipated to impact drug product performance.

Extended Release Claim
PERSERIS™ when injected subcutaneously at 90 mg and 120 mg doses every 28 days produced similar steady-state C_{avg} of risperidone and total active moiety and lower C_{max}-to-C_{min} fluctuation index as compared to 3 and 4 mg oral risperidone (given once daily), respectively. Based on these comparative PK study results, PERSERIS can be classified as an extended release formulation of risperidone because a single injection is able to prolong the dosing interval of the drug from once daily to once monthly.

Dose Dumping Studies
Based on the results of the *in vitro* dose dumping studies conducted, applied pressure and heat did not induce more than 10% higher risperidone drug release from RBP-7000. Note that the Pharmacology/Toxicology Reviewer confirmed that based on the results of the *in vivo* rat study, applied pressure and exercise did not increase the systemic exposure to risperidone and its metabolite (paliperidone).

In Vitro – In Vivo Correlation (IVIVC)
The Applicant was not successful in demonstrating IVIVC for the proposed QC *in vitro* drug release method, (b) (4)
(b) (4)

List of Submissions reviewed:
SDN-1, 09/28/2017; Original Submission
SDN-13, 12/14//2017; Response to Quality Information Request
SDN-14, 12/15/2017; Response to Clinical Pharmacology Information Request
SDN-18, 02/09/2018; Response to Quality Information Request
SDN-23, 3/19/2018; Response to Quality Information Request
SDN-24, 3/19/2018; Response to Quality Information Request
SDN-27, 3/28/2018; Response to Quality Information Request (Stability Update)
SDN-29, 03/30/2018; Response to Quality Information Request
SDN-30, 04/03/2018; Response to FDA Information Request
SDN-34, 05/15/2018; Response to Quality Information Request
SDN-40, 05/30,2018; Response to Biopharmaceutics Information Request

Concise Description of Outstanding Issues:
None

BCS Designation

Reviewer's Assessment: *NOT APPLICABLE*

A BCS-based biowaiver request is not applicable to extended-release drug products. For general information, refer to the drug substance solubility/permeability and drug product dissolution/drug release details below.

Solubility: *Low***.** After 24 hours incubation at 40 °C, the measured solubility of risperidone is highest in pH 4.0 buffer (25.481 mg/mL) and decreases with increasing pH (≥ 0.087 mg/mL). Risperidone is practically insoluble in water, soluble in 0.1N HCl, in RBP-7000 ATRIGEL® Delivery System (b) (4) and NMP (b) (4)

Permeability: The Applicant considers risperidone as a *High* permeability drug substance; however, supporting data are not available.

Dissolution: *Slow*. RBP-7000 (PERSERIS) exhibits (b) (4)% drug release within 10 days, when using the proposed QC *in vitro* accelerated drug release (IVR) method, and within 28 days when using the real-time IVR method.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

NOTE: During the development of RBP-7000, a total of three *in vitro* drug release (IVR) test methods were used, i.e., one 28-day real-time method and two accelerated methods. The initial (b) (4) accelerated (b) (4)) IVR method (b) (4) was used for the release of the clinical trial lots, whereas the final proposed commercial 7-day accelerated ("USP Apparatus IV") IVR method (b) (4) was developed (based on FDA advice) and used for the QC testing of the primary stability and the bridging stability batches, as well as some clinical trial lots. Additionally, real-time IVR data are available for late Phase 1 and aged Phase 3 clinical trial lots.

Dissolution Method: *ADEQUATE*

(b) (4)

(b) (4)

(b) (4) Of note, the proposed labeling states: "Store at 2° - 8°C (35.6° - 46.4°F). Allow PERSERIS kit to come to room temperature for at least 15 minutes prior to mixing. PERSERIS may be stored in its original carton at room temperature, (b) (4) , for up to 7 days prior to administration."

Justification for the Selected IVR Method Parameters

Per the Applicant, USP apparatus IV flow-through cell was chosen because it mimics the gentle flow of subcutaneous interstitial fluid across the drug product depot. (b) (4)

The proposed QC dissolution medium (modified Hank's Buffer Medium [HBS]) was selected as it simulates the pH and the composition of the interstitial fluid in the subcutaneous space. (b) (4)

(b) (4)

The proposed QC dissolution medium is maintained at 40 °C (b) (4)

(b) (4)

(b) (4)

(b) (4) Document WI.CMC.2027 provides the detailed

instructions on how to reconstitute the risperidone powder in Syringe B with the liquid in Syringe A, which are consistent with the instructions in the proposed package insert.

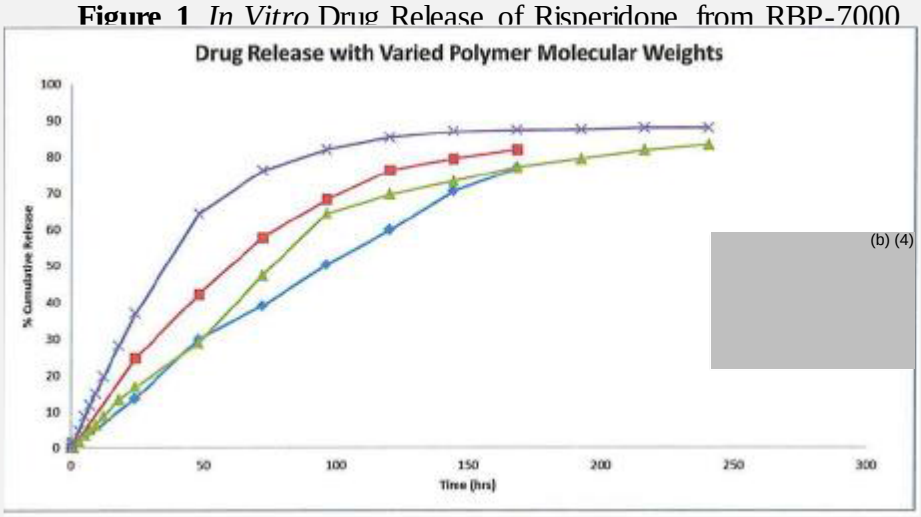
A flow rate of 16 mL/min was chosen (b) (4) (b) (4)

Discriminating Power

Unlike the initial (b) (4) accelerated IVR method, the proposed commercial QC 7-day accelerated IVR method showed discriminating power for changes in critical quality attributes related to the PLGH polymer including (***1***) PLGH Polymer molecular weight [Figures 1 and 1A], and (***2***) PLGH Polymer monomer composition (L-to-G ratio; Figure 2). Additionally, IVR testing using the proposed QC method showed trends of increasing drug release rates with increasing NMP content [Figure 3], and decreasing API particle size [Figure 4].

(b) (4)

Figure 1 *In Vitro* Drug Release of Risperidone from RBP-7000

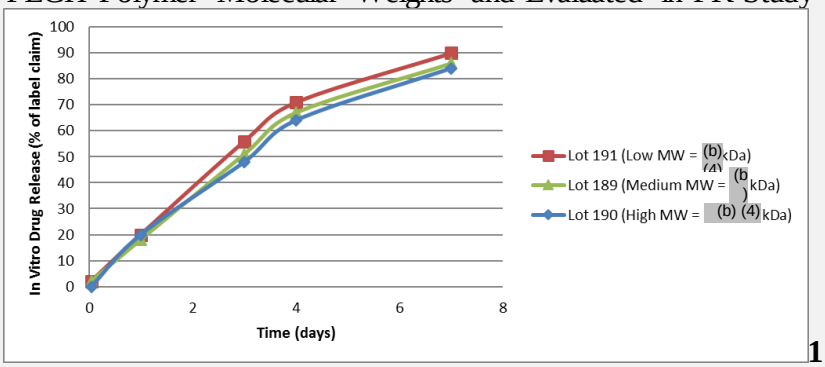


The drug product (120 mg) manufactured with low molecular weight PLGH polymer exhibited faster drug release (b) (4) Relative to (b) kDa, the profile similarity factors (f_2) of (b) kDa, (b) kDa, and (b) kDa are (b) (4) and (b) respectively. Note that (b) kDa and (b) kDa are outside the proposed PLGH MW specification for RP-7100 (b) (4) kDa). Thus, this Reviewer acknowledges the proposed QC method's limited capability to reject drug product batches manufactured with polymer MW as high as (b) kDa, particularly because the Applicant did not agree with the (originally) recommended acceptance range that would have allowed for the rejection of the (b) kDa variant. However, as pointed out by the Applicant, polymer MW will be independently controlled because it is part of the finished product QC specification.

Note that using the proposed QC IVR method, the drug products manufactured with varying PLGH polymer molecular weights (b) (4) and evaluated in PK Study 15-

0001 did not show significantly different *in vitro* drug release profiles; see Figure 1A. This lack of *in vitro* drug release profile difference is consistent with the acceptable *in vivo* systemic drug exposures following subcutaneous injections of the low and high polymer MW variant RBP-7000 lots relative to the intermediate polymer MW (reference) lot in PK Study 15-0001 (as confirmed by the Clinical Pharmacology Reviewer, Dr. Praveen Balimane). The Applicant stated that the inability to show bioequivalence of the test lots to the reference lot was due to the low sample size.

Figure 1A. Comparative *In Vitro* Drug Release Profiles of Batches Manufactured with Varying PLGH Polymer Molecular Weights and Evaluated in PK Study 15-0001



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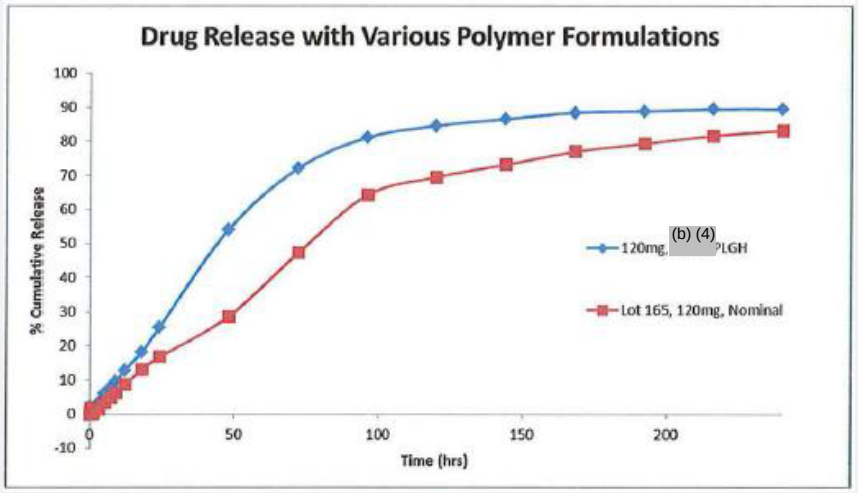
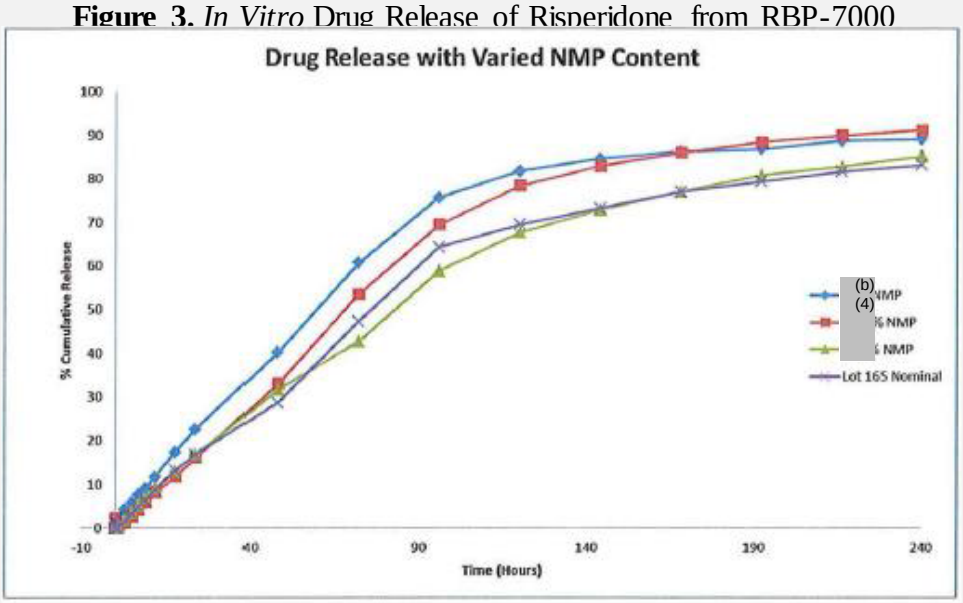
The drug product (120 mg) manufactured using a numerically lower MW polymer showed numerically faster *in vitro* dissolution rate. The IVR profile similarity factors (f_2) calculated for the RB-7000 lots manufactured using high MW and low MW polymers were 79 and (b) (4) respectively, suggesting comparability to the RB-7000 lot with medium MW polymer (PK Study 15-0001). Note that the batch manufactured using medium MW polymer (Lot 189) was also used in Phase 3 Study 13-0005.

Figure 2 *In Vitro* Drug Release of Risperidone from RBP-7000



The drug product (120 mg) containing (b) (4) L-to-G ratio in the PLGH polymer exhibited faster than target *in vitro* drug release due to (b) (4) (b) (4) The Reviewer's calculated profile similarity factor (f_2) for the drug product (120 mg) containing (b) (4) PLGH is 41, when compared to the drug product containing 80:20 PLGH. (b) (4) (b) (4)

Figure 3. *In Vitro* Drug Release of Risperidone from RBP-7000

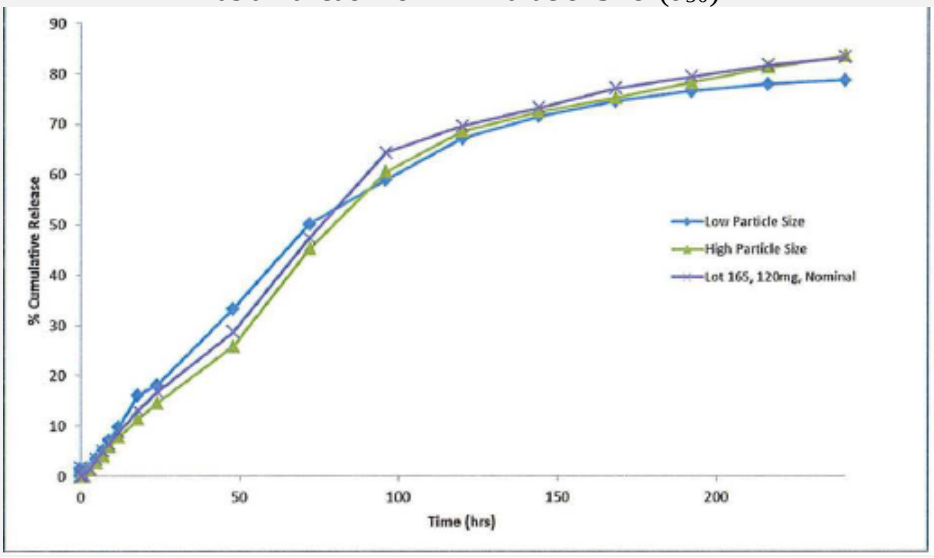


Per the Applicant, NMP (b) (4)

(b) (4)

(b) (4) he Reviewer's calculated profile similarity factors (f_2) for the drug product (120 mg) containing (b)% NMP and (b)% NMP are 51 and 57, respectively, when compared to the drug product containing the target NMP level (b)%; Clinical Lot 165). [Both NMP variant batches passed f_2 analysis; however, greater variations from the target NMP level are anticipated to produce f_2 <50.] Note that NMP content ((b) (4)% w/w) is part of the proposed finished product QC specifications for RBP-7000. Note also that suspension viscosity and syringeability influenced the selection of the NMP and PLGH levels in Syringe A.

Figure 4. *In Vitro* Drug Release of Risperidone from RBP-7000 as a Function of API Particle Size (d_{50})



Particle Size Range (microns)		Nominal Formulation	Low Particle Size	High Particle Size
d10	--	(b) (4)		
d50	(b) (4)			
d90	--			

The drug product (120 mg) with lower than target particle size of the API in Syringe B exhibited a numerically higher rate of drug release but only during the initial portion of the IVR profile than the two batches with API d_{50} within the target range. The rank-order relationship observed here between API PSD and drug release is consistent with that observed *in vivo* in rats; see Figure 1 of Report FC-FDV-0097R.] (b) (4)

(b) (4)

(b) (4)

(b) (4)

In Vitro – In Vivo Correlation/Relationship (IVIVC/IVIVR)

This Reviewer does not consider the Applicant's IVIVC to be successfully established for the proposed QC IVR method because (b) (4)

(b) (4)

(b) (4)

Analytical Method Validation

Quantification of drug in the IVR samples is accomplished (b) (4). The samples are stable up to 14 days at room temperature. The analytical method was validated for specificity, linearity, accuracy, precision. The standard and sample solutions were reported to be stable at room temperature for 7 days and 14 days, respectively. A case of intermediate precision failure was attributed to the storage of samples under freezing conditions. Note that the Applicant showed that the *in vitro* dissolution profile data are comparable with and without 9-day equilibration at 25 °C/60% RH prior to IVR testing. Note also that the Drug Product Reviewer (Dr. Andrei Ponta) considers the validation of the analytical method used for IVR Test Method (b) (4) to be adequate.

Sink Conditions

The solubility of risperidone drug substance in the QC dissolution medium at 40 °C is (b) (4) mg/mL. Per the Applicant, under the proposed conditions of QC dissolution testing, the measured solubility of risperidone reconstituted with the liquid in Syringe A is (b) (4) mg/mL, which represents (b) (4) and (b) (4) solubility (i.e., sink conditions) with respect to the 90 mg and 120 mg risperidone products, respectively.

Dissolution Acceptance Criteria: *REVISED ACCEPTANCE CRITERIA ADEQUATE*

For batch release and stability testing of both strengths of the proposed drug product, the originally proposed IVR acceptance criteria were "NMT (b) (4)% at 24 hours", (b) (4)% at 72 hours", and "NLT (b) (4)% at 168 hours".

Based mainly on the IVR profile data of the pivotal Multiple Ascending Dose (MAD) and Phase 3 (main and extension) trial lots at the time of clinical use (0 – 36 months old), i.e., generated using the proposed QC IVR method, this Reviewer initially recommended the following IVR acceptance criteria: (b) (4)% at 24 hours", (b) (4)% at 72 hours", and "NLT(b) (4)% at 168 hours".

Table 1. Proposed *In Vitro* Drug Release Acceptance Criteria

Attributes	Analytical Procedure	Acceptance Criteria
Extended Release (Cumulative % Release)	Apparatus IV Dissolution with HPLC Analysis	(b) (4)

Source: 3.2.P.5.1

A single set of *in vitro* drug release acceptance criteria is appropriate for both 90 mg and 120 mg strengths of RBP-7000 because this Reviewer did not observe strength- or dose-dependent *in vitro* drug release; see Figure 6. Such recommendation is supported by the observation that when injected into rats, the size of the *in situ* implant or the dose injected subcutaneously did not impact the rates of drug release (b) (4) see Figure 2 of Section 3.2.P.2.2 Drug Product.

(b) (4)

(b) (4)

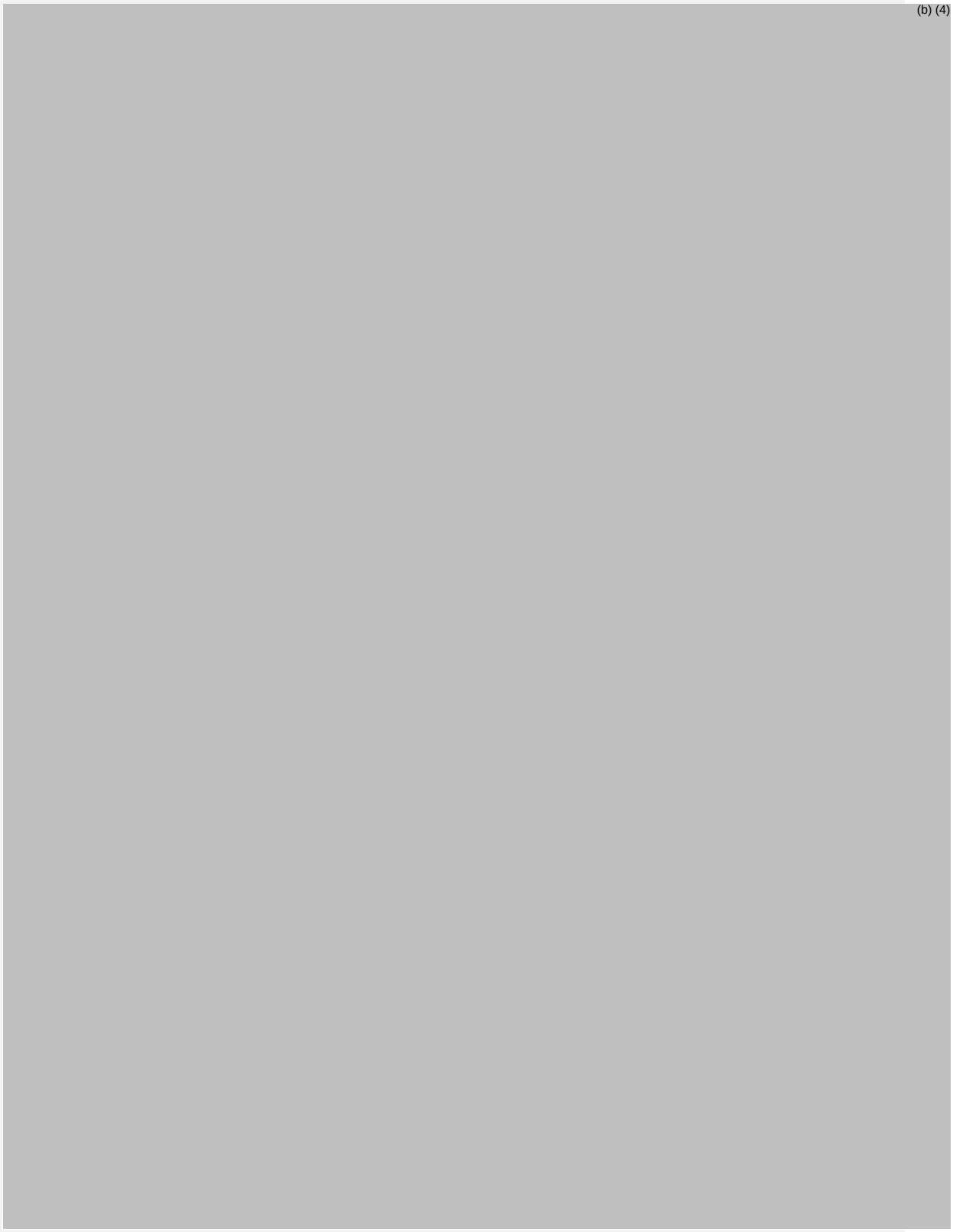


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Figure 6A

Dissolution on Stability

Note that throughout 12 months of long-term stability testing [5 ± 3°C (2 to 8°C)] all six bridging stability lots conform to the Reviewer's recommended IVR acceptance criteria (with no consistent trends), except for Lot #233 at Month 12 of long-term stability testing. Based on FDA simulation analysis (using the Division of Biopharmaceutics Automation Tool, Version R-3.3.2), the Month 12 long-term stability sample of Lot #233 is not anticipated to pass USP Level 3 testing using either the Applicant's final counter-proposed or this Reviewer's recommended acceptance criteria. However, it should be noted that the Applicant's root-cause investigation (conducted per FDA request) suggested that analyst error was the cause of the out-of-specification result of the non-conforming lot.

Note also that the proposed expiration dating period for the drug product is 18 months when stored under refrigeration (5 ± 3°C). Per the Applicant, freeze/thaw and temperature stress conditions did not affect the quality attributes of the proposed drug product.

In the 05/30/2018 Response to the Biopharmaceutics Information Request dated 05/25/2018, the Applicant revised the finished product QC specification for batch release and stability testing to reflect agreement with the FDA's final recommended IVR acceptance criteria (b) (4) % at 24 h', (b) (4) % at 72 hours', 'NLT (b) (4) % at 168 h').

LONG-ACTING INJECTIONS – Dose Dumping Potential with and without external stressors

Reviewer's Assessment: *ACCEPTABLE*

Per the Applicant, therapeutic risperidone plasma concentrations are attained after the first injection of RBP-7000, without a loading dose nor any supplemental oral risperidone. Following subcutaneous injection of RBP-7000, two absorption peaks with similar C_{max} values are observed. (b) (4)

(b) (4)

Based on the results of the PK simulation study, the Applicant reported that approximately (b) (4)% of the risperidone load of RBP-7000 is associated with the first peak and thus, concluded that the dose dumping potential of the proposed drug product is minimal. This Reviewer attempted to use *in vitro* drug release data to estimate the amount of drug release prior to solid depot formation *in vivo*. Judging from the standard test procedure provided (where the first step is the addition of 8 mL of the dissolution medium to transform the sample into a solid mass), this Reviewer believes that the IVR method is able to simulate mainly the drug release after the solid depot forms *in vivo*. However, the maximum amount of the drug that is released immediately i.e., prior to solidification of the depot, can be estimated graphically as the y-intercept at time = 0 hours. Thus, based on the IVR profile data available for the MAD and Phase 3 clinical trial lots, this Reviewer estimates that NMT (b) (4)% of the total risperidone load is typically released prior to the formation of the solid depot. This Reviewer believes that the (b) (4)% drug release is what possibly corresponds to the first peak of the plasma concentration - time curve of RBP-7000 following subcutaneous injection. Additionally, based on the relative bioavailability results of PK Study 09-0009, this Reviewer estimates that if in case the early drug release following a subcutaneous injection of 90 mg or 120 mg risperidone-Atrigel™ one-month depot doubles (e.g., to NMT (b) (4)%), the resulting total active moiety Cmax,ss (associated with the first peak) is anticipated to be lower than that produced following chronic administration of oral risperidone 8 mg daily, and the Cmin,ss would be expected to be lower than that following 16 mg daily oral risperidone; see Figure 22 of the Applicant's 12/15/2017 Response to FDA Information Request dated 12/1/2017. Note that per the Risperdal® oral tablet USPI, for adult schizophrenia, the target maintenance dose is 4 to 8 mg and the effective dose range is 4 – 16 mg daily.

Effect of External Stressors on *In Vitro* and *In Vivo* Drug Release

To investigate the effect of external stressors (e.g., applied static pressure or intermittent pressure [depot manipulation], exercise, and applied heat) on the dose-dumping potential of the proposed drug product, *in vitro* studies and *in vivo* animal studies were conducted. Note that the *in vitro* drug release method used 100 mL of medium similar to the proposed QC IVR medium (b) (4)

(b) (4)

(b) (4) In the *in vitro* study (FC-ADV-0016R), the external stress factors were simulated as follows:

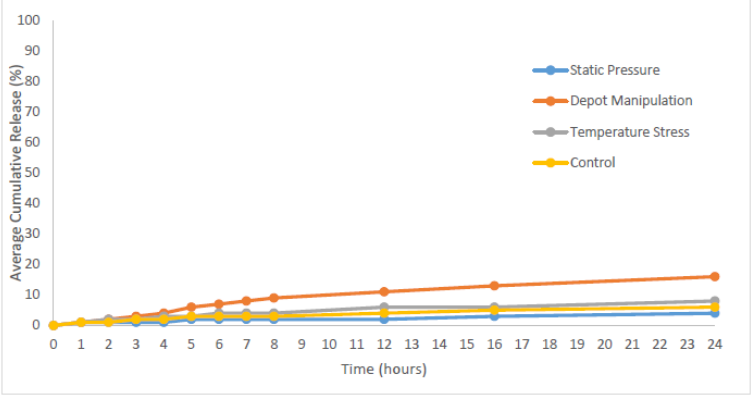
1. intermittent pressure (i.e., depot manipulation) – by compressing the formulation in a screen cassette with a 200-gram weight for 10 seconds on each side prior to each sampling time point
2. static pressure (e.g., wearing tight clothes around the abdominal area) – by compressing a group of filled screen cassettes with a 200-gram weight (12 hours per side)
3. elevated temperature (e.g., heat application, fever) – submersion of filled screen cassettes in HBSS media maintained at 42 ± 0.5°C.

Based on the protocol-specified acceptance criteria, dose dumping was to be declared if the absolute difference between the mean risperidone release (%) for each test group and the mean risperidone release (%) for the control group is greater than 20% at the 24-hour time point. The difference between the control and intermittent pressure featured the largest discrepancy (10%) following the intermittent pressure procedure, with both other conditions leading to an absolute difference of 2% release (Figure 7). This Reviewer does not consider a NMT (b) (4) % absolute difference in *in vitro* drug release (with versus without external stressor) as significant because mean (b) (4) % is typically used in the setting of the *in vitro* drug release acceptance range. Additionally, the calculated profile similarity factors for intermittent pressure, temperature, and static pressure were 63, 92, and 88, respectively, suggesting comparable drug release at 24 hours relative to the control.

Similarly, in the *in vivo* animal study, applied pressure on the injection site and exercise increased drug release over 24 hours by NMT 7% as compared to controls; see Table 2 for the amounts of residual drug in the explanted depots at 2, 12, and 24 hours post-injection. Based on the evaluation of the results of this *in vivo* animal dose-dumping study (INRS-R144-70-15), the Pharmacology/Toxicology Reviewer (Dr. Sonia Tabacova) concluded that there is no indication that implant manipulation by pressure or exercise increased the release of risperidone from the implant or the systemic exposure to risperidone and its metabolite (paliperidone).

Figure 7

In Vitro Drug Release Profiles in the Presence/Absence of Simulated Applied Pressure and Elevated Temperature [FC-ADV-0016R]



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Sample	Test Condition	RSP Release at 24 Hours	
		Mean (%)[a]	Absolute Difference from Control (%)
Control	37±0.5°C	6	-
Temperature	42±0.5°C	8	2
Static Pressure	37±0.5°C and 200-g weight for 24 hours	4	2
Intermittent Pressure	37±0.5°C and 200-g weight for 10-seconds/ side prior to sampling	16	10

RSP=risperidone
[a] N=12

Table 2. Risperidone Content in *Ex Vivo* Depots at Various Timepoints following Subcutaneous Injection with a 90 mg Dose, in the Presence/Absence of External Stressors (i.e., Applied Pressure and Exercise) [INRSR144-70-15]

Group (Description)	Time Point (h)	Mean ± SD RSP in Depots (mg)	Mean ± SD RSP Release (%)	Release Difference (Absolute) Relative to Control Group 5 (%)
Group 2: 90 mg RBP-7000, pressure applied on injection site after injection (pressure)	2	80.7 ± 3.8	10.3 ± 4.2	1.3%
	12[a]	77.6 ± 4.7	13.7 ± 5.2	3.7%
	24[a]	77.7 ± 2.6	13.7 ± 2.9	-1.4%
Group 4: 90 mg RBP-7000 exercise group (exercise)	2	75.7 ± 6.9	15.9 ± 7.6	6.9%
	12	77.0 ± 10.0	14.5 ± 11.1	4.5%
	24	72.5 ± 8.6	19.4 ± 9.6	4.3%
Group 5: 90 mg RBP-7000, control (control)	2	81.9 ± 4.8	9.0 ± 5.3	-
	12	81.0 ± 3.6	10.0 ± 4.0	-
	24	76.4 ± 3.9	15.1 ± 4.3	-

RBP-7000= (b) (4)% risperidone in ATRIGEL Delivery System ((b) (4)% 80:20 PLGH in (b) (4)% NMP); RSP=risperidone; SD=standard deviation
[a] N=11

Extended Release Claim

Reviewer's Assessment: *ADEQUATE*

The RBP-7000 formulation (PERSERIS™) is a suspension of risperidone ((b) (4)% w/w) in ATRIGEL® [a non-aqueous solution of (b) (4) polymer, 80:20 poly (DL-lactide co-glycolide) (b) (4) (PLGH), and a (b) (4) (b) (4) N-methyl-2-pyrrolidone (NMP)]. (b) (4) subcutaneously and releases risperidone for a minimum of 28 days (b) (4) (b) (4). Thus, it is appropriate to classify RBP-7000 as an extended release drug product because in the MAD Study RB-US-09-0009, 90 mg and 120 mg doses when injected subcutaneously every 28 days produced similar steady-state C_{avg} of risperidone and total active moiety, and lower C_{max}-to-C_{min} fluctuation index as compared to 3 and 4 mg oral risperidone (given once daily), respectively.

Bridging of Formulations

Reviewer's Assessment: *ADEQUATE*

The final, proposed to-be-marketed drug product has the same formulation, strengths (90 mg and 120 mg), manufacturing process steps, API and ATRIGEL® Delivery System suppliers (b) (4) as the product that was investigated in the Phase 3 clinical trials (main trial RB-US-09-0010, and extension trial RB-US-13-0005) and the reference product used in the late Phase 1 trial (RB-US-15-0001). Note that there were no formulation changes during clinical development of RBP-7000; see Tables 1 and 2 of the Applicant's 12/15/2017 Response to FDA Information Request dated 12/1/2017.

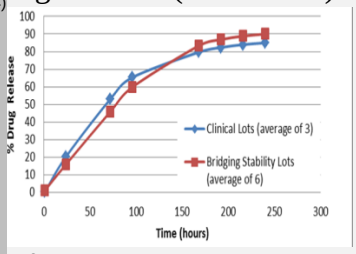
The proposed commercial Syringe B manufacturer (Patheon, NC) and the proposed commercial packager (b) (4) are different from those used for the Phase 3 clinical trial lots (b) (4) respectively). Additionally, process improvements and changes in the secondary packaging configuration occurred after the manufacture of the primary stability batches. The primary stability lots were packaged with a (b) (4) but for commercial packaging, this (b) (4) will not be included (as is the case for the bridging stability lots), similar to what was done in the Phase 3 clinical lots. The process improvements (b) (4) (b) (4) According to the Process Reviewer (Dr. Mark Johnson), the process improvements made throughout development are not anticipated to have any significant impact on the performance of the proposed drug product. Furthermore, as shown in Figure 8, the *in vitro* drug release profile data of the bridging stability lots manufactured to support these proposed changes are comparable to those for the Phase 3 clinical trial lots; the Biopharmaceutics Reviewer's calculated profile similarity factor (f_2) is 66, when using the average drug release profiles of the test and the reference lots generated using the proposed QC accelerated IVR (USP Apparatus 4) method. When using the original accelerated (b) (4) IVR method, the Reviewer's calculated f_2 between the average IVR profiles of the same test and reference batches is (b) (4)

Note that late Phase 1 Study RB-US-15-0001 investigated the impact of varying PLGH molecular weight (b) (4) on the PK of risperidone and paliperidone. The MAD PK Study RB-US-09-0009 compared the steady-state plasma risperidone and paliperidone concentrations following administrations of oral risperidone [generic; Wockhardt Ltd.] 2, 3, or 4 mg/day vs. RBP-7000 60, 90, or 120 mg every 28 days. Refer to the Clinical Pharmacology Review for the evaluation of the PK and safety/tolerability results of these two PK Studies.

Figure 8

Comparative *In Vitro* Drug Release Profiles of the Clinical Trial Lots and the Bridging Stability/Proposed Commercial Lots of the Proposed Drug Product (at Month 0)

(b) (4)



f_2 = 66

Biowaiver Request

Reviewer's Assessment: *NOT APPLICABLE*

A biowaiver request was not submitted nor required. The PK, efficacy and safety of both strengths of the proposed to-be-marketed formulation were evaluated in clinical trials (Multiple Ascending Dose PK Study RB-US-09-009 and in Phase 3 Clinical Trials 09-0010 and 13-0005).

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer Name and Date: Gerlie Gieser, Ph.D. (6/4/2018)

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Ta-Chen Wu, Ph.D. (6/5/2018)

Gerlie Gieser

Digitally signed by Gerlie Gieser
Date: 6/05/2018 10:14:55PM
GUID: 507592ba00003d190b2ea34fe8fb8ccb

Ta-Chen Wu

Digitally signed by Ta-Chen Wu
Date: 6/05/2018 10:17:57PM
GUID: 508da6df000269e151ff37cd8f4e13a1

MICROBIOLOGY

IQA Review Guide Reference

Product Background:

NDA/ANDA: N210655

Drug Product Name / Strength: PERSERIS™ (risperidone) (RBP-7000) Risperidone-ATRIGEL®/90 mg and 120 mg/syringe

Route of Administration: subcutaneous injection
Single dose, monthly (minimum of 28 days)

Applicant Name: Indivior, Inc.

Manufacturing Site:
Syringe A (device: ATRIGEL® Delivery System)-Albany Molecular Research, Inc (AMRI Burlington), 99 South Bedford St., Burlington, MA 01803

Syringe B (drug: Risperidone™)- Patheon Manufacturing Services, LLC, 5900 Martin Luther King Jr. Highway, Greenville, NC 27834

Method of Sterilization: (b) (4)

Review Recommendation: Adequate

Review Summary: The drug product and delivery (b) (4) packaged in 2 different syringes are (b) (4).

List Submissions Being Reviewed:
09/28/2017 (Original submission)
10/10/2017 (Revised Labeling)
10/19/2017 (Revised Labeling)
12/14/2017 (Revised Batch Analyses)
12/22/2017 (Updated Stability Data)
03/15/2018 (Micro IR responses)
04/13/2018 (Micro IR responses)
05/02/2018 (Micro IR responses)
05/14/2018 (Micro IR responses)

Highlight Key Outstanding Issues from Last Cycle:
N/A

Remarks: RBP-7000 is a combination product (drug/device) presented as a 2-syringe system with 1 syringe (Syringe B) containing risperidone (the drug) and the other syringe (Syringe A) containing ATRIGEL® delivery system (b) (4) The two syringes are packaged in individual (b) (4) pouches and placed into a (b) (4) carton with a pre-packaged, sterile safety needle, (b) (4)

Per the filing meeting on 02 Nov 2017, DMA will review (b) (4) .

Concise Description Outstanding Issues Remaining: None

Supporting Documents:

(b) (4)

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

The drug substance (risperidone) and the excipients (components of the ATRIGEL® delivery system) that compose the drug product are (b) (4) See discussion of Microbial Attributes in Section P.2.5.

P.1 Description of the Composition of the Drug Product

- **Description of drug product**
  RBP-7000 is a sterile, non-aqueous suspension for subcutaneous injection for the treatment of schizophrenia. RBP-7000 is a combination product (drug/device) presented as a 2-syringe mixing system with 1 syringe (Syringe B) containing risperidone, and the other syringe (Syringe A) containing ATRIGEL® delivery system (a non-aqueous solution of excipients of a (b) (4) polymer and a (b) (4) (b) (4) The final RBP-7000 formulation is a suspension of risperidone (b) (4) % w/w) and polymer (b) (4) that results after the contents of the two syringes mixed together. RBP-7000 forms a solid depot when injected subcutaneously and releases risperidone for a minimum of 28 days (b) (4) The constituted product appears as a white to yellow-green viscous suspension.

- **Drug product composition**
  The drug product is formulated in two strengths of 90 mg and 120 mg. The composition is summarized below:

Syringe	Ingredient	Delivered mass	
		90 mg dose (mg / %)	120 mg dose (mg / %)
B	Risperidone	90 mg (b) (4)	120 mg (b) (4)
A	PLGH Polymer	228 mg	304 mg
	N-methyl-2-pyrrolidone	282 mg	376 mg
A/B constituted (in Syringe A)	Target formulation weight	600 mg	800 mg
A/B constituted (delivered from A)	Target delivered volume	0.6 mL	0.9 mL

- **Description of container closure system –**
The container closure system for drug and delivery system is shown in the table below. Syringe A (the ATRIGEL® delivery system) is a 1 mL syringe with a (b) (4) (b) (4) tip, tip cap, rubber plunger stopper, and plunger rod. The container closure system for Syringe B (the drug substance, risperidone powder) is a 1.2 mL syringe with a (b) (4) tip, tip cap, plunger stopper, and plunger rod. Syringe A and Syringe B are each placed individually into separate (b) (4) pouches (secondary packaging) that are (b) (4) and placed in a (b) (4) carton" along with a sterile safety needle supplied in a separate individual package by (b) (4) Information below is reproduced from Figures 1 and 2 and Tables 1 and 2 in 3.2.P.7. The same containers and closures are used for both the 90 mg and 120 mg dosage forms.

Figure 1 Schematic of Syringe A (Liquid Syringe, L) and Syringe B (Powder Syringe, P) (not to scale)

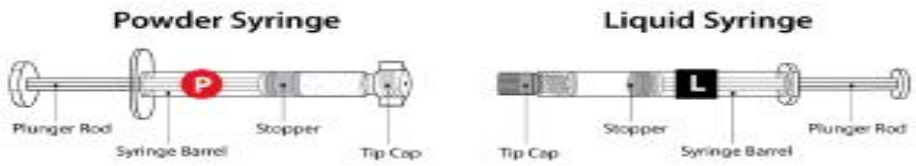
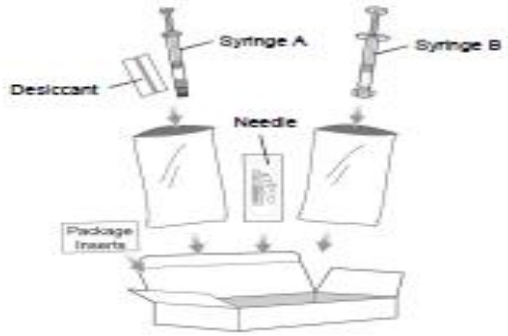


Figure 2 Commercial Packaging Configuration (not to scale)



Syringe	Component	Description	Manufacturer
A	Syringe	(b) (4)	
	Stopper		

(b) (4)

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

The applicant provides an adequate description of the components that will be tested for sterility, and provides an adequate Drug Product Release and Stability Specification.

P.7 Container Closure

See above

Reviewer's Assessment: ***Adequate***
See above

P.8 Stability

P. 8.1 Stability Summary and Conclusion

The current proposed shelf life of the product is 18 months at 2-8°C.

The start of the product shelf-life is set at the initial filling of the ATRIGEL® delivery system manufactured at AMRI and the initial filling of each Syringe B unit at Patheon, therefore, each syringe will have its own respective shelf life. The kit shelf life (Syringe A and B in the finished packaging paper carton) will be based on the shortest shelf life assigned to each of the Syringe A and B units.

Multiple stability studies are ongoing, however, only the bridging stability studies use the commercial container closure system and commercial packaging configuration. Therefore, only bridging stability data will be reviewed.

Bridging stability data are presented from 3 lots of each strength of 90 mg and 120 mg after 6-month storage at the ICH Q1A conditions of 2 to 8°C and 25°C/60% RH (b) (4) The samples stored at 2-8°C are removed from refrigeration 9 days prior to the long-term storage testing time point and then stored at 25°C/60% RH prior to analysis at the ICH suggested time points (b) (4) (b) (4). Table 2 of Section 3.2.P.8.1, (microbiological tests reproduced below) shows the analysis schedule.

Attribute	Time Point (Months)								(b) (4)
	1	3	6	9	12	15 [a]	17 [b]	18	
Constituted Product									
Bacterial Endotoxins	-	-	25°C	-	5°C	-	-	5°C, 25°C	
Sterility	-	-	5°C, 25°C	-	5°C, 25°C	-	-	5°C, 25°C	

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

The applicant has adequately summarized stability testing for the drug product.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant states that after approval of the NDA, the first three production batches of each strength will be tested for sterility (b) (4) . Yearly thereafter, the applicant will add a minimum of one production batch of each strength to the long-term stability program (b) (4) .

Endotoxin is proposed to be tested at release (T0), 24 and 36 months (until desired expiration date is reached) under long term storage conditions (2-8°C), and sterility testing is proposed (b) (4)

Per Section 3.2.P.2.5, p. 2 of 7, "during stability evaluation, the constituted product is assessed for sterility (Section 3.2.P.8.3). Package integrity testing of syringe pouches (b) (4) ensures the container closure system is suitable to maintain the sterility of the drug product throughout shelf-life. (b) (4) (b) (4)

IR sent 03/02/18:

(b) (4)

IR response of 03/15/2018:

(b) (4)

IR sent 03/30/18:

7. *We acknowledge your commitment to perform sterility and endotoxin testing on the stability program at the beginning and end of shelf-life. Additionally we acknowledge that CCIT will be performed on the stability program at the end of shelf life using a* (b) (4) *method on the pouches containing Syringe A and Syringe B. Therefore, provide a revised stability protocol indicating the performance of sterility and endotoxin testing at the 0 and 18 month time points and the performance of CCIT at the 18 month time point. Additionally, the stability specification should indicate the CCIT method, the associated*

acceptance criteria, and a reference to the method protocol. A revised stability protocol and specification are required to complete the review process.

IR response of 04/13/2018:

The applicant provided an updated drug product stability protocol to indicate performance of the sterility and endotoxin testing at the 0 and 18 month time points, and the performance of the CCIT at the 18 month time point. The revised Regulatory Post-Approval Stability Protocol is included in Section 3.2.P.8.2. The protocol indicates that stability data post 18 months that support an increased shelf life will be used as the end of the shelf life test. The regulatory specification for finished product release and stability testing in Section 3.2.P.5.1 was updated to reflect the changes. The "Leak Testing by (b) (4) is listed under the testing for Syringe A and again under Syringe B, it is not clear from the specification that this applies to the "pouched" syringes.

IR sent 04/23/18:

5. *We acknowledge your revised regulatory specification, and the revised stability protocol indicating the performance of container closure integrity testing (CCIT) using a (b) (4) method at the 18 month time point. However, the regulatory specification and the post-approval stability protocol are unclear because container closure integrity (CCI) is listed as an attribute for Syringe A and Syringe B, implying that the syringes themselves will be tested. Clarify if both syringes and pouches (containing the syringes) will be tested for CCI or if only the sealed pouches will be tested. Modify the regulatory specification and post-approval stability protocol for clarity to reflect the component(s) that will be subject to CCIT.*

IR response of 05/02/2018:

The applicant updated the RBP-7000 Drug Product Release and Stability Specification in Section 3.2.P.5.1, and the Post-Approval Stability Protocol in Section 3.2.P.8.2 (p. 3 of 4) to include a footnote stating that CCIT testing will encompass the individually sealed pouch, containing the filled syringe (not the individual syringe). Excerpts from the revised protocol are as follows:

Table 1 RBP-7000 Post-Approval Stability Protocol

Attribute	Test Intervals (months) / Storage Condition					
	0 [a]	3	6	9	12	18
		LT	LT	LT	LT	LT
Pouch Integrity						
Pouch A Container Closure Integrity [b]						X
Pouch B Container Closure Integrity [b]						X
Constituted Product						
Endotoxins [c]	X					X
Product Sterility						
Sterility [c]	X					X

[b] Container closure integrity (CCI) testing will be performed at the end of shelf life. Testing will encompass the individually sealed pouch containing the filled syringe A and individually sealed pouch containing the filled syringe B.
[c] Endotoxin and sterility testing will be performed at the beginning and end of shelf life. Sterility is performed on the syringe A contents and assembly (syringe, tip cap, plunger and plunger rod) and syringe B contents and assembly (syringe, tip cap, plunger and plunger rod).

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

The applicant provides a stability protocol indicating the 18 month time point for endotoxin and sterility testing and revised specification. "Leak Testing by (b) (4) is listed under the testing for Syringe A and again under Syringe B with a footnote clarifying that the testing is performed on the individually sealed pouch containing the filled syringe.

P.8.3 Stability Data

The applicant provides stability testing data for primary stability, bridging stability, and clinical stability lots. Only the bridging stability studies use the commercial container closure system and commercial packaging configuration. Therefore, only bridging stability data will be reviewed. Identification of bridging stability lots, including the timing between date of manufacture and date or (b) (4) is shown below, reproduced from Table 1 in Section 3.2.P.8.1.

Lot Number	Finished Packaged Units	Strength	(b) (4)	Date of Manufacture and Site	(b) (4) (b) (4)	Batch Use
Lot 218	4210	90 mg				
Lot 221	4160	90 mg				
Lot 224	2630	90 mg				
Lot 227	4320	120 mg				Bridging Stability
Lot 230	3720	120 mg				
Lot 233	4080	120 mg				

For endotoxins, all 6 lots met the proposed acceptance criteria for endotoxin (NMT (b) (4) EU/Unit) at time of release.

For sterility, per Section 3.2.P.8.1.4.4.5, "Bridging stability up to 6 months at 2-8°C with 7 days in -use storage at 25°C / 60% RH and 6 months at 25°C / 60% RH have demonstrated results within the proposed acceptance criteria."

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

The applicant has provided adequate data for stability.

A Appendices

A.2 Adventitious Agents Safety Evaluation

N/A

A.2.1 Materials of Biological Origin

TSE/BSE statements have been provided from AMRI Burlington and Patheon to certify that incoming materials at their respective facilities do not contain ruminant-derived materials from bovine spongiform encephalopathy (BSE) countries.

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

The firm provided sufficient information to justify that there are no known materials of biological origin in the product.

A.2.2 Testing at Appropriate Stages of Production

N/A

A.2.3. Viral Testing of Unprocessed Bulk

N/A

A. 2.4 Viral Clearance Studies

N/A

R Regional Information

Executed Batch Records

Batch records were consistent with the process described and contained appropriate certificates from raw material suppliers as related to sterility assurance.

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

Batch records were consistent with microbiological testing indicated in the application.

Comparability Protocols

N/A

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

2.A. Package Insert

The package insert indicates that the drug product should be stored at 2-8°C.

- **Post-dilution/constitution hold time**

No hold times are indicated on the package insert for drug product after constitution with the ATRIGEL® delivery system (10/10/17 submission). Instructions for use indicate to "Allow package to come to room temperature for at least 15 minutes (b) (4)

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

The absence of any information regarding a maximum storage time before and after mixing in the package insert has been identified and will be addressed by the labeling reviewers and medical officers.

Post-Approval Commitments:
N/A

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date: *Amy McDaniel, Ph.D. (05/17/2018)*

Secondary Reviewer Name and Date: *Marla Stevens-Riley, Ph.D. (05/17/2018)*

Amy McDaniel

Digitally signed by Amy McDaniel
Date: 5/22/2018 09:14:29AM
GUID: 59de8336003fd4c45db4076388ff0398

Marla Stevens Riley

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