

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212849Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

Executive Summary.....	2
Drug Substance..... see previous CMC IQA's dated 11 Jan 2022, 9 Dec 2019 and 28 Mar 2019	
Drug Product..... see previous CMC IQA's dated 11 Jan 2022, 9 Dec 2019 and 28 Mar 2019	
Environmental..... see previous CMC IQA's dated 11 Jan 2022, 9 Dec 2019 and 28 Mar 2019	
Labeling.....	6
Process/Manufacturing... see previous CMC IQA's dated 11 Jan 2022, 9 Dec 2019 and 28 Mar 2019	
Biopharmaceutics.....	19
Microbiology..... see previous CMC IQA's dated 11 Jan 2022, 9 Dec 2019 and 28 Mar 2019	



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	20 Oct 2022	Revision:	00
Total Pages:	3		



Template Revision: 03

NDA 212849 Executive Summary Assessment 3

1. Application/Product Information

NDA Number.	212849		
Applicant Name	Shandong Luye Pharmaceutical Co., Ltd. 12.5 mg, 25 mg, 37.5 mg and 50 mg		
Drug Product Name	Risperidone Injection, extended release		
Dosage Form.	Injection, extended release		
Proposed Strength(s)	12.5 mg, 25 mg, 37.5 mg and 50 mg		
Route of Administration	Intramuscular		
Maximum Daily Dose	N/A		
Rx/OTC Dispensed	Rx		
Proposed Indication	treatment of schizophrenia and bipolar I disorder		
Drug Product Description	(b) (4) Risperidone microspheres must be suspended in the diluent provided in dose pack prior to injection.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	2°- 8°C (36°- 46°F)		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	N/A	N/A
	<i>Drug Product/ Labeling</i>	Andrei Ponta	Julia Pinto
	<i>Manufacturing</i>	Yongming Lu	Jingbo Xiao



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	20 Oct 2022	Revision:	00
Total Pages:	3		



Template Revision: 03

	<i>Biopharmaceutics</i>	Kalpana Paudel	Ta-Chen Wu
	<i>Microbiology</i>	N/A	N/A
	<i>Other (specify):</i>		
	<i>RBPM</i>	Teshara Bouie	
	<i>ATL</i>	Valerie Amspacher	
Consults			

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: The final packaged drug product containing the risperidone microspheres and diluent is granted a 24 month shelf life when stored under refrigerated conditions 2°- 8°C (36°- 46°F).

The vial containing risperidone microspheres has been granted 24-month expiry when stored under refrigerated conditions 2°- 8°C (36°- 46°F) based on the long-term stability data provided. The diluent vial has been granted 36-month expiry when stored under refrigerated conditions 2°- 8°C (36°- 46°F) based on the long-term stability data provided. The dose pack expiry is to be determined by the shortest of the two vials.

b. Additional Comments for Action

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

This resubmission is in response to a Complete Response Letter dated 18 Feb 2022. In this resubmission, no new information is submitted for drug substance, drug product, process/facilities and microbiology. Those disciplines recommended approval in the previous review cycle and remain approval in this review cycle.



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	20 Oct 2022	Revision:	00
Total Pages:	3		



Template Revision: 03

See CMC IQA dated 11 Jan 2022 in which a previous resubmission dated 19 Aug 2021 was reviewed in response to a Complete Response Letter dated 28 Jan 2020. See also previous CMC IQA dated 9 Dec 2019 which is a review of the original NDA submission dated 28 Mar 2019.

The information provided supports the proposed product design, commercial formulation, dosage form, compatibility, specification, expiration and overall control strategy of the drug product. The information provided is adequate to assure the identity, strength, quality, purity, and potency, and bioavailability of the drug product so that future commercial production batches are comparable to the pivotal clinical batches for the clinical performance in terms of the safety and efficacy.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Quality Labeling	-	Adequate
Manufacturing	-	Adequate
Biopharmaceutics	-	Adequate
Microbiology	-	Adequate

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No

Comments:

Additional Lifecycle Comments:



Valerie
Ampacher

Digitally signed by Valerie Ampacher

Date: 12/01/2022 10:54:01AM

GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	RYKINDO (risperidone) for extended-release injectable suspension, for intramuscular use
Dosage form, route of administration	For extended-release injectable suspension, intramuscular
Controlled drug substance symbol	Not Applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	For extended-release injectable suspension: 12.5 mg, 25 mg, 37.5 mg, and 50 mg

Is the information accurate? Yes No

The Applicant will be asked to update the established name to: RYKINDO (risperidone) for extended-release injectable suspension, for intramuscular use.

The Applicant will be asked to update the dosage form from vial kits to for extended-release injectable suspension.

This will be communicated to the Applicant as part of DP labeling negotiations.

2. Section 2 Dosage and Administration

(b) (4)



(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation	Conforms

Is the information accurate? Yes No

The Applicant is being asked by DP to remove section 2 instructions in a separate IFU document.

3. Section 3 Dosage Forms and Strengths

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	For extended-release injectable suspension
Strengths: in metric system	12.5 mg, 25 mg, 37.5 mg, and 50 mg risperidone
Active moiety expression of strength with equivalence statement	Not Applicable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Each strength is provided as a kit, including: a vial containing the a white to almost white powder, a pre filled syringe containing 2 mL of a colorless, clear diluent, a vial adapter, and a needle for IM injection (20 gauge 2-inch needle with needle protection device).

Is the information accurate? Yes No

The Applicant will be asked to update the established name to: RYKINDO (risperidone) for extended-release injectable suspension, for intramuscular use.

The Applicant will be asked to include a description of the identifying characteristics of the dosage forms.

The Applicant will be asked to remove (b) (4)

This will be communicated to the Applicant as part of DP labeling negotiations

(b) (4)

(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	RYKINDO (risperidone) for extended-release injectable suspension, for intramuscular use
Dosage form and route of administration	For extended-release injectable suspension: 12.5 mg, 25 mg, 37.5 mg, and 50 mg
Active moiety expression of strength with equivalence statement (if applicable)	Not Applicable
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>)	The powder consists of risperidone, mannitol (5.38 mg/100 mg risperidone) polylactide-co-glycolide (PLGA) 5050 (24.2 mg/100 mg risperidone) and polylactide-co-glycolide (PLGA) 7525 (96.7 mg/100 mg risperidone). The diluent contains: 1.10 mg/mL citric acid monohydrate, 1.02 mg/mL dibasic sodium phosphate anhydrous, 1 mg/mL polysorbate 80, 6 mg/mL sodium carboxymethyl cellulose, 6 mg/mL sodium chloride, 0.54 mg/mL sodium hydroxide, and water.
Statement of being sterile (if applicable)	Sterile
Pharmacological/ therapeutic class	Atypical antipsychotic
Chemical name, structural formula, molecular weight	Present
If radioactive, statement of important nuclear characteristics.	Not Applicable
Other important chemical or physical properties (such as pKa or pH)	Risperidone is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl

Is the information accurate? Yes No

The Applicant will be asked to update the established name to: RYKINDO (risperidone) for extended-release injectable suspension, for intramuscular use.

The Applicant will be asked to include sterility information for the powder vial.

The Applicant will be asked to include the quantitative composition of the powder vial.

The Applicant will be asked to remove (b) (4).

This will be communicated to the Applicant as part of DP labeling negotiations.

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	For extended-release injectable suspension: 12.5 mg, 25 mg, 37.5 mg, and 50 mg
Available units (e.g., bottles of 100 tablets)	Kit
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Each strength is provided as a kit, including: a vial containing the a white to almost white powder, a pre filled syringe containing 2 mL of a colorless, clear diluent, a vial adapter, and a needle for IM injection (20 gauge 2-inch needle with needle protection device).
Special handling	Protect from light.
Storage conditions	Store kit in refrigerator at 2° to 8°C (36° to 46°F).
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Present

Is the information accurate? Yes No

The Applicant will be asked to update the established name to: RYKINDO (risperidone) for extended-release injectable suspension, for intramuscular use.

The Applicant will be asked to remove (b) (4).

This will be communicated to the Applicant as part of DP labeling negotiations.

Reviewer’s Assessment of Package Insert: Adequate

Prescribing Information complies with all regulatory requirements from a CMC perspective.

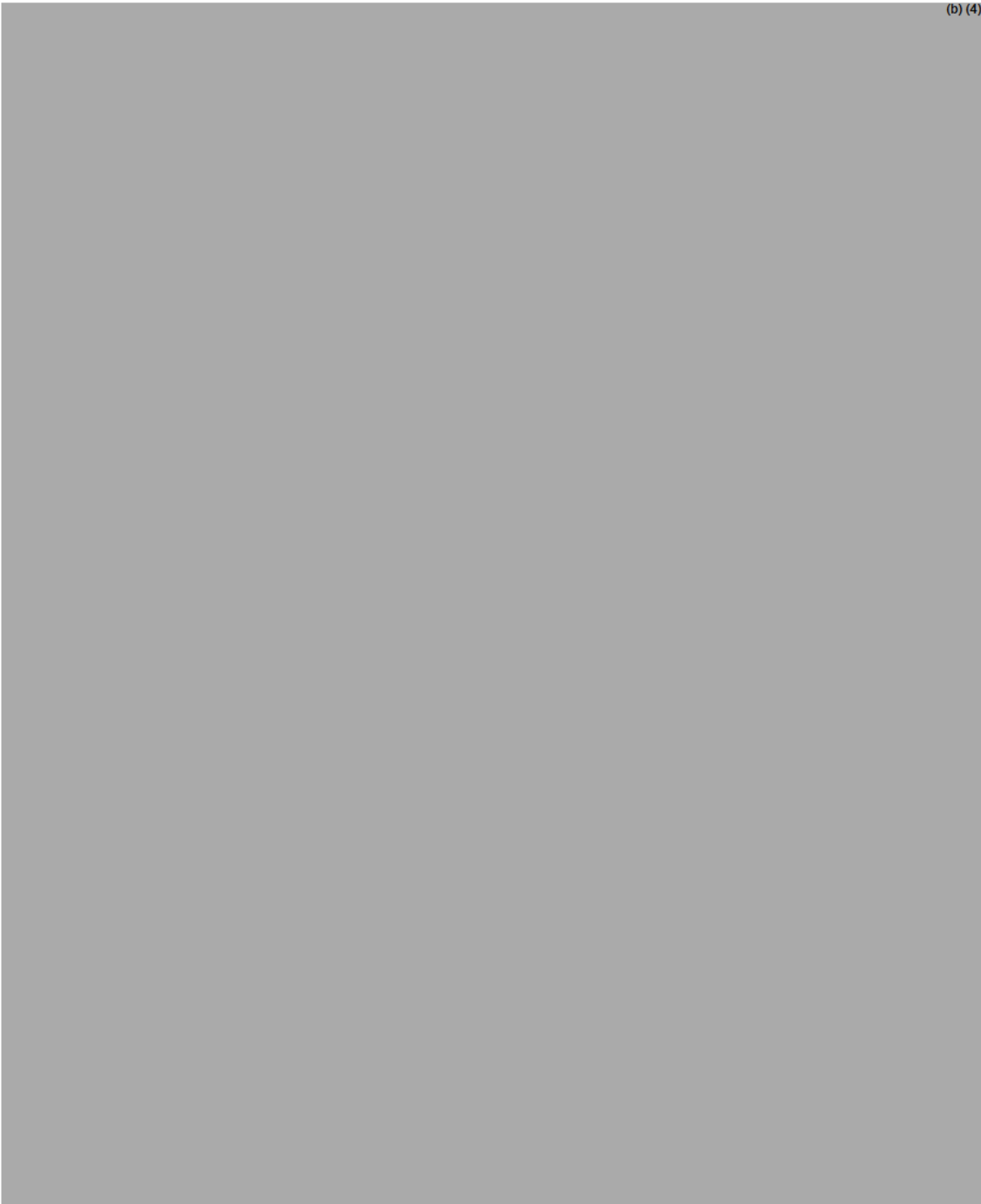
However, some revisions have been identified and will be communicated to the Applicant as part of DNP labeling negotiations.

II. Labels:

1. Carton Labels



(b) (4)



Item	Information provided in the carton label(s)	Information provided in the vial label(s)	Information provided in the syringe label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Complies	Complies	Complies

Dosage strength	Complies	Complies	Complies
Net contents	Complies	Complies	Complies
“Rx only” displayed prominently on the main panel	Complies	Complies	Complies
NDC number (21 CFR 207.35(b)(3)(i))	Complies	Complies	Not Present
Lot number and expiration date (21 CFR 201.17)	Complies	Complies	Complies
Storage conditions	Complies	Complies	Complies
Bar code (21CFR 201.25)	Complies	Complies	Complies
Name of manufacturer/distributor	Complies	Complies	Complies
And others, if space is available	Not Applicable	Not Applicable	Not Applicable

Reviewer’s Assessment of Labels: Adequate Pending Updates During Labeling Negotiations.

The labels largely comply with regulatory requirements from a CMC perspective. They bear the “Rx only” statement, the NDC number, name of manufacturer, net contents, strength, and the name (proprietary and established).

However, issues have been identified:

- The diluent does not contain the NDC number.
- The Applicant will be asked to update the established name to: RYKINDO (risperidone) for extended-release injectable suspension, for intramuscular use.
- The Applicant will be asked to consistency in the label, using “for intramuscular use” throughout (b) (4)
- The Applicant will be asked to change, (b) (4) to “single-dose” and (b) (4) to “kit.”
- The Applicant will be asked to remove (b) (4)

This will be communicated to the Applicant as part of DNP labeling negotiations.

Overall Assessment and Recommendation: Adequate, Pending Labeling Negotiations

Primary Labeling Reviewer Name and Date: Andrei Ponta



Andrei
Ponta

Digitally signed by Andrei Ponta
Date: 10/05/2022 09:12:50AM
GUID: 53b58e0b00004a630e714ee170af4c26



Julia
Pinto

Digitally signed by Julia Pinto
Date: 10/05/2022 03:54:01PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

CHAPTER VI: BIOPHARMACEUTICS

[IQA NDA Assessment Guide Reference](#)

NDA Number	NDA-212849-ORIG-1-RESUB-41
Assessment Cycle Number	3
Drug Product Name/ Strength	RYKINDO™ (risperidone) Extended-Release Injectable Suspension/12.5 mg, 25 mg, 37.5 mg, and 50 mg.
Route of Administration	Intramuscular Injection (IM)
Applicant Name	Shandong Luye Pharmaceutical Co., Ltd.
Therapeutic Classification/ OND Division	Psychiatry/CDER/ON/DP
Listed Drug/NDA Number	Risperdal Consta®; NDA 21346
Proposed Indication	Treatment of schizophrenia; as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder.
Primary Reviewer	Kalpana Paudel, Ph.D.
SPQA	Ta-Chen Wu, Ph.D.

Assessment Recommendation: Adequate

Assessment Summary:

The original NDA for RYKINDO™ (risperidone) Extended-Release Injectable Suspension was submitted on 3/28/2019 and resulted in Complete Response (CR) from FDA on 1/28/2020. The Applicant's request to waive the in vivo BA/BE studies for the proposed to-be-marketed 12.5 mg, 37.5 mg, and 50 mg strengths was not granted at the time because the submitted pivotal BE study (LY03004/CT-USA-102) for the 25 mg strength was deemed NOT acceptable by the Office of Clinical Pharmacology (OCP) due to the clinical safety concerns related to the pharmacokinetic (PK) spikes observed in the study.

The Applicant submitted root-cause analysis report for the spikes of drug plasma concentration observed in the pivotal BE study on 8/19/2021. The justification provided by the Applicant was deemed inadequate by OCP and another CR was issued on 2/18/2022 because possibility of dose-dumping could not be ruled out. The Applicant was requested to provide additional PK and safety data to assess the safety issues associated with LY03004 (risperidone). A CR comment with respect to the decision for not granting the biowaiver for the additional strengths (12.5 mg, 37.5 mg, and 50 mg) was conveyed to the Applicant from Division of Biopharmaceutics (Refer to Appendix for the comment).

In the current submission, the Applicant submitted detailed study reports including all PK and safety data of LY03004 from the clinical studies conducted in European Union (EU) and China in an attempt to explain the plasma concentration spikes observed in the

pivotal BE study in the US (LY03004/CT-USA-102). Additionally, post-marketing surveillance data from the approved LY03004 product in China were submitted to support the safety of the product. The data provided by the Applicant are deemed adequate by OCP as per the review in *Multi-Disciplinary Review and Evaluation* document. Therefore, OCP recommends approval of the proposed injectable product based on the current resubmission.

The Applicant's request to waive the in vivo BA/BE studies for the proposed to-be-marketed 12.5 mg, 37.5 mg, and 50 mg strengths can be granted because 1) the submitted pivotal BE study for the 25 mg strength is deemed acceptable by the OCP because the clinical safety concerns regarding the PK spikes observed in the study has been adequately addressed, and (2) the in vitro drug release profile of each reconstituted strength was found to be similar to the bio-strength (25 mg) supported by the similarity factor (f2) (refer to the link below for review dated 12/14/2021 in Panorama). The in vitro drug release method and acceptance criteria, and formulation bridging for the proposed drug product were found to be acceptable as noted in the same review.

<https://panorama.fda.gov/task/view?ID=6155ef2800639fcbcd4b59d8464b39e8>

RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 212849 for the proposed RYKINDO™ (risperidone) Extended-Release Injectable Suspension is recommended for approval.

List of Submissions reviewed

Document(s) Assessed	Date Received
Sequence 0040 (Resubmission, CR Response)	07/24/2022

Highlight of Key Issues from Last Review Cycle:

From Biopharmaceutics perspective, a COMPLETE RESPONSE was recommended for NDA 212849 for RYKINDO™ (Risperidone) Extended-Release Injectable Suspension, 12.5 mg, 25 mg, 37.5 mg, and 50 mg because of the outstanding biowaiver request.

Concise Description of Outstanding Issues:

None

APPENDIX

Biopharmaceutics deficiency in Complete Response Letter dated 02/18/2022

Biopharmaceutics deficiency:

The biowaiver request for the additional strengths (12.5 mg, 37.5 mg, and 50 mg strengths) cannot be granted at this time because of the continued clinical concerns related to results of the pivotal BE study. Therefore, satisfactory resolution of the clinical and clinical pharmacology concerns is required to establish the adequate BE between the proposed and Listed Drug products.

Applicant's response:

Luye acknowledges that FDA is not able to grant the biowaiver request for the additional strengths (12.5 mg, 37.5 mg, and 50 mg strengths) at this time.



Kalpana
Paudel

Digitally signed by Kalpana Paudel
Date: 11/09/2022 10:03:38AM
GUID: 562e1e15002f200f35c6ccac959cdb34



Ta-Chen
Wu

Digitally signed by Ta-Chen Wu
Date: 11/10/2022 11:16:23AM
GUID: 508da6df000269e151ff37cd8f4e13a1



Valerie
Ampacher

Digitally signed by Valerie Ampacher

Date: 12/01/2022 11:13:33AM

GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

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/

VALERIE R AMSPACHER
12/01/2022 11:55:16 AM

Table of Contents

Executive Summary.....	4
Drug Substance.....	11
Drug Product.....	19
Environmental.....	42
Labeling.....	No review performed because of the complete response recommendation
Process/Manufacturing.....	45
Biopharmaceutics.....	126
Microbiology.....	143

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 212849 Assessment 2

Drug Product Name	Risperidone Extended-Release Microspheres for Injection
Dosage Form	suspension
Strength	12.5 mg, 25 mg, 37.5 mg and 50 mg
Route of Administration	intramuscular (IM) injection
Rx/OTC Dispensed	Rx
Applicant	Shandong Luye Pharmaceutical Co., Ltd.
US agent, if applicable	Qi Cheng, Ph.D, Associate Director, Global Regulatory Affairs; Luye Pharma (USA) Ltd.

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 27; eCTD 0026	19 Aug 21	All, original resubmission
Supporting document 28; eCTD 0027	8 Sep 21	Facilities
Supporting document 35; eCTD 0034	24 Nov 21	Biopharmaceutics
Supporting document 36; eCTD 0035	13 Dec 21	Microbiology
Supporting document 37; eCTD 0036	22 Dec 21	Drug product
Supporting document 38; eCTD 0037	5 Jan 21	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Fred Burnett	Donna Christner
Drug Product	Andrei Ponta	Julia Pinto
Manufacturing	Yongming Lu	Jingbo Xiao

Microbiology	Xia Xu	Nandini Bhattacharya
Biopharmaceutics	Kalpana Paudel	Ta-Chen Wu / Okponanabofa Eradiri
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	1	9 Nov 2021	Reviewed by Fred Burnett
	IV		4			
	V		4			
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			

Action codes for DMF Table:
1 – DMF Reviewed.

- 2 –Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

B. OTHER DOCUMENTS: IND, RLD, RS, Approved NDA

Document	Application Number	Description
IND	116108	
NDA	021346	Risperdal Consta (risperidone) long-acting injection

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends complete response for this application based on the biopharmaceutics review in consultation with the Office of Clinical Pharmacology (OCP). Drug substance, drug product, process and facilities and microbiology all recommend approval.

The final packaged drug product containing the risperidone microspheres and diluent is granted a 24 month shelf life when stored under refrigerated conditions 2°- 8°C (36°- 46°F).

The vial containing risperidone microspheres has been granted 24-month expiry when stored under refrigerated conditions 2°- 8°C (36°- 46°F) based on the long-term stability data provided. The diluent vial has been granted 36-month expiry when stored under refrigerated conditions 2°- 8°C (36°- 46°F) based on the long-term stability data provided. The dose pack expiry is to be determined by the shortest of the two vials.

See also previous CMC IQA dated 9 Dec 2019.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Risperidone Extended-Release Microspheres for Injection is available in dosage strengths of 12.5 mg, 25 mg, 37.5 mg and 50 mg risperidone. The drug product is provided as a dose pack, consisting of a vial containing the Risperidone Extended-Release Microspheres, a pre-filled syringe with 2 mL of diluent, a vial adapter, and one safety needle with needle safety sheath.

_____ (b) (4)

_____ Risperidone microspheres must be suspended in the diluent provided in dose pack prior to injection.

This resubmission is in response to a complete response letter dated 28 Jan 2020. See also previous CMC IQA dated 9 Dec 2019.

Proposed Indication(s) including Intended Patient Population	treatment of schizophrenia and bipolar I disorder
Duration of Treatment	chronic
Maximum Daily Dose	N/A
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The Complete Response Letter did not have any drug substance CMC issue, and the NDA was recommended for approval from the drug substance perspective on 06-NOV-2019; K. Shahjahan, OPQ Platform. The resubmission includes the unchanged specification of the drug substance and satisfactory test results on three batches.

One Amendment (# 25) has come in for DMF _____ (b) (4) which was reviewed by F. Burnett (09-NOV-2021) and found to remain adequate. The CMC changes in the DMF since the NDA Complete Response Letter have not changed the quality of the drug substance.

The DMF Holder currently has a retest period of _____ (b) (4) -months for the drug substance with a shelf-life condition of _____ (b) (4).

The drug substance CMC information remains adequate; and the NDA remains recommended for approval from the drug substance perspective. See previous CMC IQA dated 9 Dec 2019.

Drug Product: Adequate

The microspheres consist of the drug substance and the following excipients: mannitol, PLGA 5050 (b) (4), and PLGA 7525 (b) (4). The Applicant has provided release results for at least three microsphere batches of each strength. All batches met the proposed specifications. The Applicant has provided release results for three diluent batches, all of which met the proposed specifications.

The container closure system consists of a vial containing one dosage strength of risperidone microspheres, a prefilled syringe containing 2 mL volume of diluent, a vial adapter, and one safety needle with needle protection packaging for intramuscular injection. The vial adapter and needle come with original blister pouch (both are sterile ready-to-use). All components are (b) (4) sealed (b) (4) (b) (4).

The vial containing risperidone microspheres has been granted 24-month expiry when stored under refrigerated conditions based on the long-term stability data provided. The diluent vial has been granted 36-month expiry when stored under refrigerated conditions based on the long-term stability data provided. The dose pack expiry is to be determined by the shortest of the two vials.

See previous CMC IQA dated 9 Dec 2019.

Labeling: Choose an item.

Not performed because this will be a complete response.

Manufacturing: Adequate

The major steps for the manufacture of Drug Product-Diluent involve (b) (4)

The major steps for the manufacture of Drug Product-Risperidone ER Microspheres include (b) (4)

(b) (4). The clinical/primary stability batches are at (b) (4) g scale. Sponsor proposed commercial batches at (b) (4) g scale and (b) (4) g scale. The process controls and IPC tests are in place for the manufacture of drug product-Risperidone ER microspheres for each of the major process steps.

Based on the review of inspection and application documents, all the listed facilities are acceptable.

See previous CMC IQA dated 9 Dec 2019.

Biopharmaceutics: Inadequate

Biowaiver Request

The applicant's request to waive the in vivo BA/BE studies for the proposed to-be-marketed 12.5 mg, 37.5 mg, and 50 mg strengths was not granted in the original review cycle because the submitted BA/BE study for the 25 mg strength was deemed NOT acceptable by the Office of Clinical Pharmacology (OCP) because of clinical safety concerns related to the PK

spikes observed in the study. In addition, the submitted in vitro drug release data for microspheres only, without reconstitution and same 20 mg amount, were not acceptable because the method itself does not reflect the clinical use and dosing of the proposed drug product.

In the response, the applicant submitted in vitro release profiles for each reconstituted strength which are acceptable based on the similarity factor (f2). The applicant also submitted root cause analysis report for the origin of the concentration spikes observed in the pivotal BE study as requested by the OCP in the CRL. The justification provided by the applicant, however, is deemed inadequate by OCP as per the review in Multi-Disciplinary Review and Evaluation document. Therefore, OCP has recommended a “complete response”. Therefore, the applicant’s request to waive the in vivo BA/BE studies for the proposed to-be-marketed 12.5 mg, 37.5 mg, and 50 mg strengths cannot be granted at this time because of the unresolved clinical safety concerns regarding the unacceptable BA/BE study on the 25 mg strength. A CR comment related to this issue will be conveyed to the applicant.

Dose-Dumping Potential

In the original submission, the results of in-vitro drug release studies indicated a temperature-induced dose dumping potential compared to the control. In the CRL, the applicant was recommended to conduct relevant in vivo animal studies to demonstrate the absence of dose-dumping under applied heat using the proposed drug product.

The applicant’s submitted in vitro release profiles under intermittent heat conditions for final to-be-marketed (reconstituted) drug product was similar to that at 37°C based on the similarity (f2) values. However, the results of in-vitro drug release studies under continuous elevated temperature indicated dose-dumping potential with 38.5°C compared to the control (37°C). The Division of Biopharmaceutics (DB) defers the overall assessment of justification provided by the applicant to OCP.

The data provided for bridging between the commercial and clinical-BE batches are acceptable.

The in vitro drug release method was found to be acceptable for Quality Control (QC) purposes in the original submission. However, drug release acceptance criteria were inadequate, and revised acceptance criteria were recommended by the Agency. The table below describes the accepted method and acceptance criteria for the in vitro drug release of all strengths of the proposed drug product.

Strengths/sample per vessel	Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criteria

For all strengths/ 20 mg microsphere per vessel	Thermostatic water bath with cylinder bottle (static method)	None	10 mM Dihydrogen Phosphate 40 mM Sodium Chloride 0.01% (w/v) Tween-80 0.05% (w/v) Sodium Azide pH 7.4/ 45°C ± 0.5°C	200 mL	0.5 h: NMT (b) (4) 24 h: (b) (4) 56 h: (b) (4) 72h: (b) (4) 120 h: ≥ (b) (4)

From the Biopharmaceutics perspective, complete response is recommended for NDA 212849.
See previous CMC IQA dated 9 Dec 2019.

Microbiology (if applicable): Adequate

(b) (4)

(b) (4) Supporting information provided in the Complete Response amendment meets quality microbiology review criteria.
See previous CMC IQA dated 9 Dec 2019.

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (*Deficiencies that affect multiple sub-disciplines*)

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

The biowaiver request for the additional strengths (12.5 mg, 37.5 mg, and 50 mg strengths) cannot be granted at this time because of the continued clinical concerns related to results of the pivotal BE study. Therefore, satisfactory resolution of the clinical and clinical pharmacology concerns is required to establish the adequate BE

between the proposed and Listed Drug products. Note that an acceptable BA/BE study is required to support the biowaiver for the other proposed strengths not evaluated in an in vivo human clinical/PK study.

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

Screenshot showing approval for facilities taken 11 Jan 22

The first screenshot shows the 'Inspection View - Overall' for NDA-212849-ORIG-1-RESUB-27. It displays a table with the following data:

Task Number	Task Name	Comments	Assignments	Pln Comp	Act Comp	Task Status	Actions	Additional Information
74	Overall Manufacturing Inspection Recommendation		J. Yongming Lu	9/10/21	1/12/21	Complete	Go to Form	Approve

The second screenshot shows the 'Submission Facility Status View' for the same NDA. It displays a summary of manufacturing status:

- Latest Overall Manufacturing Inspection Recommendation: **Approve** (Completion Date: 11/02/2021, NDA-212849-ORIG-1-RESUB-27)
- Inspection Requested: **0**
- Inspection Completed: **1**
- pOAI/OAI Alerts: **No**
- Pending Profile: **No**



Valerie
Ampacher

Digitally signed by Valerie Ampacher

Date: 1/11/2022 03:28:00PM

GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

CHAPTER VI: BIOPHARMACEUTICS

[IQA NDA Assessment Guide Reference](#)

NDA Number	NDA-212849-ORIG-1-RESUB-27
Assessment Cycle Number	2
Drug Product Name/ Strength	RYKINDO™ (Risperidone) Extended-Release Injectable Suspension/12.5 mg, 25 mg, 37.5 mg, and 50 mg.
Route of Administration	Intramuscular Injection (IM)
Applicant Name	Shandong Luye Pharmaceutical Co., Ltd.
Therapeutic Classification/ OND Division	Psychiatry/CDER/ON/DP
Listed Drug/NDA Number	NDA 21346; Risperdal Consta®
Proposed Indication	Treatment of schizophrenia; as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder.
Primary Reviewer	Kalpna Paudel, Ph.D.
Secondary Reviewer	Okpo Eradiri, Ph.D.

Assessment Recommendation: Inadequate

Assessment Summary:

The original NDA for RYKINDO™ (Risperidone) Extended-Release Injectable Suspension was submitted on 3/28/2019 and resulted in Complete Response (CR) from FDA. In the current submission, the applicant responded to the deficiencies in the Agency’s CR letter provided on 1/28/2021 for the original submission. This review focuses on the assessment of applicant’s response to the biopharmaceutics deficiencies communicated in the CRL.

In Vitro Drug Release Method and Acceptance Criteria

The in vitro drug release method was found to be acceptable for Quality Control (QC) purposes in the original submission. However, drug release acceptance criteria were inadequate, and revised acceptance criteria were recommended by the Agency. The table below describes the accepted method and acceptance criteria for the in vitro drug release of all strengths of the proposed drug product.

Strengths/sample per vessel	Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criteria
For all strengths/ 20 mg microsphere per vessel	Thermostatic water bath with cylinder bottle (static method)	None	10 mM Dihydrogen Phosphate 40 mM Sodium Chloride 0.01% (w/v) Tween-80 0.05% (w/v) Sodium Azide pH 7.4/ 45°C ± 0.5°C	200 mL	0.5 h: NMT (b) (4) 24 h: (b) (4) 56 h: 72h: 120 h: ≥ (b) (4)

Formulation Bridging

In the original submission, bridging between the commercial and clinical-BE batches could not be established via an in vitro drug release similarity approach because of the difference between the pivotal BE and commercial batches (b) (4) and the average drug release of the microspheres at the 72- and 80-h sampling time points (greater than 15% for 3 out of the 7 commercial scale-up batches).

In the CRL response, the applicant noted that the differences (b) (4) between the scale-up and clinical batches (b) (4)

(b) (4) with no significant difference in other quality attributes. Three batches of risperidone extended-release microspheres for injection (one batch each for 25mg, 37.5mg, and 50mg strength, respectively) were manufactured at (b) (4) g scale following the optimized process and monitored under the stability program. The drug release profiles of the new (b) (4) g scale-up batches were similar to the clinical batches (b) (4) g based on the similarity factor (f_2) and no differences were observed at 72 hours and 80 hours sampling time points. The data provided for bridging between the commercial and clinical-BE batches are acceptable.

Biowaiver Request

The applicant's request to waive the in vivo BA/BE studies for the proposed to-be-marketed 12.5 mg, 37.5 mg, and 50 mg strengths was not granted in the original review cycle because the submitted BA/BE study for the 25 mg strength was deemed NOT acceptable by the Office of Clinical Pharmacology (OCP) because of clinical safety concerns related to the PK spikes observed in the study. In addition, the submitted in vitro drug release data for microspheres only, without reconstitution and same 20 mg amount, were not acceptable because the method itself does not reflect the clinical use and dosing of the proposed drug product.

In the response, the applicant submitted in vitro release profiles for each reconstituted strength which are acceptable based on the similarity factor (f_2). The applicant also submitted root cause analysis report for the origin of the concentration spikes observed in the pivotal BE study as requested by the OCP in the CRL. The justification provided by the applicant, however, is deemed inadequate by OCP as per the review in *Multi-Disciplinary Review and Evaluation* document. Therefore, OCP has recommended a "complete response". Therefore, the applicant's request to waive the in vivo BA/BE studies for the proposed to-be-marketed 12.5 mg, 37.5 mg, and 50 mg strengths cannot be granted at this time because of the unresolved clinical safety concerns regarding the unacceptable BA/BE study on the 25 mg strength. **A CR comment related to this issue will be conveyed to the applicant (See below).**

Dose-Dumping Potential

In the original submission, the results of in-vitro drug release studies indicated a temperature-induced dose dumping potential compared to the control. In the CRL, the applicant was recommended to conduct relevant in vivo animal studies to demonstrate the absence of dose-dumping under applied heat using the proposed drug product.

In the response, the applicant conducted *in vitro* studies, noting that currently, there is no suitable method to directly investigate the effect of elevated temperature on PK profile *in vivo*. The applicant concluded that no dose dumping took place with elevated temperature (intermittent and continuous heat conditions) at any studied time period in the in vitro studies; the product was able to maintain its stable and long-acting release characteristics and thus LY03004 has minimum risk of dose dumping for patients with fever and that based on the clinical data, there is no significant impact to patient safety.

The applicant's submitted in vitro release profiles under intermittent heat conditions for final to-be-marketed (reconstituted) drug product was similar to that at 37°C based on the similarity (f2) values. However, the results of in-vitro drug release studies under continuous elevated temperature indicated dose-dumping potential with 38.5°C compared to the control (37°C). The Division of Biopharmaceutics (DB) defers the overall assessment of justification provided by the applicant to OCP.

RECOMMENDATION:

From the Biopharmaceutics perspective, a COMPLETE RESPONSE is recommended for NDA 212849 for the proposed RYKINDO™ (risperidone) Extended-Release Injectable Suspension. Biopharmaceutics deficiency as listed below should be conveyed to the applicant in the CR letter.

BIOPHARMACEUTICS DEFICIENCY COMMENTS

1. The biowaiver request for the additional strengths (12.5 mg, 37.5 mg, and 50 mg strengths) cannot be granted at this time because of the continued clinical concerns related to results of the pivotal BE study. Therefore, satisfactory resolution of the clinical and clinical pharmacology concerns is required to establish the adequate BE between the proposed and Listed Drug products. Note that an acceptable BA/BE study is required to support the biowaiver for the other proposed strengths not evaluated in an in vivo human clinical/PK study.

BIOPHARMACEUTICS ASSESSMENT

List of Submissions reviewed

Document(s) Assessed	Date Received
Sequence 0026 (Resubmission, CR response)	08/19/2021
Sequence 0034 (IR response)	11/24/2021

Highlight of Key Issues from Last Review Cycle:

From Biopharmaceutics perspective, a COMPLETE RESPONSE was recommended for NDA 212849 for RYKINDO™ (Risperidone) Extended-Release Injectable Suspension, 12.5 mg, 25 mg, 37.5 mg, and 50 mg because of the outstanding biopharmaceutics deficiencies regarding the in vitro drug release test, bridging between clinical and commercial drug products, biowaiver request, and dose-dumping potential.

Concise Description of Outstanding Issues:

Biowaiver request is not granted due to unresolved PK spikes in pivotal BE study.

Applicant's Response to the CRL Deficiencies

Biopharmaceutics related issues contained in the 01/28/2020 CR letter are provided below in bold text, followed by Reviewer's comments that includes a summary of the applicant's response in the current submission and reviewer's assessment.

IN VITRO RELEASE METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

Deficiency 1 (FDA COMMENT 4a in CRL)

a. In vitro drug release acceptance criteria: The following revisions are recommended for the acceptance criteria of the in vitro drug release test:

i. Inclusion of an additional sampling time point at 72 hours to control the middle phase of the drug release profile, with acceptance criteria limits of (b) (4) (based on mean value $\pm 10\%$ of the bio-batch).

ii. For the 56-hour time point, the proposed acceptance range is wider than the FDA's recommended (b) (4) range and is not acceptable. Therefore, we request that you revise the acceptance range for this sampling time point to (b) (4) (based on mean value $\pm 10\%$ of the bio-batch).

Please note that wider drug release acceptance criteria ranges may be accepted, if a justification based on clinical/PK data or data from an acceptable IVIVC/IVIVR model is provided. Refer to the Additional Biopharmaceutics Comments.

Reviewer's comments:

The applicant agreed for an additional sampling point at 72 hours to control the middle phase of the drug release profile. For both 56-and 72-h sampling time points, the applicant proposed slightly revised ranges (b) (4) for

both release and stability testing specifications considering data from eleven primary stability batches that were produced at the same manufacturing site, with same scale and process. The applicant noted that acceptance criteria at 56-h is proposed to be (b) (4) (b) (4) with the target value of (b) (4) which is close to the mean value of the bio-batches (b) (4) at this time point. Similarly, the acceptance criteria at 72-h are proposed to be (b) (4) with the target value of (b) (4) which is also close to the mean value of bio-batches (b) (4). The applicant has not proposed a change in the range at 120-h, thus indicating that the drug is available as intended up to 120 hours. Hence, the applicant's justification is acceptable.

BRIDGING OF FORMULATIONS

Assessment: Adequate

Deficiency 2 (FDA COMMENT 4b in CRL)

Bridging of clinical and commercial products:

The bridging between the proposed commercial drug product and the drug product used in the clinical-BE study has not been adequately established because of the following reasons:

- i. the differences between the commercial and clinical drug product-batches (microsphere) (b) (4);**
- ii. although the similarity f2 values indicate that the in vitro drug release profiles are similar, for extended-release products it is required that the difference between the profiles at each sampling time point is <15%. However, when the drug release profiles of the clinical and commercial batches are compared, the average differences in the cumulative percent of drug release from the microspheres at the 72 hours and 80 hours sampling time points, are greater than 15%, for 3 out of 7 commercial scale-up batches.**

To support the bridging between the clinical and commercial drug products, address the following requests:

- i. Provide the details for all the changes made to the manufacturing process(es) during scale-up, explain why there are significant differences (b) (4) between the clinical and commercial batches, and provide a justification with supporting data that the differences (b) (4) would not have an impact on the pharmacokinetics, efficacy, and safety of your drug product.**

Reviewer's comments:

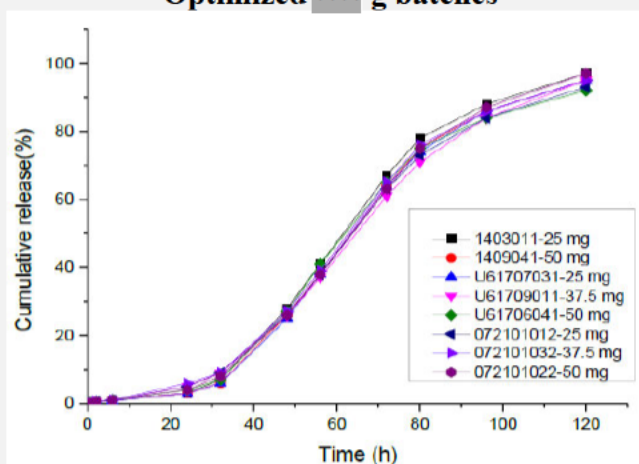
The applicant noted that differences (b) (4) between the scale-up batches and the clinical batches (b) (4)

(b) (4) with no significant difference in other quality attributes. Three batches (072101012CO, 072101022CO, 072101032CO) of risperidone extended-release

microspheres for injection (one batch each for 25mg, 37.5mg, and 50mg strength, respectively) were manufactured at (b) (4) g scale following the optimized process and monitored under the stability program. This reviewer verified with the Drug Product reviewer that the applicant's response is acceptable and there are no issues from drug product perspective.

The drug release profiles of the (b) (4) g scale-up batches produced with new manufacturing process are similar to the clinical batches ((b) (4) g) based on the similarity factor (f2) as verified by this reviewer using Division of Biopharmaceutics (DB) review automation tool. The release profiles of these batches are provided in the figure below.

Figure 1: *In Vitro* Drug Release Profiles Comparison between (b) (4) g and Optimized (b) (4) g batches



ii. Provide a justification that the observed differences in the *in vitro* drug release at 72 hours and 80 hours time points for some commercial batches would not significantly impact the pharmacokinetics, efficacy, and safety of your proposed drug product.

As an alternative approach, consider developing an acceptable IVIVC/IVIVR model to support the bridging.

Reviewer's comments:

As noted above, manufacturing process for the (b) (4) g scale products has been optimized. As seen in the Table below, the *in vitro* drug release at both 72-hour and 80-hour time points for the new (b) (4) g scale batches are consistent with those from the bio-batches, therefore do not have any adverse impact on the pharmacokinetics (PK), efficacy or safety. *In vitro* release profiles from the three new (b) (4) g scale batches along with the two bio-batches are similar as provided in the Figure 1 above.

Table 1: The *in vitro* Release Results of Bio-batches and the Optimized Scale-up Batches

Sampling Point	Bio-batches		Optimized Scale-up Batches							
	1403011	1409041	072101012CO	072101022CO	072101032CO					
0.5h	(b) (4)									
2h										
6h										
24h										
32h										
48h										
56h										
72h										
80h										
96h										
120 h										
n						/	/	82	91	90

Based on the above study results, bridging between the commercial and clinical-BE batches are acceptable.

BIOWAIVER REQUEST

Assessment: *Inadequate*

Biopharm Deficiency 3 (FDA COMMENT 4c in CRL)

The biowaiver request for the additional strengths (12.5 mg, 37.5 mg, and 50 mg strengths) cannot be granted at this time because of the following:

- i. The unresolved clinical concerns related to the PK spikes observed in the pivotal BE study. Therefore, satisfactory resolution of the clinical and clinical pharmacology concerns is required to establish the adequate BE between the proposed and Listed Drug products. Note that an acceptable BA/BE study is required to support the biowaiver for the other proposed strengths not evaluated in an in vivo human clinical/PK study.

Reviewer’s comments:

The applicant submitted root cause analysis report to understand the origin of the concentration spikes observed in the pivotal BE study as requested by the OCP in the CRL. The report can be found in the link below:

<\\CDSESUB1\evsprod\nda212849\0026\m1\us\111-information-amendment\rctrl-appendix-1-root-cause-analysis-report.pdf>

The justification provided by the applicant, however, is deemed NOT acceptable by OCP as per the review in *Multi-Disciplinary Review and Evaluation* document (assessed on 12/07/2021). It states that “The office of clinical pharmacology has determined that the sponsor’s root cause analysis is inadequate and does not explain the cause for the concentration spikes with LY product. It failed to conclusively rule out the dose-dumping with the product and thus we recommend “complete response”. Therefore, the applicant’s request to waive the in vivo BA/BE studies for the proposed to-be-marketed 12.5 mg, 37.5 mg, and 50 mg strengths not evaluated on in vivo studies cannot be granted at this time because of the continued unresolved clinical safety concerns

observed in the BA/BE study on the 25 mg strength. A CR comment related to this issue will be conveyed to the applicant (See Appendix 2 below).

ii. Lack of adequate in vitro drug release profile data to support the biowaiver request using the final to-be-marked drug product (both microsphere and diluent) and the same testing conditions including the same volume of dissolution medium. Therefore, we request that you provide the supporting in vitro drug release profile comparison data, i.e., n=12, and the samples be prepared for each strength per the proposed labeling instructions [using the equivalence of (b) (4) microspheres for 12.5 mg, 25 mg, 37.5 mg, and 50 mg strengths, respectively], and the resulting suspension sample volume be equivalent to that delivered to patients (i.e., approximately 2 mL), per Section 2.8 (b) (4). In addition, include the similarity profiles comparison values (using the f2 test or other appropriate statistical test), estimated by comparing the in vitro drug release profile of the bio-strength (used in acceptable PK study) vs. the drug release profiles of the other proposed strengths not evaluated in a clinical/PK study.

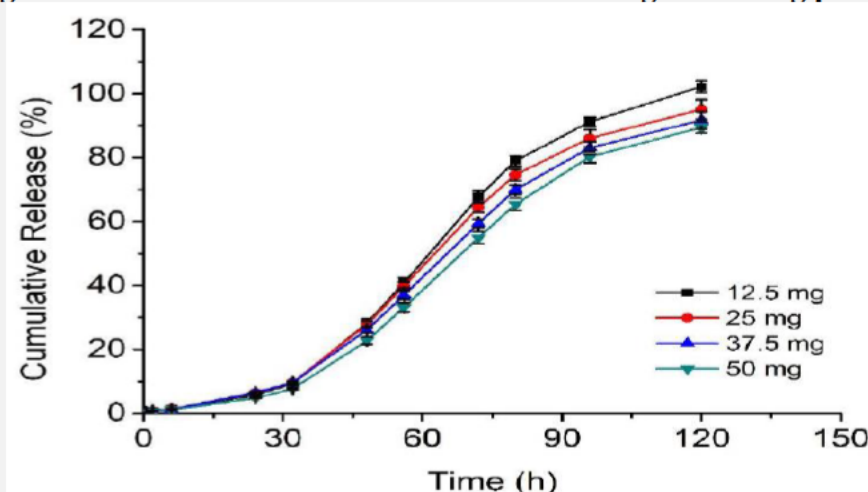
Reviewer's comments:

As requested in the CRL letter, the applicant conducted in vitro release studies with the to-be-marketed products with samples prepared per the proposed labeling instructions and the resulting suspension sample volume of ~2mL, which is equivalent to that delivered to patients to support the biowaiver request. The in vitro release study was performed under the same testing conditions. Details of the study design and the results are provided in the link below:

<\\CDSESUB1\evsprod\nda212849\0026\m1\us\111-information-amendment\rtc-appendix-3-report-ter-ly03004-pa-006-biowaiver-studies.pdf>

The release profile of risperidone from all strengths are provided below.

Figure 2: In vitro release curves of different strengths of drug product



This reviewer verified f2 similarity factor provided by the applicant in the Table below. The f2 values for in vitro release of 12.5 mg, 37.5 mg and 50 mg strengths are all greater than 50 when compared to 25 mg strength, indicating similar drug release profiles to the bio-strength (25 mg).

Table 2: Results of f2 factors of different strengths of drug product

Reference Strength	Test Strength	f ₂	Similarity (Acceptance criteria: f ₂ =50-100)
25 mg	12.5 mg	74	Similar
	37.5 mg	73	Similar
	50 mg	63	Similar

ADDITIONAL BIOPHARMACEUTICS COMMENTS in CRL

1. We strongly suggest that you consider developing an in vitro-in vivo model to establish the correlation or relationship (IVIVC/IVIVR) between human PK data and the in vitro drug release data generated using the proposed in vitro drug release method (without reconstitution), which can be used to support postmarketing changes. This is recommended because:

a) The proposed in vitro drug release method does not reflect the clinical use of the proposed drug product (i.e., does not include the reconstitution step of the microspheres with the diluent to form the final drug product for intramuscular administration).

b) The proposed in vitro drug release method does not include individual drug release tests for each of the proposed strengths.

c) The quality and clinical risks associated with the in vitro and in vivo release of the drug from the product are considered high, because the proposed drug product is a reconstituted biodegradable polymeric parenteral microspheres product for intramuscular injection.

d) There are concerns with regard to the change (b) (4) during manufacturing scale-up and bridging of commercial batches, effectiveness of reconstitution, and un-resolved clinical safety concern related to the PK spikes observed in the pivotal BE study.

Reviewer's comments:

(b) (4)

2. The effects of exercise and pressure on the PK profile of the proposed drug product in dogs were included in the NDA. We have concerns with regard to the reported increase on the in vitro drug release at elevated temperature and its impact on in vivo PK performance and safety. Therefore, we recommend that you investigate the effects of applied intermittent and continuous heat on the PK profile of the final to-be-marketed (reconstituted) drug product.

Reviewer's comments:

The applicant conducted *in vitro* studies, noting that currently, there is no suitable method to directly investigate the effect of elevated temperature on PK profile *in vivo*. The applicant concluded that no dose dumping took place with elevated temperature (intermittent and continuous heat conditions) at any studied time period in the *in vitro* studies; the product was able to maintain its stable and long-acting release characteristics and thus LY03004 has minimum risk of dose dumping for patients with fever and that based on the clinical data, there is no significant impact to patient safety.

The applicant's submitted *in vitro* release profiles under intermittent heat conditions for the final to-be-marketed (reconstituted) drug product was similar to that at 37°C based on the f2 similarity values (verified by this reviewer). The *in vitro* drug release profiles under continuous elevated temperature indicated dose-dumping potential with 38.5°C compared to the control (37°C), however, the profiles were comparable to the listed product Risperdal Consta®.

A summary of the *in vitro* testing and clinical justification is provided below. Detailed study report can be found in the link:

<\\CDSESUB1\evsprod\nda212849\0026\m1\us\111-information-amendment\rtc-appendix-4-ter-ly03004-pa-010-effect-of-elevated-tempera.pdf>

1. In Vitro Testing

In vitro drug release studies were conducted to evaluate the temperature effect on the release of risperidone from LY03004 microspheres of the to be-marketed (reconstituted) drug product. The *in vitro* release at 37°C was used as the reference. The *in vitro* release of the drug product was studied based on the literatures as listed in the following table:

Heat applied	Temperature	Duration	Release stage studied
Intermittent	Moderate (39°C)	4 days	Initial, middle and late
Intermittent	High (41.5°C)	4 hrs	Middle
Continuous	Moderate (38.5°C)	25 days	Complete

The initial phase of release is defined as the period that the cumulative release is (b) (4), which is generally the first day after administration; the middle phase is defined as the period during which the cumulative release is (b) (4); the late phase is defined as the period during which the cumulative release is (b) (4)

Table 3: Experimental design of effect of elevated temperature on *in vitro* release

SN	Group	Experimental conditions	Note
1	Control group	Day 0-Day 25: placed at 37°C for 25 days	Control temperature
2	Experimental group	Day 1-Day 5: placed at 39°C for 4 days The rest of time: placed at 37°C	Intermittent moderately elevated temperature in initial phase
3		Day 12-Day 16: placed at 39°C for 4 days The rest of time: placed at 37°C	Intermittent moderately elevated temperature in middle phase
4		Day 15-Day 19: placed at 39°C for 4 days The rest of time: placed at 37°C	Intermittent moderately elevated temperature in late phase
5		Day 13: placed at 41.5°C for 4 hours The rest of time: placed at 37°C	Intermittent highly elevated temperature in middle phase
6		Day 0-Day 25: placed at 38.5°C for 25 days	Continuous elevated temperature

The results are summarized below.

Intermittent Elevated Temperature

Figure 3: (A) *In vitro* release curves at 37°C and intermittent heat of 39°C (B) *In vitro* release curves at 37°C and intermittent heat of 41.5°C

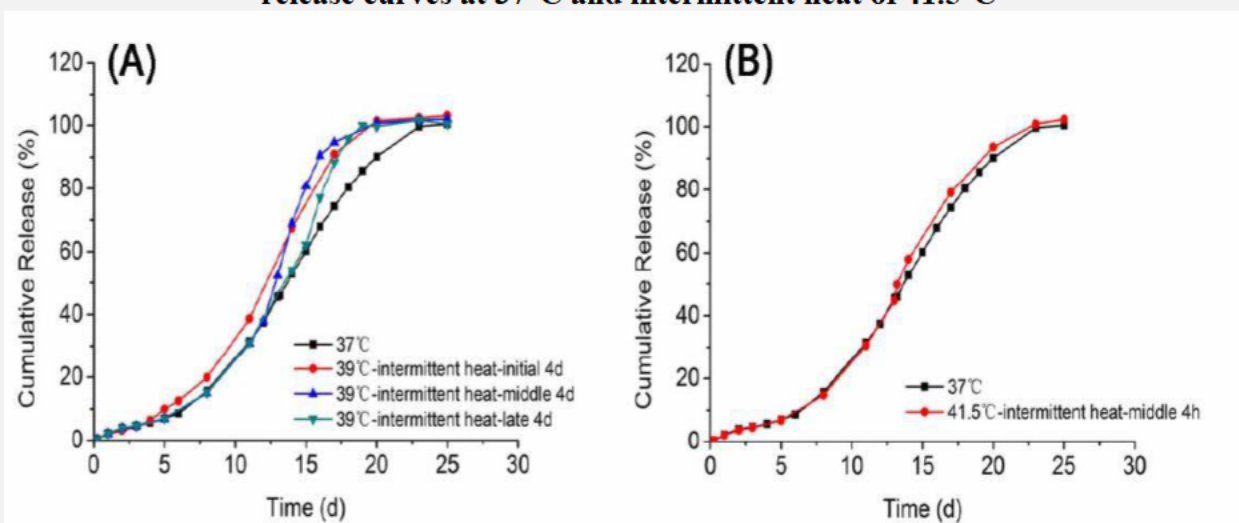


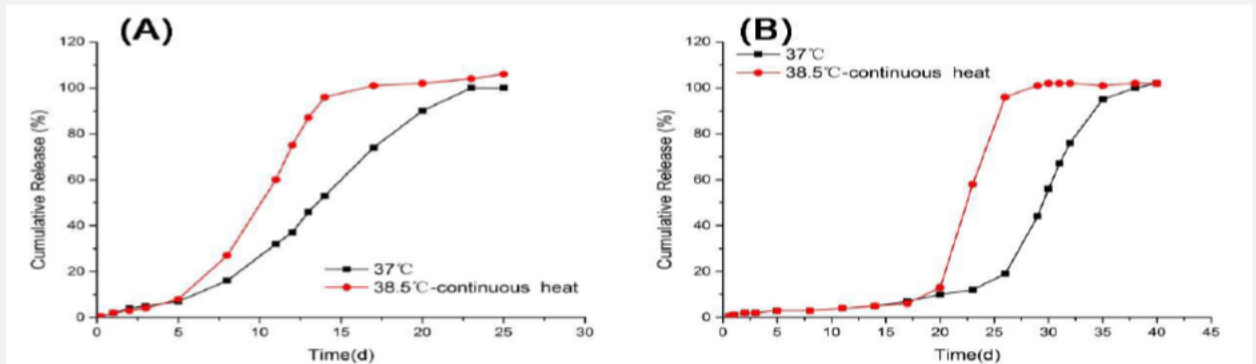
Table 4: Results of f2 factors of elevated temperatures

	37°C	39°C Initial Phase 4 days	39°C Middle Phase 4 days	39°C Late Phase 4 days	41.5°C Middle Phase 4 h
f ₂ factor*	Control group	60	61	96	83

*: Based on the FDA guidelines^[7], the release data of 7 time points uniformly distributed in the release curve i.e. 1d, 5d, 8d, 11d, 14d, 17d, 20d are selected for the calculation of the f₂ factor.

Continuous Elevated Temperature

Figure 4: (A) *In vitro* release curves of Rykindo® at continuous heat (B) *In vitro* release curves of Risperdal Consta® at continuous heat



2. In Vivo Study: Assessment of the Impact of Fever on the Safety of Patients with Increased Plasma Concentration

As *in vitro* studies showed that drug release increased under heat, and that fever may cause an increase in plasma drug concentration, the plasma concentration of patients who had fever during the three completed clinical trials of Rykindo® and the impact of fever on patient safety were analyzed. The applicant noted that in these completed clinical trials, 10 of 102 patients were identified having fever with body temperatures higher than 37.5°C during the trial. No increase of clinical significance in plasma concentrations or corresponding adverse events were observed in these patients. Hence, the impact of fever on plasma concentration is minimal and pose little safety risk. The applicant also justified that even if the plasma concentration increases moderately due to fever, the C_{ss}-max of patients who receive Rykindo® is much lower than the safety alert concentration of 120 ng/mL, which does not raise extra safety concerns. DB defers the overall assessment of justification provided by the applicant to OCP.

Drug Product deficiency on (b) (4) in CRL

1. REGARDING THE RISPERIDONE MICROSPHERE COMPONENT: The (b) (4) has not been adequately justified. (b) (4)

(b) (4) Provide data (e.g., bioequivalence study results) to ensure that the product performance is equivalent for drug products manufactured at extremes of the proposed range. Alternatively, tighten the (b) (4) specification.

We note the additional analysis of the drug release profiles provided in a response to an information request dated November 22, 2019. It remains unclear whether the commercial formulation was used in these studies and whether the f2 analysis was performed comparing the different compositions to the pivotal clinical batch. Furthermore, a change in (b) (4) (b) (4) excipients of this magnitude typically require more than in-vitro results.

Reviewer’s comments:

In the response, the applicant noted that (b) (4) specification is tightened from (b) (4) to (b) (4) with the target (b) (4) set at (b) (4). With the revised (b) (4) (b) (4) range, the composition differences in (b) (4) excipients have been reduced to ~ (b) (4) w/w. Summary of the (b) (4) data for clinical batches, primary stability batches, and the scale-up batches manufactured under optimized processes is presented in the Table below. The (b) (4) average of the clinical batches is (b) (4), which is at the target value, while (b) (4) for all the primary stability batches and the new scale-up batches are within the newly proposed range.

Table 5: Summary of (b) (4) Data from Clinical/Primary/Scale up Batches

Batch No.	Usage	(b) (4)
140301	Clinical Batches (Bio-batches)	(b) (4)
140904		
U61706011	Primary Batches	
U61706021		
U61706031		
U61706041		
U61707011		
U61707021		
U61707031		
U61707041		
U61708011		
U61708021		
U61709011		
072101012CO	Optimized Scale-Up Batches	
072101022CO		
072101032CO		
Range		
Average (Clinical Batches)		

The applicant provided f2 analysis comparing the commercial and primary stability batches to bio-batches in the table below. This reviewer verified that release profiles of all batches with various (b) (4) are similar to the pivotal clinical batches based on the f2 values. The overall

assessment of response provided by the applicant is under the purview of Drug Product review team.

Table 6: f2 Analysis between Bio-Batches and Registration Batches

Test Batch number	Batches Purpose	Strength (mg)	(b) (4) (%)	f ₂ factor (Comparing to Bio-batches 1403011 and 1409041)	
U61706011	Primary Stability Batches	12.5	(b) (4)	97	
U61706021		12.5		87	
U61706031		12.5		90	
U61706041		50		85	
U61707011		50		89	
U61707021		50		95	
U61707031		25		90	
U61707041		37.5		73	
U61708011		12.5		76	
U61708021		37.5		84	
U61709011		37.5		78	
072101012CO		Optimized Scale-Up Batches		25	82
072101022CO				50	91
072101032CO	37.5		90		

Primary Biopharmaceutics Assessor's Name: Dr. Kalpana Paudel, Ph.D.

Secondary Assessor Name: Dr. Okpo Eradiri, Ph.D.

2 Page(s) have been Withheld in Full as b4
(CCI/TS) immediately following this page



Kalpana
Paudel

Digitally signed by Kalpana Paudel
Date: 12/14/2021 07:04:44PM
GUID: 562e1e15002f200f35c6ccac959cdb34



Okponanabofa
Eradiiri

Digitally signed by Okponanabofa Eradiiri
Date: 12/14/2021 11:43:30PM
GUID: 50bdfe8d00003559ede66be3fd299f65

CHAPTER VII: MICROBIOLOGY

[IQA NDA Assessment Guide Reference](#)

Product Information	Rykindo® (risperidone) Extended-Release Microspheres for Injection is indicated for the treatment of schizophrenia, and as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder.
NDA Number	212849
Assessment Cycle Number	02
Drug Product Name/ Strength	Rykindo® Risperidone Extended-Release Microspheres for Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial
Route of Administration	Intramuscular
Applicant Name	Shandong Luye Pharmaceutical Co., Ltd.
Therapeutic Classification/ OND Division	Atypical antipsychotics
Manufacturing Site	<u>Shandong Luye Pharmaceutical Co. Ltd.</u> No. 15 Chuangye Road, High-Tech Industrial Development Zone Yantai City, Shandong Province China 264003
Method of Sterilization	Microspheres: (b) (4) (b) (4) (b) (4) Diluent: (b) (4)

Assessment Recommendation: Adequate

Assessment Summary: (b) (4)

(b) (4)

(b) (4) Supporting information provided in the Complete Response amendment meets quality microbiology review criteria.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Supporting Document # 27 (Seq-0026)	08/19/2021
Supporting Document # 36 (Seq-0035)	12/13/2021

Highlight Key Issues from Last Cycle and Their Resolution: Previous key quality microbiology deficiencies pertained to validations for container closure integrity, [REDACTED] (b) (4) [REDACTED].

Remarks: Both the drug product and the diluent will be manufactured at Luye for commercial production. [REDACTED] (b) (4) will be no longer the manufacturer of the Diluent. IR responses dated 12/13/2021 were incorporated into this review.

Concise Description of Outstanding Issues: None.

Supporting Documents:

- Microbiology review N212849MR01 (Inadequate) dated 12/04/2019 for container closure integrity validation, [REDACTED] (b) (4) validation, viability study of organic phase, and [REDACTED] (b) (4) validation.

Product Quality Microbiology Assessment

The subject amendment is in response to microbiology deficiencies conveyed to the applicant in the Agency's Complete Response Letter dated 01/28/2020. The original microbiology deficiencies are italicized.

Rykindo® (risperidone) Extended-Release Microspheres for Injection (12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial) is a sterile, nonpyrogenic, preservative-free, single dose lyophilized powder packaged in a glass vial for intramuscular gluteal injection. The drug product is co-packaged with a pre-filled syringe (PFS) containing 2 mL sterile, nonpyrogenic, preservative-free Diluent solution, one vial adapter and one safety needle.

(b) (4)

MICROBIOLOGY LIST OF DEFICIENCIES

None.

Primary Microbiology Assessor Name and Date: Xia Xu, Ph.D. 12/23/2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Nandini Bhattacharya, Ph.D. 12/23/2021



Xia
Xu

Digitally signed by Xia Xu

Date: 12/23/2021 01:15:28PM

GUID: 585c30e50015a0ac941cb21671c188ce



Nandini
Bhattacharya

Digitally signed by Nandini Bhattacharya

Date: 12/27/2021 10:01:43AM

GUID: 508da70c00028f454473851fced0e9d4



Valerie
Ampacher

Digitally signed by Valerie Ampacher

Date: 1/11/2022 03:50:26PM

GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

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/

VALERIE R AMSPACHER
01/11/2022 03:59:44 PM

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 212849 Assessment # 1

Drug Product Name	Risperidone
Dosage Form	For Extended-Release Injectable Suspension
Strength	12.5 mg, 25 mg, 37.5 mg, and 50 mg
Route of Administration	Intramuscular
Rx/OTC Dispensed	Rx
Applicant	Shandong Luye Pharmaceutical Co., Ltd.
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
0000	03/28/2019	All
0002	05/30/2019	Drug Product/Facilities/Micro
0008	08/02/2019	Drug Product
0009	08/09/2019	Process
0010	08/20/2019	Biopharm
0015	09/26/2019	Micro
0016	09/27/2019	Drug Product/Process/CDRH
0018	10/18/2019	Biopharm
0019	11/22/2019	Drug Product/Biopharm/CDRH

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Kabir Shahjahan	Hari Sarker
Drug Product	Andrei Ponta	Wendy Wilson-Lee/David Claffey
Manufacturing	Krishnaiah Yellela	Ubrani Venkataram
Microbiology	Xia Xu	Nandini Bhattacharya
Biopharmaceutics	Qi Zhang	Ta-Chen Wu
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	David Claffey	

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Recommend a Complete Response action from a product quality perspective based on the inadequate findings from the drug product, biopharmaceutics, OPMA, and microbiology review teams and the withhold recommendation for the (b) (4) drug substance manufacturing site.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Shandong Luye Pharmaceutical Co., Ltd. developed Rykindo, an extended release injectable suspension formulation of risperidone with four strengths -12.5 mg, 25 mg, 37.5 mg, and 50 mg, for the treatment of schizophrenia and bipolar I disorder. It has the same dosage form, indications and strengths as its reference drug RISPERDAL CONSTA (NDA 21346)- the main difference being that COSTA requires three weeks of oral dosing after the first injection, whereas this product (b) (4). (Note that the OCP reviewers found that some oral dosing would also be needed for this product). (b) (4)

The drug product is provided as a dose pack, consisting of a vial containing the solid component of the suspension (informally referred to as 'risperidone microspheres'), a pre-filled syringe with 2 mL of diluent, a vial adapter, and one safety needle with needle safety sheath. The drug product is designed to be administered every two weeks by intramuscular (IM) gluteal injection. (b) (4)

Unexpected spikes in serum active drug were seen in the pivotal clinical studies in three of the 50 patients. Although no link was made to a product quality or administration errors, this cannot yet be ruled out. A range of outstanding product quality deficiencies remain from the drug product, microbiology, biopharmaceutics review teams. A Withhold recommendation is in place for the drug substance manufacturing site. These deficiencies will require resolution

before this application can be found acceptable from a product quality perspective.

Proposed Indication(s) including Intended Patient Population	Treatment of schizophrenia and bipolar I disorder
Duration of Treatment	Chronic
Maximum Daily Dose	N/A
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

CMC information for the risperidone drug substance is referenced to DMF (b) (4). Amendments SD #11-21 of this DMF were reviewed and the DMF was found to be adequate to support this application. The proposed release specification complied with the risperidone USP monograph. Impurities are controlled as per USP monograph, ICH Q3A, ICH M7, ICH Q3C, ICH Q3D where applicable. The polymorph and particle size are controlled by the drug substance manufacturer. The applicant excluded the particle size distribution test (b) (4). Batch analyses data of eight batches are described in the application, including the commercial validation, primary stability, clinical, and toxicological batches – all of which meet specification. Data in the DMF support a (b) (4)-month retest period.

Drug Product: Inadequate

The drug product is a ‘for extended release injectable suspension’ formulation of risperidone with four strengths -12.5 mg, 25 mg, 37.5 mg, and 50 mg. The drug product is provided as a dose pack, consisting of a vial containing the solid component of the suspension (aka ‘risperidone microspheres’), a pre-filled syringe with 2 mL of diluent, a vial adapter, and one safety needle with needle safety sheath. The drug product is designed to be administered every two weeks by intramuscular (IM) gluteal injection.

The microspheres consist of the drug substance and two (b) (4) polymers PLGA 5050 (b) (4), and PLGA 7525 (b) (4), in addition to mannitol (b) (4). The excipients are present at lower levels than in the currently approved products. Release results were provided for three registration batches of the 12.5 mg, 37.5 mg, and 50 mg strengths and for one microsphere batch of the 25 mg strength, at smaller scale. Additionally, results from the commercial scale size batch of each strength was provided. All batches met the proposed specification.

The diluent consists of the following USP/NF grade excipients: sodium chloride, sodium hydroxide, citric acid, dibasic sodium phosphate, polysorbate 80, water for injection, and carboxymethylcellulose sodium. All excipients in the diluent are present at lower levels than the currently approved products. The Applicant provided release results for three batches from each of the diluent manufacturers (Luye and (b) (4)), all of which met the proposed specification. Note that the same volume of diluent is used for each of the strengths.

The container closure system consists of a vial for the solid, a prefilled syringe of diluent. In addition, the kit includes a vial adapter, and one safety needle with needle protection packaging for intramuscular injection. The vial adapter and needle come with original blister pouch (both are sterile ready-to-use). All components are (b) (4) sealed (b) (4) (b) (4).

There are number of outstanding issues with the drug product which are described below:

Risperidone Microsphere PLGA Molecular Weight

Polymer molecular weight directly impacts drug product performance. Polymer molecular weight decreases on storage and under aqueous conditions such as the manufacturing process. In a response to an information request dated 22-Nov-2019, the Applicant indicated that (b) (4)

(b) (4). As such, the Applicant proposes a control (b) (4)

(b) (4). The applicant has not demonstrated that this will adequately detect and control (b) (4).

Risperidone Microsphere (b) (4)

The Applicant proposed an (b) (4) (b) (4). This range is not adequately supported by data. Furthermore, the variability (b) (4)

(b) (4) is significant and greater than what is typically acceptable according to the guidance, “*SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation.*” (b) (4)

(b) (4)

The Applicant will be asked to tighten the (b) (4) control or, alternatively to provide data justifying the currently proposed range.

Risperidone Microsphere Overfill

There is an overfill in the microsphere vial depending on the strength to account for loss during drug product administration (e.g. loss in the microsphere vial, in the needle, in the syringe). The 12.5 mg, 25 mg, 37.5 mg, and 50 mg strengths have an overfill of (b) (4)%, (b) (4)%, and (b) (4)%, respectively. This overfill is included to ensure that the drug product can deliver the labeled amount of risperidone. However, the composition of the drug product used in these studies is unclear. The Applicant will be asked to provide data justifying the risperidone microsphere overfill over the range of possible drug product composition (b) (4).

(b) (4)

Risperidone Microsphere Related Substance/Impurity Method

In the initial related substance/impurity method, the two impurities (b) (4) (b) (4) eluted at almost the same time ((b) (4) minutes and (b) (4) minutes). In a response to an information request dated 22-Nov-2019, the Applicant developed a completely new related substance method. This method has yet to be evaluated as there was insufficient time to do so in this review cycle.

Combined Product Delivered Dose

As part of a response to an information request dated 27-Sep-2019, the applicant added deliverable assay as part of the combined product release and stability acceptance criteria. Results ranged from (b) (4) – (b) (4)%, with almost no results with (b) (4)% of the labeled amount. After an investigation, the Applicant concluded that the variation in the results is due to the relatively complicated sample preparation procedure. In order to reduce variation, the Applicant optimized the delivered assay method by including additional details regarding sample preparation. It is concerning that very slight variation to the preparation procedure can lead to inconsistent drug product delivery (e.g. underdosing). Additionally, the updated method description did not seem to include the optimized language. This issue will require further justification and modification of the instructions for use to ensure that the patients are administered a consistent dose.

Combined Product Resuspendability

Once the diluent is combined with the microspheres, a milky suspension is formed. The microspheres settle quickly after shaking is stopped. The labeling instructions state that, “just before injection, shake syringe vigorously for 20-30 seconds until there is no deposition of (b) (4), as some settling will have occurred.” In a response to an information request dated 6-Sep-2019, the Applicant provided results (b) (4)

(b) (4)

(b) (4) Therefore, a very slight deviation from the IFU can lead to inconsistent drug product delivery (e.g. underdosing).

Labeling: Choose an item.

N/A. Deficiencies precluded labeling review in this review cycle.

Manufacturing: Inadequate

The diluent and microspheres are manufactured separately, and co-packaged with a vial adapter and safety needle.

The major steps for the **manufacture of the Diluent** involve (b) (4). The clinical and primary stability batches of diluent were manufactured at two sites ((b) (4) and Luye) at the same (b) (4) kg batch size. These two sites were proposed for commercial batches. The process controls and IPC tests at both sites are consistent and adequately reflected in the revised versions of respective Intended MBRs.

The major steps for the manufacture the solid component of the drug product suspension (aka, ‘microspheres’) include (b) (4). The clinical/primary stability batches are at (b) (4) g scale whereas the commercial batches will be at (b) (4) g and (b) (4) g scale. The process controls and IPC tests were found to be adequate, with the exception of the (b) (4) acceptance criterion which was addressed by the drug product review team.

Based on the review of inspection and application documents, all the listed facilities are acceptable except for the drug substance manufacturing facility (b) (4) is inadequate with an Overall Manufacturing Inspection Recommendation (OMIR) to “withhold”.

Biopharmaceutics: Inadequate

The Biopharmaceutics review focused on (1) evaluation of the adequacy of the proposed in vitro drug release method and acceptance criteria, (2) bridging throughout product development, (3) biowaiver request, (4) dose-dumping potential, and (5) extended-release claim for the proposed risperidone extended-release injectable suspension.

1) In Vitro Drug Release Method and Acceptance Criteria:

The proposed in vitro drug release method was found unacceptable because of the use of the same amount of 20 mg microsphere samples regardless of strength and without reconstitution for the in vitro drug release. The dissolution risk is considered high, considering that the proposed drug product contains a drug loaded-biodegradable polymeric parenteral product for intramuscular injection, and no IVIVC based on human PK data was demonstrated. In addition, there are concerns regarding the effectiveness of reconstitution and the drug product and process issues described above. To mitigate these risks, the biopharm

review team requests that the applicant develop an adequate in vitro drug release method for the reconstituted products that reflects the clinical use of the proposed drug product or, alternatively, establish an acceptable IVIVC to correlate human PK data with in vitro drug release data using the currently proposed in vitro drug release method (without the reconstitution).

Bridging through development: The commercial drug product has the same formulation in both microsphere and diluent, API supplier, and manufacture site as the product batches used in the pivotal BE study. However, there are differences in batch size and manufacturing process between the pivotal BE/stability and commercial batches. From the Biopharmaceutics perspective, the similarity of the drug release and the product bridging between the commercial and clinical BE batch cannot be established via in vitro bridging approach for the following reasons: (1) the difference between the pivotal and commercial drug product (b) (4); (2) the average differences in drug release of the microspheres at the sampling time points 72 h and 80 h are greater than 15%, compared to pivotal clinical batches, for 3 out of 7 commercial scale-up batches; (3) no *in vitro-in vivo* correlation based on human PK data has been demonstrated.

Biowaiver request: Waiver of the *in vivo* BA/BE studies for the non-bio-strengths (12.5 mg, 37.5 mg, and 50 mg strengths) cannot be granted for the following reasons: (1) PK data for the bio-strength 25 mg are not deemed acceptable (by Office of Clinical Pharmacology (OCP)) due to the clinical safety concerns regarding the PK spikes observed in the BA/BE study; (2) Per 21 CFR 320.22(d)(2)(iv), a full biowaiver would not apply for all the non-bio-strengths of the proposed long acting injection. PK data for the lowest (12.5 mg) and highest (50 mg) proposed strengths of the final to-be-marketed product (including both microsphere and diluent) are needed to bracket all the proposed non-bio-strengths; (3) The proposed in vitro drug release method without the commercial diluent cannot support bridging across all the strengths, because the *in vivo* release has not been correlating with this in vitro release method based on the human PK data, and the method itself does not reflect the clinical use of the proposed drug product (i.e. reconstituted products).

Dose dumping potential: The results of in-vitro drug release studies indicate a temperature-induced dose dumping potential with 41°C for 4 days of middle phase and 39°C for 29 days, as the difference in drug release profiles appears significant (approximately (b) (4)%) compared to the control. The Applicant should conduct relevant *in vivo* animal studies to demonstrate the absence of dose-dumping under applied heat using the proposed drug product (e.g., heat applied to injection site after the injection).

Extended release claim: Though bioequivalence at steady state was established between the proposed drug product and the LD, the proposed drug product does

not fully meet the CFR 21 CFR 320.25 (f) requirements to support an extended-release claim, because of unsolved quality issues, dose-dumping potential, and clinical concerns for the unexplained PK spikes. Therefore, RYKINDO cannot be labelled as an extended-release formulation of risperidone at this time.

RECOMMENDATION:

From the Biopharmaceutics perspective, the recommendation of approvability for NDA 212849 PENDING due to the biopharmaceutics deficiencies regarding the in vitro drug release, biowaiver and dose-dumping potential.

Microbiology: Inadequate



The applicant proposes a complicated (b) (4) manufacturing process for the subject drug product (Microspheres) which contains different process details for each of the two scales. (b) (4)

(b) (4). Microbiology review for DMFs (b) (4) (b) (4) for the various packaging components were found adequate to support this NDA.

Concise Description of Outstanding Issues:

Quality microbiology deficiencies pertain to container closure integrity validation, bioburden level, bacterial retention study for the (b) (4) (b) (4), holding time, validations (b) (4) (b) (4) for diluent, (b) (4) (b) (4), and bacterial endotoxin release test protocol.

C. Risk Assessment Refer to DRUG PRODUCT section.

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)



2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

1. Regarding the risperidone microspheres:

- a. The (b) (4) control for (b) (4) risperidone has not been adequately justified. The variability between the possible formulations (b) (4) (b) (4) is significant. (b) (4) (b) (4)
- (b) (4) Provide data (e.g. bioequivalence study results) to ensure that the product performance is equivalent for drug products manufactured at extremes of the proposed range. Alternatively, tighten the (b) (4) specification.

We note the additional analysis of the drug release profiles provided in a response to an information request dated 22-Nov-2019. It remains unclear whether the commercial formulation was used in these studies and whether the f2 analysis was performed comparing the different compositions to the pivotal clinical batch. Furthermore, a change (b) (4) excipients of this magnitude typically require more than in-vitro results.

- b. There is an overfill in the microsphere vial depending on the drug product strength ((b) (4)%) to account for loss during drug product administration (e.g. loss in the microsphere vial, in the needle, in the syringe). Results from studies (transfer efficiency and mass balance) provided a justification for the overfill. However, the composition of the drug product used in these studies is unclear. Provide data justifying the risperidone microsphere overfill over the range of possible drug product composition (b) (4) (b) (4), or any future tightened range.
- c. In a response to an information request dated 22-Nov-2019, you indicated that (b) (4) (b) (4) and proposed a control (b) (4) (b) (4) (b) (4) (b) (4) You have not demonstrated that this method is capable of adequately controlling (b) (4) (b) (4). Develop a method (b) (4), or propose an alternative validated control.

d. Note time did not allow the evaluation of the revised related substance/impurity method, submitted on 22 NOV 2019 in this review cycle.

2. Regarding the combined product:

- a. As part of a response to an information request dated 22-Nov-2019, you performed an investigation regarding the delivered assay results. You indicate that the method was optimized by including additional details regarding sample preparation. These differences could not be found in the method description section. Provide an up-to-date method description.
- b. Data demonstrate that very slight variation to the preparation procedure can lead to inconsistent drug product administration (e.g. underdosing). Provide information on how you plan to mitigate the risk of improper sample preparation once the product is commercialized.

3. Labeling Deficiencies

N/A

4. Manufacturing Deficiencies

During a recent inspection of the [REDACTED] (b) (4) [REDACTED] manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

5. Biopharmaceutics Deficiencies

1. *In vitro drug release method:*

The proposed in vitro drug release method is not acceptable as the test does not use commercial diluent and individual tests were not proposed for each strength. The risk associated with drug release is considered high since the proposed drug product is reconstituted biodegradable polymeric parenteral microspheres for intramuscular injection, with no in vitro-in vivo correlation (IVIVC) based on human PK data. In addition, concerns remain with regards to the effectiveness of reconstitution for the unresolved quality and clinical issues [e.g., PK spikes observed in the pivotal BE study, biowaiver request, dose-dumping potential, etc.].

To address the Agency's concerns and mitigate the risk, you may consider the following approach(es):

- 1) *Implement an adequate in vitro drug release method for the reconstituted products, reflecting the clinical use of the proposed drug product. Specifically, with respect to the sample preparation step of the in vitro*

drug release test, FDA recommends that the samples be prepared for each strength (i.e., using the equivalence of (b) (4) mg, (b) (4) mg, (b) (4) mg and (b) (4) mg microspheres for 12.5 mg, 25 mg, 37.5 mg, and 50 mg strengths, respectively) per the proposed labeling instructions (Section 2.8

(b) (4)) and the resulting suspension sample volume be equivalent to that delivered to patients (i.e., approximately 2 mL).

- 2) Alternatively, establishing an acceptable IVIVC to correlate human PK data with in vitro drug release data using the currently proposed in vitro drug release method (without the reconstitution).

If you pursue the option 1 (i.e., adequate in vitro drug release method), provide the following information/data:

Generate in vitro drug release profile data (n=12, mean, %RSD, min, max, individual; at 0.5, 2, 6, 24, 32, 45, 56, 72, 80, 96, 120 hours until complete drug release is achieved) for the following drug product lots using the two sets of drug release method conditions tabulated below:

Suspension Sample per vessel	Apparatus	Agitation Speed	Medium Volume	Temp.	Medium
For each strength: prepare samples per Section 2.8 Instructions for Use and make sure that the suspension sample volume is equivalent to the injection volume	Thermostatic water bath with cylinder bottle (static method)	0 rpm	200 mL	45 °C	10 mM Dihydrogen Phosphate 40 mM Sodium Chloride 0.01% (w/v) Tween-80 0.05% (w/v) Sodium Azide pH 7.4
			1000 mL		

- 3) the clinical/stability batches and commercial batches for all strengths (ensure that the new BE study uses the final commercial (scale up) batch),
- 4) the variant and target drug product lots that were used to demonstrate the current in vitro drug release method's discriminating power (e.g., products A, B, C in Table 43 and Figure 18 of the Method Report (TER-LY03004-PA1-008-EN), and
- 5) the stressed stability sample (i.e., Table 54 and Figure 21 of the Method Report (TER- LY03004-PA1-008-EN).

Submit the drug release profile data presented in graphical and tabular formats (with profile similarity (f2) analysis using the target product as the reference) and indicate the ages of the lots at the time of in vitro drug release testing. Submit all complete in vitro drug release data in Microsoft Excel "xlsx" format.

Please note that depending on our assessment of the generated data above, we may request additional data/information (e.g., analytical method validation, and/or in vitro drug release method development).

2. Biowaiver:

Per 21 CFR 320.22(d)(2)(iv), a full biowaiver would not apply for all the non-bio-strengths (12.5 mg, 37.5 mg, and 50 mg strengths) of your proposed long acting injection. Therefore, to address this review issue, please provide the following data:

- 1) *Provide PK data for the lowest and highest proposed strengths of the final to-be-marketed product, i.e., in order to bracket all the proposed non-bio-strengths.*
- 2) *Alternatively, develop and establish an IVIVC with the proposed in vitro drug release that used to support in vitro bridging approach. Refer to Comment 1 regarding in vitro drug release method.*

3. Dose-dumping potential:

The effect of exercise and pressure on the in vivo drug release profile of the proposed drug product were included in the NDA. Please submit similar data showing the effect of applied (intermittent and continuous) heat on the in vivo drug release profile of your proposed drug product.

3) Microbiology Deficiencies

- 1) Regarding the responses of 26 September 2019 (pages 1-7 of 40, 1.11.1 Response to Information Request dated 05Sep2019.pdf) for the container closure integrity validation studies, address the following issues:

(b) (4)



11) Other Deficiencies (Specify discipline, such as Environmental)

[Redacted text box]

*Application Technical Lead Name and Date:
David Claffey 9 DEC 2019.*



David
Claffey

Digitally signed by David Claffey

Date: 12/09/2019 08:34:59PM

GUID: 508da71e00029e20b201195abff380c2

CHAPTER VII: MICROBIOLOGY

[IQA NDA Assessment Guide Reference](#)

Product Information	Pykindo® (risperidone) Extended-Release Microspheres for Injection is indicated for the treatment of schizophrenia, and as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder.
NDA Number	212849
Assessment Cycle Number	01
Drug Product Name/ Strength	Pykindo® Risperidone Extended-Release Microspheres for Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial
Route of Administration	Intramuscular
Applicant Name	<u>Shandong Luye Pharmaceutical Co., Ltd.</u> No. 15 Chuangye Road, Hi-tech Industrial Development Zone Yantai, Shandong Province, China 264003 <u>US Agent: Luye Pharma USA, Ltd.</u> 502 Carnegie Center, Suite 100, Princeton NJ 08540
Therapeutic Classification/ OND Division	Atypical antipsychotics
Manufacturing Site	<u>Shandong Luye Pharmaceutical Co. Ltd.</u> <u>(For drug product and diluent)</u> No. 15 Chuangye Road, High-Tech Industrial Development Zone Yantai City, Shandong Province China 264003 (b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: Inadequate

Assessment Summary:

(b) (4)

(b) (4)

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Supporting Document # 1	03/28/2019
Supporting Document # 3	05/30/2019
Supporting Document # 9	08/02/2019
Supporting Document # 10	08/09/2019
Supporting Document # 16	09/26/2019
Supporting Document # 20	11/22/2019

Highlight Key Issues from Last Cycle and Their Resolution: None.

Remarks: This is a 505(b)(2) NDA submission. The Reference Listed Drug is Risperdal CONSTA[®] (risperidone) Long-Acting Injection from Janssen Pharmaceuticals, Inc (NDA 021346). The RLD's strengths are 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial of risperidone. The RLD is provided as a dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent for Risperdal CONSTA[®], a vial adapter, and two Terumo SurGuard[®] 3 Needles for intramuscular injection (a 21 G UTW 1-inch needle with needle protection device for deltoid administration and a 20 G TW 2-inch needle with needle protection device for gluteal administration). The indication, dosage form, strengths, and the dose pack of the subject drug product are the same as those of the RLD, except that the dose pack of the subject drug product contains only one (b) (4) Needle for intramuscular gluteal injection. Pykindo[®] (risperidone) extended-release microspheres for Injection has been developed under IND 116108. The subject NDA product is intended (b) (4) (b) (4) (b) (4) to reach steady state after less doses compared to the RLD.

The applicant's information request responses of 05/30/2019, 08/02/2019, 08/09/2019, 09/26/2019, and 11/22/2019 are incorporated in this review.

The applicant proposes a complicated (b) (4) manufacturing process for the subject drug product (Microspheres) which contains different process details for two scales. (b) (4)

(b) (4). Therefore, this review is atypically long.

Concise Description of Outstanding Issues:

Quality microbiology deficiencies pertain to container closure integrity validation, bioburden level, bacterial retention study (b) (4) (b) (4), holding time, validations (b) (4) process, (b) (4)

(b) (4) for diluent, (b) (4)
(b) (4), and bacterial endotoxin release test
protocol.

Supporting Documents:

Microbiology reviews (b) (4) (Inadequate) (b) (4)
(b) (4) (Adequate) (b) (4)
(b) (4)

Microbiology review (b) (4) (Adequate) (b) (4)
(b) (4)
(b) (4)

- Microbiology review (b) (4) (Adequate) for (b) (4)
(b) (4)
- Microbiology review (b) (4) (Adequate) (b) (4)
(b) (4)
- Microbiology review (b) (4) (Adequate) (b) (4)
(b) (4)

- Microbiology review (b) (4) (Adequate) (b) (4)
(b) (4)
- Microbiology review (b) (4) (Adequate) (b) (4)
(b) (4) (Adequate) (b) (4)
(b) (4)

S DRUG SUBSTANCE

The drug substance (Risperidone USP), manufactured by (b) (4)
(b) (4), is supplied as non-sterile powder. (b) (4)
(b) (4) The drug

substance, excipients and (b) (4) are tested for bacterial endotoxin and microbial limits or sterility with the following acceptance criteria:

Drug Substance/ Excipient	Endotoxin Limit	Microbial Limits
Microsphere* (Shandong Luye)		
Risperidone, USP	NMT (b) (4)	TAMC: NMT (b) (4); TYMC: NMT (b) (4) <i>Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli:</i> (b) (4) <i>Salmonella:</i> (b) (4)
Mannitol (b) (4) USP	< (b) (4)	Absence of microbial growth, per USP <71>
PLGA 5050 (b) (4)	< (b) (4)	TAMC: NMT (b) (4) <i>P. aeruginosa, S. aureus, E. coli:</i> (b) (4) <i>Salmonella:</i> (b) (4)
PLGA 7525 (b) (4)		
Diluent		
Carboxymethylcellulose Sodium USP	<u>Shandong Luye &</u> (b) (4): < (b) (4)	<u>Shandong Luye:</u> TAMC: NMT (b) (4); TYMC: NMT (b) (4) <i>P. aeruginosa, S. aureus, E. coli:</i> (b) (4) <i>Salmonella:</i> (b) (4)
Citric Acid Monohydrate, USP	<u>Shandong Luye &</u> (b) (4): < (b) (4)	(b) (4) TAMC: NMT (b) (4); TYMC: NMT (b) (4)
Dibasic Sodium Phosphate Anhydrous, USP	<u>Shandong Luye &</u> (b) (4): < (b) (4)	<u>Shandong Luye:</u> TAMC: NMT (b) (4); TYMC: NMT (b) (4) <i>P. aeruginosa, S. aureus, E. coli:</i> (b) (4) <i>Salmonella:</i> (b) (4) (b) (4) TAMC: NMT (b) (4); TYMC: NMT (b) (4)
Sodium Chloride, USP**	<u>Shandong Luye:</u> < (b) (4) (b) (4): Meets the requirements per USP <85>	<u>Shandong Luye:</u> TAMC: NMT (b) (4) CFU/g; TYMC: NMT (b) (4) <i>P. aeruginosa, S. aureus, E. coli:</i> (b) (4) <i>Salmonella:</i> (b) (4) (b) (4): Meets the requirements per USP <71>**
Polysorbate 80, NF	<u>Shandong Luye:</u> < (b) (4)	<u>Shandong Luye:</u> TAMC: NMT (b) (4); TYMC: NMT (b) (4) <i>P. aeruginosa, S. aureus, E. coli:</i> (b) (4) <i>Salmonella:</i> (b) (4)
Water for Injection, USP#	<u>Shandong Luye &</u> (b) (4): < (b) (4)	<u>Shandong Luye:</u> TAMC: NMT (b) (4) (b) (4): Sterile, per USP <71>

TAMC: Total Aerobic Microbial Count; TYMC: Total Combined Yeasts and Molds Count

(b) (4)

Assessment: {Adequate}

Microbiological quality acceptance criteria for drug substance/excipients comply with those specified by USP <1111> for non-sterile substances/excipients for pharmaceutical use.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product

Rykindo® (risperidone) Extended-Release Microspheres for Injection (12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial) is a sterile, nonpyrogenic, preservative-free, single dose lyophilized powder packaged in a glass vial and copackaged with a pre-filled syringe (PFS) containing 2 mL sterile, nonpyrogenic, preservative-free Diluent solution, for intramuscular gluteal injection. One vial adapter and one safety needle are packaged together with the drug product vial and the diluent PFS in the dose pack.

Drug product composition

Risperidone Extended-Release Microspheres:

Ingredients	Function	Unit Formula (in mg per vial) Strength				Unit Formula in w/w (%)
		12.5 mg	25 mg	37.5 mg	50 mg	
Risperidone, USP	Active Ingredient	12.5	25	37.5	50	(b) (4)
PLGA 5050 (b) (4)	(b) (4)					(b) (4)
PLGA 7525 (b) (4)						
Mannitol (b) (4) USP						
Total (in mg)						(b) (4) 100

Diluent:

Ingredients	Function	Unit Formula (in mg/syringe)	Unit Formula in w/w (%)
Carboxymethylcellulose Sodium (SCMC), USP	(b) (4)		(b) (4)
Sodium Chloride, USP			
Sodium Hydroxide, NF			
Citric Acid Monohydrate, USP			
Dibasic Sodium Phosphate Anhydrous, USP			
Polysorbate 80, NF			
Water for Injection, USP		q.s. to 2 mL	q. s. (b) (4)
Total		2 mL	100

Description of container closure system

The containers and closures to be used in the commercial production of the drug product and the diluent are briefly described in 3.2.P.7. Information regarding the vial volume, stopper formulation and configuration, (b) (4) catalog

numbers, are obtained from 3.2.R and Letters of Authorization for the referenced DMFs.

Components	Description	Manufacturers
Risperidone Extended-Release Microspheres 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial		
Vial	(b) (4) glass tubular vial (8 mL, 20 mm neck size)	(b) (4)
Stopper	(b) (4) rubber stopper (b) (4), FluroTec-05) (20 mm)	(b) (4)
Seal	20 mm aluminum-plastics caps 12.5 mg: Orange; 25 mg: Green; 37.5 mg: Purple; 50 mg: Blue	(b) (4)
Diluent		
Syringe	3 mL (b) (4) syringe barrel with Luer tip (b) (4)	(b) (4)
Plunger Stopper	(b) (4) 1-3 mL plunger stopper for syringe (b) (4)	(b) (4)
Plunger rod	Plunger rod for syringe barrels	(b) (4)
Device		
Vial Adapter	Transparent (b) (4) vial adapter (b) (4)	(b) (4)
Needle	(b) (4) 20-gauge (b) (4) 2-inch stainless steel safety injection needles with needle protection and Luer connection, for intramuscular gluteal injection (b) (4) Safety Needle)	(b) (4)

One drug product vial, one diluent prefilled syringe, one vial adapter and one safety needle are packaged together in (b) (4) kit (b) (4). The vial adapter is used to connect the vial and the prefilled syringe. (b) (4)

(b) (4) Then the entire contents of diluent in the prefilled syringe are injected into the vial through the vial adapter and the microspheres are suspended by shaking vigorously for at least 30 seconds. The entire contents of the microsphere suspension are subsequently pulled back into the prefilled syringe. Following removal of the vial adapter and vial, the disposable safety sterile needle is attached to the prefilled syringe. The syringe is shaken for 20-30 seconds and the product is administered to patient by deep intramuscular gluteal injection.

The following deficiency (italicized below) was issued in the Agency's Information Request dated 05/17/2019:

The Letter of Authorization from DMF (b) (4) dated 11/5/2018 indicates the Ready-to-Sterilize stoppers proposed to be used for commercial production of the drug product (b) (4). However, the formulation and configuration of stoppers for the drug product are not specified in

Section 3.2.P.7 of the submission. Specify the formulation and configuration of the routine production stopper.

Response of 05/30/2019: Information from the LOAs for DMF (b) (4) dated 11/05/2018 and DMF (b) (4) dated 11/05/2018, and the referenced “Microsphere 3.2.P.7 Container Closure System- Vial, Stopper and Cap”, is incorporated above.

Assessment: {Adequate}

The drug product composition and container-closure system are adequately described. The container-closure system is adequate for the drug product intramuscular route of administration.

(b) (4)

CHAPTER VI: BIOPHARMACEUTICS

NDA Number	212849; 505(b)(2)
Drug Product Name/ Strength	RYKINDO™ (Risperidone) for extended-release injectable suspension, 12.5 mg, 25 mg, 37.5 mg, and 50 mg. RYKINDO® is provided as a dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing the diluent, a vial adapter, and a (b) (4) Needles (20 G (b) (4) 2-inch needle with needle protection device for gluteal administration).
Route of Administration	Intramuscular injection (IM)
Applicant Name	Shandong Luye Pharmaceutical Co., Ltd.
Therapeutic Classification/ OND Division	Psychiatry/CDER/ON/DP
RLD/RS Number	NDA 21346; Risperdal Consta®
Proposed Indication	Treatment of schizophrenia; as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder.
Primary Reviewer	Qi Zhang, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

REVIEW SUMMARY

The Biopharmaceutics review focused on (1) evaluation of the adequacy of the proposed in vitro drug release method and acceptance criteria, (2) bridging throughout product development, (3) biowaiver request, (4) dose-dumping potential, and (5) extended-release claim for the proposed risperidone extended-release injectable suspension.

1) In Vitro Drug Release Method and Acceptance Criteria:

The proposed in vitro drug release method is deemed not acceptable for the finished drug product's batch release and stability testing, considering the use of the same amount of 20 mg microsphere samples regardless of strength and without reconstitution for the in vitro drug release. The dissolution risk is considered high, considering that the proposed drug product contains drug-loaded-biodegradable polymeric parenteral microspheres for intramuscular injection, whereas no *in vitro-in vivo* correlation (IVIVC) based on human PK data has been demonstrated. In addition, there are lingering concerns regarding the effectiveness of reconstitution as the Applicant claimed (b) (4) for the unresolved quality and clinical issues [e.g., change (b) (4) during manufacturing scale-up, wide (b) (4) acceptance criteria, PK spikes during the pivotal BE study, biowaiver request, and dose dumping potential, etc.]. To address the concerns and mitigate the risk, the Applicant should implement an adequate in vitro drug release method for the reconstituted products that reflects the clinical use of the proposed drug product or, alternatively, establish an acceptable IVIVC to correlate human PK data with in vitro drug release

data using the currently proposed in vitro drug release method (without the reconstitution). Refer to **LISTING OF BIOPHARMACEUTICS DEFICIENCIES** section. The setting of the appropriate drug release acceptance criteria (time points and ranges) for the proposed drug product will be determined after the proposed release method is optimized and deemed acceptable.

2) Bridging Throughout Product Development:

The commercial drug product has the same formulation in both microsphere and diluent, API supplier, and manufacture site as those of the product batch used in the pivotal BE study. However, there are differences in batch size and manufacturing process between the pivotal BE/stability and commercial batches. From the Biopharmaceutics perspective, the similarity of the drug release and the product bridging between the commercial and clinical BE batch cannot be established via in vitro bridging approach for the following reasons: (1) the difference between the pivotal and commercial drug product (b) (4) (2) the average differences in drug release of the microspheres at the sampling time points 72 h and 80 h are greater than 15%, compared to pivotal clinical batches, for 3 out of 7 commercial scale-up batches; (3) no *in vitro-in vivo* correlation based on human PK data has been demonstrated.

3) Biowaiver Request:

Waiver of the in vivo BA/BE studies for the non-bio-strengths (12.5 mg, 37.5 mg, and 50 mg strengths) cannot be granted for the following reasons: (1) PK data for the bio-strength 25 mg are not deemed acceptable (by Office of Clinical Pharmacology (OCP)) due to the clinical safety concerns regarding the PK spikes observed in the BA/BE study; (2) Per 21 CFR 320.22(d)(2)(iv), a full biowaiver would not apply for all the non-bio-strengths of the proposed long acting injection. PK data for the lowest (12.5 mg) and highest (50 mg) proposed strengths of the final to-be-marketed product (including both microsphere and diluent) are needed to bracket all the proposed non-bio-strengths; (3) The proposed in vitro drug release method with the microspheres only cannot support bridging across all the strengths, because the *in vivo* release has not been correlating with this in vitro release method base on the human PK data, and the method itself does not reflect the clinical use of the proposed drug product (i.e. reconstituted products). Refer to **LISTING OF BIOPHARMACEUTICS DEFICIENCIES** section.

4) Dose-Dumping Potential:

The results of in-vitro drug release studies indicate a temperature-induced dose dumping potential with 41°C for 4 days of middle phase and 39°C for 29 days, as the difference in drug release profiles appears significant (approximately (b) (4) %) compared to the control. The Applicant should conduct relevant in vivo animal studies to demonstrate the absence of dose-dumping under applied heat using the proposed drug product (e.g., heat applied to injection site after the injection). Refer to **LISTING OF BIOPHARMACEUTICS DEFICIENCIES** section.

5) Extended-Release Claim:

Though bioequivalence at steady state was established between the proposed drug product and the LD, the proposed drug product does not fully meet the CFR 21 CFR 320.25 (f) requirements to support an extended-release claim, because of unsolved quality issues, dose-dumping potential, and clinical concerns for the unexplained PK spikes. Therefore, RYKINDO cannot be labelled as an extended-release formulation of risperidone at this time.

RECOMMENDATION:

From the Biopharmaceutics perspective, the recommendation of approvability for NDA 212849 for RYKINDO™ (Risperidone) extended-release injectable suspension, 12.5 mg, 25 mg, 37.5 mg, and 50 mg, is PENDING due to the biopharmaceutics deficiencies regarding the in vitro drug release, biowaiver and dose-dumping potential.

Biopharmaceutics deficiencies, as detailed in **LISTING OF BIOPHARMACEUTICS DEFICIENCIES** section, should be conveyed to the Applicant in the Complete Response (CR) letter.

BIOPHARMACEUTICS ASSESSMENT

I. LIST of SUBMISSIONS BEING REVIEWED

eCTD # (SND #)	Received date	Document
0000 (1)	3/28/2019	Original submission
0010 (11)	8/20/2019	Response to Information Request
0017 (18)	10/17/2019	Response to Information Request
0019 (20)	11/20/2019	Response to Information Request

II. BIOPHARMACEUTICS RELATED INFORMATION

BCS Class Designation	Not applicable to extended-release drug products.						
Solubility	Low; Risperidone is practically insoluble in water. It is very slightly soluble in pH = 8.0, and slightly soluble in pH = 6.8, soluble in pH = 4.5 and freely soluble in pH = 3.0.						
Permeability	Not provided in the submission.						
In Vitro Drug Release	RYKINDO (LY03004) exhibits > ^{(b) (4)} ₍₄₎ % drug release within 5 days, when using the proposed QC in vitro accelerated drug release (IVR) method (45°C), and within 23 days when using the real-time IVR method (37°C).						
Particle Size (Drug substance)	(b) (4)						
Polymorphic form							
Particle Size (Microsphere)							
Formulation	Diluent composition:						
	Ingredients	Function	Unit Formula (in mg/syringe)	Unit Formula in w/w (%)			
	Carboxymethylcellulose Sodium (SCMC), USP	(b) (4)		(b) (4)			
	Sodium Chloride, USP						
	Sodium Hydroxide, NF						
	Citric Acid Monohydrate ^a , USP						
	Dibasic Sodium Phosphate Anhydrous, USP						
	Polysorbate 80, NF						
	Water for Injection, USP				q.s. to 2 mL	Q.s.	(b) (4)
	Total				2 mL	100	(b) (4)

	Microsphere composition:							
	Ingredients	Function	Unit Formula (in mg per vial)				Unit Formula in w/w (%)	Quality standard
			Strength					
			12.5 mg	25 mg	37.5 mg	50 mg		
	Risperidone	Active Ingredient	12.5	25	37.5	50	(b) (4)	USP
	PLGA 5050 (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	In-house
	PLGA 7525 (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	In-house
	Mannitol (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	USP
		(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	NF
		(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	USP
		(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	USP
	Total (in mg)		(b) (4)				100	-
	Overfill ⁷		(b) (4)				-	-
	Fill amount		(b) (4)				-	-
	(b) (4)							
Dosing	25 mg IM every 2 weeks; The maximum dose should not exceed 50 mg every 2 weeks.							
Absolution	After a single IM injection of RYKINDO of 12.5 mg, 25 mg, 37.5 mg or 50 mg, the release profile consists of a small initial release of risperidone (same for all doses), followed by a main increase phase for drug release without an apparent lag time, which is different from RISPERDAL CONSTA® with a lag time of 3 weeks following an injection. (Study CT-USA-104)							
Dose Proportionality	12.5 mg to 50 mg (Study CT-1S01)							
BE	Steady state PK profiles of LY03004 and RISPERDAL CONSTA® were compared and steady state bioequivalence was established. (Pivotal Study: CT-USA-102)							
Tmax	Risperidone and 9-hydroxyrisperidone (active metabolite): 14-19 days							
Food Effect	Not Applicable							

III. DISSOLUTION

1. Applicant's Proposed Dissolution Method and Acceptance Criteria:

Strengths/sample per vessel	Apparatus	Agitation Speed	Medium Volume	Temp.	Medium	Acceptance Criteria
For all strengths/ 20 mg microsphere per vessel	Thermostatic water bath with cylinder bottle (static method)	0 rpm	200 mL	45 °C	10 mM Dihydrogen Phosphate 40 mM Sodium Chloride 0.01% (w/v) Tween-80 0.05% (w/v) Sodium Azide pH 7.4	NMT (b) (4) in 0.5 h (b) (4) in 24 h (b) (4) in 56 h (b) (4) in 120 h

2. Dissolution Method Development:



5. Dissolution Acceptance Criteria:

The acceptance ranges are proposed based on the in vitro drug release profile data generated using the proposed drug release method for the clinical (13, 18, 20, and 24 M) and stability/registration (initial, 3, 6, 9, and 12 M) lots of microsphere during long-term stability study. Per the Applicant, the analytical procedure for current in vitro release was adapted in Nov 2015, therefore, data of the current method is only available from 20 M for the pivotal clinical batches 1403011 and from 13 M for 1409041 (Figures 1 and 2 of *Quality Response dated 8/20/2019*). In response to Biopharmaceutics IR dated 11/08/2019, The Applicant confirmed that the primary registration/stability batches are representative of the clinical batch #1403011 (bio-batch, 25 mg) in terms of formulation/manufacturing process & controls with supporting data including the drug release results (Table 16 of *Quality Response dated 11/22/2019*).

The proposed acceptance criteria include four time points to characterize the drug release profile at the initial release, lag, and main release phases, i.e. 0.5 h to control burst release, 24 h for early/lag stage, 56 h for middle stage and 120 h for late stage. The appropriateness of the drug release acceptance criteria (time points and ranges) for the proposed drug product cannot be determined until the proposed release method is deemed adequate.

Figure 1: Release Trends of Each Sampling Time Point for Pivotal PK/Clinical (1403011) under Long-term (5°C ± 3°C) Storage Condition

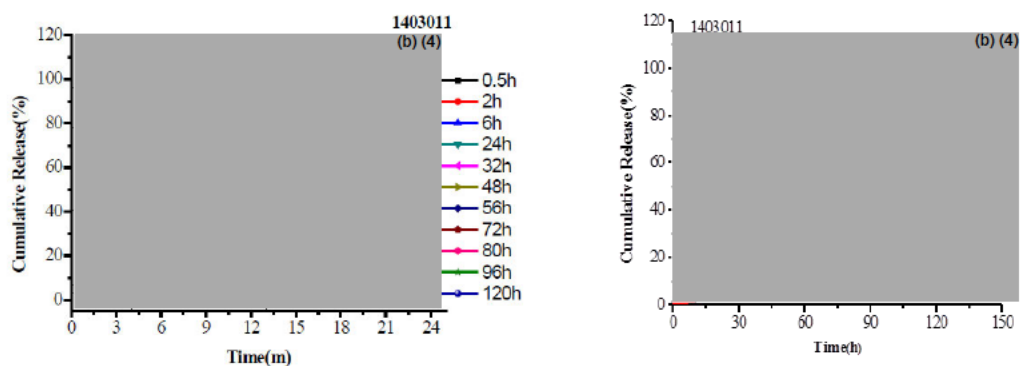


Figure 2: Release Trends of Each Sampling Time Point for Pivotal PK/Clinical (1409041) under Long-term (5°C ± 3°C) Storage Condition

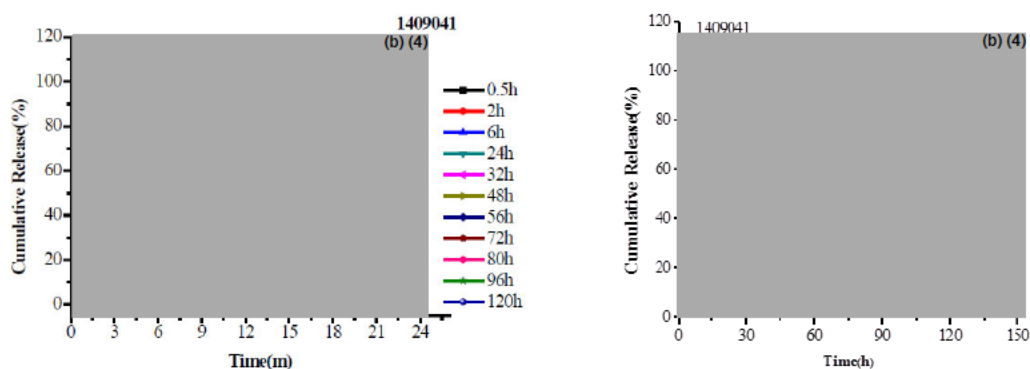


Table 16: Release Profile Comparison by Current *In Vitro* Release Method for Clinical and Primary Stability Batches

Test	Acceptance Criteria	Clinical Batch	Primary Stability Batches			
		1403011 (25 mg) (20 M)*	U61706011 (12.5 mg)	U61707031 (25 mg)	U61707041 (37.5 mg)	U61706041 (50 mg)
Release (%)	0.5 h	NMT	(b) (4)			
	24 h		(b) (4)			
	56 h		(b) (4)			
	120 h	NLT	(b) (4)			

*The clinical batch of microspheres was studied within the shelf life period when the current *in vitro* release method was developed.

Reviewer's Overall Assessment: INADEQUATE

The Applicant provided detailed in vitro drug release method development report for the proposed drug product. However, the proposed in vitro drug release method is not considered acceptable for the finished drug product batch release and stability testing in view of use of the same amount

of 20 mg microsphere samples regardless of strength and without reconstitution for the in vitro drug release, as explained below for the major concerns:

1. The dissolution risk is high, considering that the drug product is biodegradable polymeric parental microspheres (reconstituted in vehicle) for injection, and no in vitro-in vivo correlation (IVIVC) based on human PK data and using the currently proposed in vitro drug release has been demonstrated. It is noted that the LD uses the same drug release method (except for differences in (b) (4)) with only 20 mg of microsphere samples for all strengths. However, a strong IVIVC for the LD was shown when the approved drug release method was employed. Noted that the proposed drug product has different formulation (both microsphere and diluent) and different PK profiles (refer to OCP Review) and safety concerns as a result.

2. There are lingering concerns regarding the effectiveness of reconstitution as the Applicant claimed (b) (4) for the unresolved quality and clinical issues [e.g., change (b) (4) during manufacturing scale-up, wide (b) (4) acceptance criteria, PK spikes during the pivotal BE study, biowaiver request, and dose dumping potential, etc.]. Refer to the CMC, Clinical Pharmacology, and Clinical Reviews for additional information.

Gathering the totality of the information, it is this Reviewer's view that the following strategies would provide necessary data or link to address concerns and mitigate the risk:

- (i) Implementing an in vitro drug release method for the reconstituted products, reflecting the clinical use of the proposed drug product.
- (ii) Alternatively, establishing an acceptable IVIVC to correlate human PK data with in vitro drug release data (without the reconstitution) using the currently proposed in vitro drug release method.

Refer to **LISTING OF BIOPHARMACEUTICS DEFICIENCIES** section.

IV. BRIDGING THROUGHOUT PRODUCT DEVELOPMENT

There are 3 clinical studies conducted to support the approval of this NDA: Phase I pivotal relative BA/BE study at steady state (LY03004/CT-USA-102); Phase I single ascending dose PK study (LY03004/CT-1S01), and Phase I single dose study (LY03004/CT-USA-104). The same LY03004 microsphere formulation was used in all Phase I studies; however, different (b) (4) formulations with changes (b) (4) (Table 2 of 2.7.1 Summary of Biopharmaceutics Studies). Biopharmaceutics defers to the Clinical Pharmacology Review for the determination of the adequacy of PK bridging among different diluent formulations.

Table 2: Diluents Used in LY03004 Clinical Studies

Diluent	Composition		Justification for Formulation Changes	Used in Studies
	Component	Amount per Unit (mg/2 mL)		
I	(b) (4)		(b) (4)	Clinical Study LY03004-/CT-1S01
II				Clinical Study LY03004/CT-USA-104
III				Clinical Study LY03004/CT-USA-104 Pivotal Clinical Study LY03004/CT-USA-102 Registration and commercial batches
(b) (4)				

Source: Module 3.2.P.2.1 Formulation Development

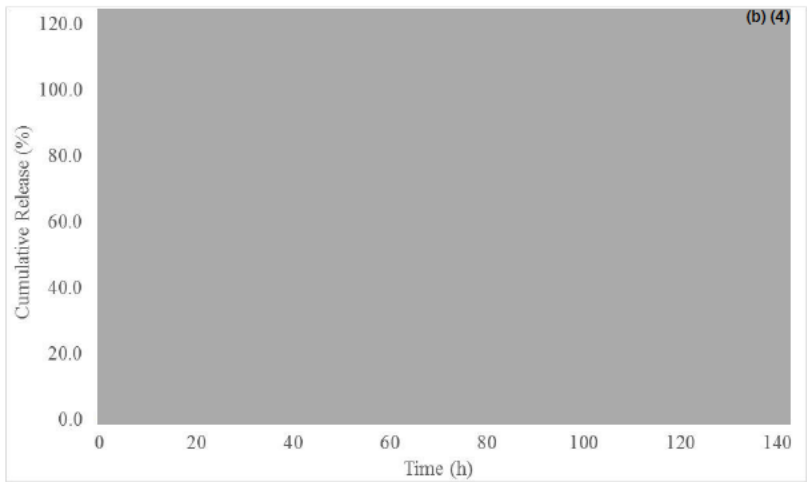
The proposed to-be-marketed drug product has the same formulations in both microsphere and diluent, API supplier, and microsphere and diluent manufacture (Shandong Luye Pharmaceutical Co.) as those of the products used in the pivotal studies. However, there are differences in batch size and manufacturing process between the pivotal clinical/stability and commercial batches. This appears to have resulted in differences in the drug product batches, (b) (4)
 (b) (4)
 (b) (4). The Applicant submitted comparative drug release profile data between the pivotal clinical and commercial batches on 8/20/2019 in response to the Biopharmaceutics IR dated 08/13/2019. Though f_2 values suggest the similar drug release profiles, the average differences at the sampling time points 72 h and 80 h are greater than 15%, compared to pivotal clinical batches, for 3 out of 7 commercial scale-up batches (Table 2 of Quality Response dated 8/20/2019).

Table 2: The Complete *in vitro* Release Data of the Pivotal Clinical and Commercial Batches

Batch No. / Time	Remark	0.5 h (%)	2 h (%)	6 h (%)	24 h (%)	32 h (%)	48 h (%)	56 h (%)	72 h (%)	80 h (%)	96 h (%)	120 h (%)
1403011-20M	Clinical Batches	(b) (4)										
1409041-13M												
Average ^a												
071901012CO	Commercial Batches											
071901022CO												
071901042CO												

Batch No. / Time	Remark	0.5 h (%)	2 h (%)	6 h (%)	24 h (%)	32 h (%)	48 h (%)	56 h (%)	72 h (%)	80 h (%)	96 h (%)	120 h (%)
071902012CO		(b) (4)										
071902022CO												
071902032CO												
071903012CO												

^a Average is calculated from raw data of each pivotal clinical batch before rounding



Reviewer’s Assessment: *INADEQUATE*

*This Reviewer considers the proposed *in vitro* approach unacceptable to support the formulation bridging between pivotal clinical and commercial drug products for the following reasons: (1) the difference between the pivotal and commercial drug product (b) (4); (2) the average differences in drug release of the (b) (4)*

microspheres at the sampling time points 72 h and 80 h are greater than 15%, compared to pivotal clinical batches, for 3 out of 7 commercial scale-up batches; (3) no in vitro-in vivo correlation based on human PK data has been demonstrated.

V. **BIOWAIVER REQUEST**

Reviewer's Assessment: INADEQUATE

A request of biowaiver for the additional strengths (12.5 mg, 37.5 mg, and 50 mg strengths) cannot be granted, for the following reasons:

(1) PK data for the bio-strength 25 mg are not deemed acceptable (by the Office of Clinical Pharmacology (OCP)) due to the clinical safety concerns regarding the PK spikes observed in the BA/BE study; (2) Per 21 CFR 320.22(d)(2)(iv), a full biowaiver would not apply for all the non-bio-strengths of the proposed long acting injection. PK data for the lowest (12.5 mg) and highest (50 mg) proposed strengths of the final to-be-marketed product (including both microsphere and diluent) are needed to bracket all the proposed non-bio-strengths; (3) The proposed in vitro drug release method with the microspheres only cannot support bridging across all the strengths, because the in vivo release has not been correlating with this in vitro release method base on the human PK data, and the method itself does not reflect the clinical use of the proposed drug product (i.e. reconstituted product).

Refer to **LISTING OF BIOPHARMACEUTICS DEFICIENCIES** section for details.

Note that LY03004 is currently under clinical development in EU. In lieu of providing the requested bracketing PK data of the lowest and highest strengths, PK data for the 50 mg strength being evaluated in the PK/efficacy/safety studies, conducted in the EU, may provide support for the biowaiver, if the final proposed drug product (including drug-loaded microspheres and diluent) to be marketed in the US has the same formulation and manufacturing process as the investigational EU drug product. In response to the Biopharmaceutics IR, the Applicant clarified that formulation of diluent is different, (b) (4)

. The PK studies in the EU are ongoing and data are unavailable.

VI. **DOSE DUMPING**

1. In Vitro Testing

In vitro drug release studies were conducted to evaluate the temperature effect on the release of risperidone from LY03004 microspheres without added vehicle (Table 3 of TER-LY03004-PA1-001-EN Report and 2.7.1 Summary of Biopharmaceutics). The Applicant concluded that no dose-dumping took place with elevated temperature and thus LY03004 has minimum risk of dose dumping for patients with fever. Note that this conclusion was made based on the claimed similar maximum daily drug releases (5% at 37°C compared to 7%, 9%, and 7% when the temperature

was elevated to 41°C for 2 days, 41°C for 4 days, and 39°C during the whole process of drug release 29 days). However, based on the results of cumulative drug release profiles, there appears to be a potential for dose-dumping, most noticeably with 41°C for 4 days of middle phase and 39°C for the duration of 29 days, as observed by the approximately 10-20% difference in drug release profiles between control and middle or continuous fever (Figure 1 of TER-LY03004-PA1-001-EN Report and 2.7.1 Summary of Biopharmaceutics).

It is this Reviewer’s view that the potential effect of applied heat on risperidone release from the microspheres and vehicle to reach site of absorption is unknown. In the absence of in vitro evaluation or study in animal for effect of heat on in vitro drug release (with added vehicle or proposed drug product), the potential of dose-dumping in vivo cannot be completely ruled out.

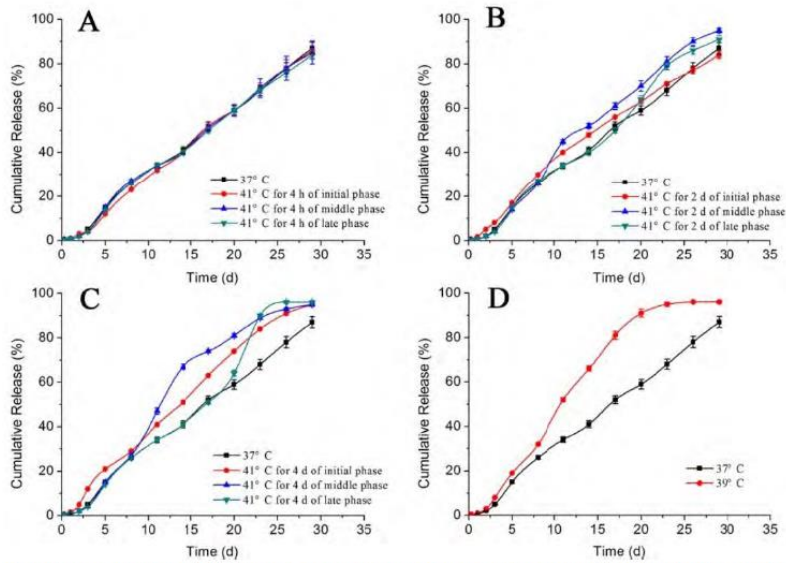
Table 3: Experimental Design of In Vitro Release Studies to Evaluate the Effect of Heat on LY03004 Release

Condition Number	Experimental Design*	Remarks
1	37°C from Day 0 - 29	Mimic normal body temperature
2	39°C from Day 0 - 29	Mimic continuous moderate fever
3	41°C for 4 h on Day 0, 37°C otherwise	Mimic hyperpyrexia for 4 hour, 2 days, and 4 days during the initial phase of drug release
4	41°C from Day 0 - 2, 37°C otherwise	
5	41°C from Day 0 - 4, 37°C otherwise	
6	41°C for 4 h on Day 10, 37°C otherwise	Mimic hyperpyrexia for 4 hour, 2 days, and 4 days during the middle phase of drug release
7	41°C from Day 9 - 11, 37°C otherwise	
8	41°C from Day 9 - 13, 37°C otherwise	
9	41°C for 4 h on Day 19, 37°C otherwise	Mimic hyperpyrexia for 4 hour, 2 days, and 4 days during the late phase of drug release
10	41°C from Day 19 - 21, 37°C otherwise	
11	41°C from Day 19 - 23, 37°C otherwise	

*The in vitro release method was as described in Module 3.2.P.5.2 except for experimental temperature and sampling time points.

Source: CMC Study TER-LY03004-PA1-001-EN Report, Table 3

Figure 1: Cumulative Release Profiles at Elevated Temperatures



Conditions: 41°C for 4 hours (A), 2 days (B), and 4 days (C) during initial, middle, and late phases of in vitro drug release and at 39°C during the whole process of in vitro release (D).
Source: CMC Study TER-LY03004-PA1-001-EN Report, Figure 1

2. In Vivo Study

The Applicant provided comparative PK profiles and drug exposure (C_{max} and AUC) to show that neither excise nor pressure (applied on injection site after injection) affects the PK of risperidone (LY03004) in dogs (Figure 3 and Table 4 of 2.7.1 Summary of Biopharmaceutics). Note that the Applicant did not evaluate the residual drug content on the explanted depots following injection, nor did the Applicant assess the dose-dumping potential with applied heat in animal species. Refer to Pharmacology/Toxicology Reviewer for the final assessment of the dose-dumping potential under excise, and applied pressure and heat stress conditions in animal studies.

Figure 3: Mean Plasma Concentration-time Profiles of Risperidone and Active Moiety After a Single IM Injection of 12.5 mg LY03004 in Beagle Dogs

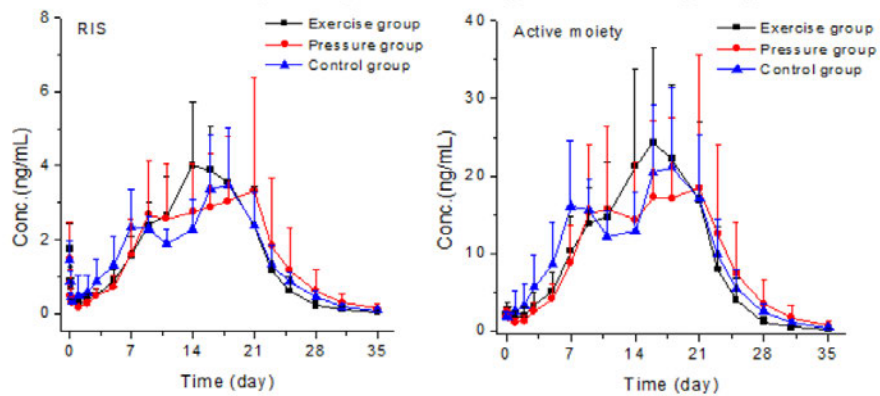


Table 4: Pharmacokinetic Parameters (Mean ± SD) of Risperidone and Active Moiety After a Single IM Injection of LY03004 (12.5 mg/dog)

Treatment Group	T _{max}	C _{max}	AUC _{last}	AUC _{inf}	t _{1/2}	24h Initial	C _{max} ratio*	AUC _{last} ratio*
	Day	h*ng/ml	h*ng/ml	h*ng/ml	h	Release %	%	%
Risperidone								
Exercise	16.0 ± 1.8	4.349 ± 1.713	1322.5 ± 347.0	1331.3 ± 344.7	56.1 ± 13.1	0.68 ± 0.14	109.9	104.4
Pressure	17.8 ± 3.7	4.305 ± 2.661	1337.9 ± 722.8	1354.0 ± 733.2	71.2 ± 13.9	0.58 ± 0.06	108.8	105.6
Control	14.3±5.0	3.957 ± 1.355	1266.4 ± 281.0	1277.7 ± 283.9	66.4 ± 11.0	0.90 ± 0.59	/	/
Active Moiety								
Exercise	17.2 ± 2.4	26.615 ± 13.349	8040.3 ± 3351.0	8053.4 ± 3353.6	56.1 ± 8.8	0.58 ± 0.15	109.5	98.84
Pressure	17.5 ± 3.7	24.501 ± 16.192	7727.1 ± 4388.1	7792.2 ± 4447.9	64.9 ± 11.0	0.45 ± 0.04	100.8	94.99
Control	14.0 ± 5.5	24.305 ± 8.539	8134.4 ± 2182.3	8168.5 ± 2187.8	62.0 ± 8.6	0.68 ± 0.50	/	/

T_{max}: time to peak value; C_{max}: the maximum serum concentration; AUC_{last}: area under the curve from time zero to the last sampling time point; AUC_{inf}: area under the curve from time zero to the infinity; t_{1/2}: elimination half-live; 24-hour Initial Release %: percentage of area under the curve from time zero to 24 hours to AUC_{last}.

* Compared with the control group.

Source: Nonclinical Study TER-LY03004-BA-016 Report, Table 1

Reviewer's Assessment: INADEQUATE

*The results of in-vitro drug release studies indicate that there appears to be temperature-induced dose-dumping potential with 41°C for 4 days of middle phase and 39°C for 29 days. The Applicant should conduct relevant in vivo animal studies with the final to-be-marketed product to demonstrate the absence of dose-dumping with applied (intermittent and continuous) heat (e.g., heat applied on injection site after injection). Refer to **LISTING OF BIOPHARMACEUTICS DEFICIENCIES**.*

VII. EXTENDED RELEASE CLAIM

Reviewer's Assessment: INADEQUATE

The 21 CFR 320.25(f) requirements to support an extended-release designation claim are as follows:

- (I) The drug product meets the extended-release claims made for it.*
- (II) The bioavailability profile established for the drug product rules out the occurrence of any dose dumping.*
- (III) The drug product's steady-state performance is equivalent to a currently marketed non-extended release or extended release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application.*
- (IV) The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.*

Though bioequivalence at steady-state was established between the proposed drug product and the LD, the proposed drug product does not fully meet the CFR 21 CFR 320.25(f) requirements to

support an extended-release claim because of unresolved quality and clinical concerns for the potential dose-dumping and the observed PK spikes. Therefore, the proposed RYKINDO cannot be classified as an extended-release formulation of risperidone at this time.

VIII. LISTING OF BIOPHARMACEUTICS DEFICIENCIES

1. *In vitro* drug release method:

The Division of Biopharmaceutics determines that the proposed *in vitro* drug release method is not acceptable with respect to the use of 20 mg microsphere samples without reconstitution for all strengths for the *in vitro* drug release testing. The risk associated with drug release is considered as high since the proposed drug product is reconstituted biodegradable polymeric parenteral microspheres for intramuscular injection, whereas no *in vitro-in vivo* correlation (IVIVC) based on human PK data and using the currently proposed *in vitro* drug release method has been demonstrated. In addition, concerns remain with regards to the effectiveness of reconstitution for the unresolved quality and clinical issues [e.g., PK spikes observed in the pivotal BE study, biowaiver request, dose-dumping potential, etc.].

To address the Agency's concerns and mitigate the risk, you may consider the following approach(es):

- 1) Implement an adequate *in vitro* drug release method for the reconstituted products, reflecting the clinical use of the proposed drug product. Specifically, with respect to the sample preparation step of the *in vitro* drug release test, FDA recommends that the samples be prepared for each strength (i.e., using the equivalence of (b) (4) mg, (b) (4) mg, (b) (4) mg and (b) (4) mg microspheres for 12.5 mg, 25 mg, 37.5 mg, and 50 mg strengths, respectively) per the proposed labeling instructions (Section 2.8 (b) (4)) and the resulting suspension sample volume be equivalent to that delivered to patients (i.e., approximately 2 mL).
- 2) Alternatively, establishing an acceptable IVIVC to correlate human PK data with *in vitro* drug release data using the currently proposed *in vitro* drug release method (without the reconstitution).

If you pursue the option 1 (i.e., adequate *in vitro* drug release method), provide the following information/data:

Generate *in vitro* drug release profile data (n=12, mean, %RSD, min, max, individual; at 0.5, 2, 6, 24, 32, 45, 56, 72, 80, 96, 120 hours until complete drug release is achieved) for the following drug product lots using the two sets of drug release method conditions tabulated below:

Suspension Sample per vessel	Apparatus	Agitation Speed	Medium Volume	Temp.	Medium

For each strength: prepare samples per Section 2.8 (b) (4) and make sure that the suspension sample volume is equivalent to the injection volume	Thermostatic water bath with cylinder bottle (static method)	0 rpm	200 mL	45 °C	10 mM Dihydrogen Phosphate 40 mM Sodium Chloride 0.01% (w/v) Tween-80 0.05% (w/v) Sodium Azide pH 7.4
			1000 mL		

- i. the clinical/stability batches and commercial batches for all strengths (ensure that the new BE study uses the final commercial (scale up) batch),
- ii. the variant and target drug product lots that were used to demonstrate the current in vitro drug release method's discriminating power (e.g., products A, B, C in Table 43 and Figure 18 of the Method Report (TER-LY03004-PA1-008-EN), and
- iii. the stressed stability sample (i.e., Table 54 and Figure 21 of the Method Report (TER-LY03004-PA1-008-EN)).

Submit the drug release profile data presented in graphical and tabular formats (with profile similarity (f2) analysis using the target product as the reference) and indicate the ages of the lots at the time of in vitro drug release testing. Submit all complete in vitro drug release data in Microsoft Excel "xlsx" format.

Please note that depending on our assessment of the generated data above, we may request additional data/information (e.g., analytical method validation, and/or in vitro drug release method development).

2. Biowaiver:

Per 21 CFR 320.22(d)(2)(iv), a full biowaiver would not apply for all the non-bio-strengths (12.5 mg, 37.5 mg, and 50 mg strengths) of your proposed long acting injection. Therefore, to address this review issue, please provide the following data:

- 1) Provide PK data for the lowest and highest proposed strengths of the final to-be-marketed product, i.e., in order to bracket all the proposed non-bio-strengths.
- 2) Alternatively, develop and establish an IVIVC with the proposed in vitro drug release that used to support in vitro bridging approach. Refer to Comment 1 regarding in vitro drug release method.

3. Dose-dumping potential:

The effect of exercise and pressure on the in vivo drug release profile of the proposed drug product were included in the NDA. Please submit similar data showing the effect of applied (intermittent and continuous) heat on the in vivo drug release profile of your proposed drug product.



Qi
Zhang

Digitally signed by Qi Zhang
Date: 12/04/2019 12:31:12PM
GUID: 547e178000007695c91eb10380b07939



Ta-Chen
Wu

Digitally signed by Ta-Chen Wu
Date: 12/04/2019 12:37:01PM
GUID: 508da6df000269e151ff37cd8f4e13a1



**DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES**

Date	11/25/2019		
To:	William Bender		
Requesting Center/Office	CDER/OND	Clinical Review Division	DPP
From	CDR Keith Marin OPEQ/OHT3/DHT3C		
Through (Division)	CAPT Alan Stevens OPEQ/OHT3/DHT3C GHDB		
Subject	NDA 212849, Rykindo (Risperidone Extended-Release Microspheres for Injection) Vial Kits: 12. 5mg, 25 mg, 37. 5 mg and 50 mg Schizophrenia and Bipolar I Disorder		
Recommendation	Filing Recommendation Date: Click or tap to enter a date. ☒ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5 for Deficiencies Mid-Cycle Recommendation Date: Click or tap to enter a date. ☒ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A. Final Recommendation Date: 11/25/2019 ☒ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table		
Reviewer	Team Lead (TL)	Division (*Optional)

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 212849
Sponsor	Luye Parma Group. Ltd.
Drug/Biologic	Risperidone Extended-Release Microspheres
Indications for Use	RYKINDO® is an atypical antipsychotic indicated: • for the treatment of schizophrenia. • as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder

Device Constituent	Co-Packaged Syringe
Related Files	None

Important Dates	
Filing	May 27, 2019
Midcycle Meeting/IRs due	August 28, 2019
Final Lead Device Review Memo Due	October 28, 2019
PDUFA Date	January 28, 2020

2. EXECUTIVE SUMMARY AND [RECOMMENDATION](#)

CDRH recommends the combination product is:

Approvable – the device constituent of the combination product is approvable for the proposed indication.

Approvable with PMC or PMR, [See Section 2.3](#)

Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, [see Section 2.2](#).

2.1. [Comments](#) to the Review Team

CDRH does not have any further comments to convey to the review team.

CDRH has the following comments to convey to the review team:

Review of the reconstituted drug batches in the stability section for break loose and glide force, it appears they have met reliability (appear to have tested 160 devices over the 16 batches), but there is question regarding the effectiveness of reconstitution that will be deferred to CDER.

2.2. [Complete Response](#) Deficiencies

There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. [Recommended Post-Market Commitments/Requirements](#)

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☐

3. PURPOSE/BACKGROUND

3.1. [Scope](#)

CDER is requesting approval of Rykindo (Risperidone Extended-Release Microspheres for Injection) for injection. The device constituent of the combination product is a Pre-Filled Syringe.

Choose an item. has requested the following consult for review of the device constituent of the combination product:

There was a CMC only meeting on July 19, 2018 and Sarah Mollo from CDRH provided comments to the Sponsor. The meeting minutes are dated August 16, 2018. We want to make sure that the Sponsor has submitted all the

v05.02.2019

Page 2 of 26

necessary information required regarding the device component. Filing meeting is scheduled for May 15, 2019; mid cycle meeting is TBD but will be scheduled sometime around the end of August.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following [review areas](#):

- Device performance
- Stability – device performance on stability
- Essential Performance Requirements (EPR) Control strategy
- Quality Systems Assessment

This review will not cover the following review areas:

- Compatibility of the drug with the device materials (deferred to CDER)
- Human Factors (deferred to DMEPA)
- Sterility (device is copackaged)
- Biocompatibility (device is copackaged)

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

None

3.2.1. Related Files

None

3.3. **Indications for Use**

Combination Product	Indications for Use
RYKINDO® (Risperidone Extended-Release Microspheres for injection)	Atypical antipsychotic indicated for the following: • for the treatment of schizophrenia. • as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder
Co-Packaged Syringe	Delivery of the Drug Product

3.4. **Materials Reviewed**

<u>Materials Reviewed</u>	
Sequence	Module(s)
NDA 212849	3.2.P Drug Product

4. **DEVICE DESCRIPTION**

4.1. **Device Description**

Rykindo® (risperidone) Extended-Release Microspheres for Injection is provided as a single-use dose pack, consisting of a vial containing one dosage strength of risperidone microspheres, a prefilled syringe (PFS) containing 2 mL volume of diluent, a vial adapter, and one safety needle with needle protection packaging for intramuscular injection. The vial adapter and needle come with original blister pouch (both are sterile ready-to-use) packaged by suppliers, they are placed (b) (4) with microspheres in vial and diluent in PFS. Each filled vial and each prefilled syringe are individually labeled. (b) (4)

(b) (4)

APPEARS THIS WAY ON ORIGINAL

Dose Pack Components	Container/Closure/Drug Device	Supplier Name and Address	Reference No.	Dose Pack Components	Container/Closure/Drug Device	Supplier Name and Address	Reference No.	
Microsphere (all strengths) in vial	Primary packaging		(b) (4)	Vial Adapter			(b) (4)	
	Container	Injection vials made of neutral borosilicate glass tubing			Auxiliary components			
	Closure	(b) (4) (b) (4) rubber stopper for injection (ready-to-sterile)			Pre-fillable syringe system assembly	Plunger rod for syringe barrels		
	Secondary packaging				Backstop for syringes			
	Seal	12.5 mg strength: 20 mm Aluminized-plastics Caps in orange color 25 mg strength: 20 mm Aluminized-plastics Caps in green color 37.5 mg strength: 20 mm Aluminized-plastics Caps in purple color 50 mg strength: Aluminized-plastics Caps in blue color						
Diluent (2 mL deliverable) in pre-filled syringe	Primary packaging			Needle				
	Syringe barrel with Luer tip	Syringe barrel with Luer tip (sterile ready-to-use)			One of (b) (4) 21-gauge (b) (4)-inch stainless steel safety injection needles with needle protection and Luer connection, for intramuscular gluteal injection (b) (4)			
	Plunger stopper for Syringes	Plunger stopper for syringes (sterile ready-to-use)					(b) (4)	

Components of the dose pack:

3ml prefilled syringe:

The diluent of Rykindo® is filled into 3 mL (b) (4) (Sterile) pre-fillable syringe systems (b) (4). The pre-fillable syringe system is composed of four components: a (b) (4) syringe barrel with Luer tip, a Plunger stopper, a plunger rod, and a backstop.

APPEARS THIS WAY ON ORIGINAL

Container / Closure / Drug Device	Component	Construction Materials
Syringe Barrel with Luer tip		(b) (4)
Plunger Stoppers for Syringes		
Plunger Rod for Syringe Barrels		
Backstop for Syringes		
a. refer to quality statement for glass in Figure 5 and compliance statements for Figure 6	(b) (4)	(b) (4)
b. refer to quality statement for (b) (4) Formulation in Figure 7.		

Vial Adapter:

The vial adapter is a needle-free vial access device that is used to connect the diluent syringe to drug product vial. The vial adapter is supplied by (b) (4). The device is cleared under (b) (4).



Table 3: Component and Material Description

Component	Material Description*
	(b) (4)

Needle:

The needle provided in the kit is cleared under (b) (4). The needle provided is a 20G 51mm Safety Hypodermic Needle. (b) (4)



4.2. Design Requirements

Basic Syringe Description/Requirements

Requirement	Reviewer Comment
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Intended to be administered intramuscularly by a health care professional
Injection Site	Intramuscular injection
Injection tissue and depth of injection	Needle is 51mm (~2''), typical IM injection needle length is 1-1.5''. Sponsor stated it is 2'' in length due to it intended to be administered in the buttocks.
Type of Use (e.g. single use, disposable, reusable, other)	Single use
Environments of use (e.g. home, clinic)	clinic
Storage conditions and expiry	The entire dose pack should be stored in the refrigerator (36° to 46°F; 2° to 8°C) and protected from light. If refrigeration is unavailable, RYKINDO® can be stored at temperatures not exceeding 77°F (25°C) for no more than 7 days prior to administration. Do not expose unrefrigerated product to temperatures above 77°F (25°C). Proposed shelf life is 24 months.
Needle connection (e.g. luer, slip tip, staked)	luer
Syringe Volume	3ml
Device materials including lubricant	Noted above for each component of the kit

Additional Syringe **Description/Requirements**

Requirement	Reviewer Comment
Hypodermic Needle: length, gauge, and configuration of the tip.	20G 51mm (b) (4) Safety Hypodermic Needle
Markings (graduated scale, position of scale, length of scale, numbering of scale, and legibility criteria (for insulin syringes). Insulin Syringes: The scale on the barrel should be in units of insulin.	Syringe is designed to be used complete without any partial dosing so no graduations are present.
Safety Features (e.g. Needle safety component/device)	Manually activated needle safety feature
Sterilization method	(b) (4)

*See [Design Verification Section](#) for verification of design requirements

4.3. Steps for Using the device



(b) (4)

Reviewer's Note: Labeling appears appropriate for a device of this type.

4.4. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☒ N/A	Mid-Cycle Deficiencies: ☒ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
Reviewer Comments The needle is 51mm (~2''), typical IM injection needle length is 1-1.5''. The sponsor should provide rationale why 2'' needle is appropriate. Additionally, it is not clear within the submission whether the syringe has markings or not. Finally, we are unable to locate the instructions for use that show how the device is used. This should all be provided by the sponsor.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

In 3.2.P.7, you have stated that the needle is 51mm (~2''). Typical IM injection needle length is 1-1.5''. The Agency is concerned that a needle too long may result in delivery of the medication in the wrong location. Please provide rationale why the 2'' needle you have selected is appropriate.	Date Sent: 7/29/2019	Date/Sequence Received: 08/08/2019
Information Request #	1	
Sponsor Response	Not sent to sponsor	

Reviewer Comments	Clarified with CDER. Based on discussion, for schizophrenia indications they tend to have longer needles, as the drugs may cause weight gain. And they do not want to administer it into fat tissue. Furthermore, this product is indicated for only gluteal administration, not deltoid.
Response Adequate:	X Yes ☐ No, See IR # Sent on Click or tap to enter a date.

It is not clear within the submission whether the syringe has markings or not. Please clarify if you syringe has graduated markings. If not, please provide a rationale on why the absence would not result in a delivery error.	Date Sent: 7/29/2019	Date/Sequence Received: 08/08/2019
Information Request #	2	
Sponsor Response	Not sent to sponsor	
Reviewer Comments	Clarified with CDER. Syringe should not have graduated markings as the content is designed to be used in the entirety and is not intended for partial dosing.	
Response Adequate:	X Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

We are unable to locate the instructions on how to use your prefilled syringe in your device labeling. Please provide this information.	Date Sent: 7/15/2019	Date/Sequence Received: Click or tap to enter a date.
Information Request #	3	
Sponsor Response	Not sent to sponsor	
Reviewer Comments	CDER clarified where in submission information could be found in 2.8 of the PI.	
Response Adequate:	X Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

Add Additional Information Request

No Additional Information Requests – Finalize Device Description Review Section

5. FILING REVIEW

CDRH performed Filing Review	☐
CDRH did not perform a Filing Review	☒

5.1. Facilities & Quality Systems Triage Inspection Recommendation Information

CDRH completed a review of the Facilities	☒ Yes ☐ No ☐ N/A
Inspection Recommendation	☐ Pre-Approval Inspection (PAI) ☐ Post-Approval Inspection ☐ Routine Surveillance ☒ No Inspection Needed ☐ N/A

CDRH completed a **review** of the Quality Systems Yes No N/A

*If a Facilities and/or Quality Systems Review is completed, the review is located in [Appendix B](#)

Reviewer's Note: Non – Emergency Use Prefilled Syringes do not need QS Review or assessment for PAI. Based on discussions with CDER, the current understanding is that Pre-filled Syringes and Piston Syringes for non-emergency treatments do not need additional CGMP/quality system review by CDRH. This type of device constituent part has basic technology and has a low risk of device-related injuries or malfunctions.

6. DEVICE PERFORMANCE REVIEW

6.1. Design Verification/Validation

6.1.1. Device Specification Standards and Guidance Documents

Syringe		Data Adequate		
		Yes	No	N/A
Pre-filled Syringe	ISO 11040-8, Prefilled syringes – Part 8: Requirements and test methods for prefilled syringes	☒	☐	☐
Co-packaged Syringe	ISO 7886-1, Sterile Hypodermic Syringes for Single Use—Part 1: Syringes for Manual Use	☒	☐	☐
Insulin Syringe	ISO 8537, Sterile single-use syringes, with or without needle, for insulin	☐	☐	☒
Needle/Sharps		Data Adequate		
		Yes	No	N/A
Needle	ISO 7864, Sterile Hypodermic Needles for Single Use	☒	☐	☐
Needle	ISO 6009, Hypodermic needles for single use – Color coding for identification	☐	☐	☒
Sharps Injury Prevention Feature	ISO 23908 - Sharps injury protection - Requirements and test methods - Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling	☒	☐	☐
Luer Lock		Data Adequate		
		Yes	No	N/A
Connection	ISO 80369-7, Small-bore connectors for liquids and gases in healthcare applications -- Part 7: Connectors for intravascular or hypodermic applications ** (replaces ISO 594-1 and 594-2 as of 2020) ISO 594-1, Conical fittings with a 6 % (Luer) taper for syringes, needles and certain other medical equipment - - Part 1: General requirements ISO 594-2, Conical fittings with 6 % (Luer) taper for syringes, needles and certain other medical equipment - - Part 2: Lock fittings	☒	☐	☐

6.1.2. Device Performance Evaluation

Essential Performance Requirement	Specification	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy	Deliverable volume is (b) (4) when tested by <USP 697>	Y	Y	Y	Y
Break loose Force	<(b) (4)>N	Y	Y	Y	Y
Glide Force	<(b) (4)>N	Y	Y	Y	Y
Vial attachment Force	?	?	?	?	?
Force to withdraw fluid into syringe	?	?	?	?	?

Reviewer Comment: In 3.2.P.7, the sponsor provided a traceability matrix that tracked the specification, verification, validation, stability, and shipping testing conducted. Break loose and glide force specifications have been provided for both diluent and reconstituted.

Design verification testing:

Studies	Method Description	Methods and References	Result	
			Min.	Max.
Deliverable volume	For Deliverable Volume, the IFU was followed to reconstitute the lyo DP and the supplied safety needle was attached to the syringe. The entire contents of the syringe were injected into a dry tared container without emptying the needle by slowly and constantly depressing the piston. The delivered weighed was obtained. The deliverable volume was calculated by dividing the delivered weight by the density of the drug suspension. The density of the drug suspension was calculated using the weight and density of the drug powder, and the fill volume and density of diluent.	ISO 11040-8 USP<697>	(b) (4) mL	(b) (4) mL
Residual Volume/Priming Volume	This was performed per ISO 11040-8 Section 6.7 and 11040-4 Section 6.5.1.3 and ISO 7886-1 Annex C as a guide and following the supplied IFU. Dry system components were used to determine the residual volume.	ISO 11040-8 Section 6.7 ISO 11040-4 Section 6.5.1.3 ISO 7886-1 Annex C	(b) (4) mL	(b) (4) mL
Break Free and Glide Force	Following the IFU, this was performed and generated 2 sets of data. The initial measurements was from the diluent syringe through the Vial Adapter directly into the lyo vial, then reconstituted, withdrawn and safety syringe attached. The second round was through the syringe fluid path. Capture the break free and glide force for each in Newtons (N).	ISO 11040-8 Section 6.2 ISO 11040-4 Annex E	Break free force first set	
			(b) (4)	(b) (4)
			Break free force second set	
			(b) (4)	(b) (4)
			Glide force first set	
(b) (4)	(b) (4)			
Glide force second set				

Studies	Method Description	Methods and References	Result	
			Min.	Max.
			(b) (4)	(b) (4)
Sealability	Reconstituted 10 vials with a methylene blue dye solution and withdrew solution into the syringe so that the fluid path was full. Inverted the whole attached combination for 1 minute. The leakage on the exterior of the system during the shaking, of the elastomer seal, and luer connection as well as the interconnectability of the luer connections were examined.	ISO8536-2:2010(E). Annex C	No leakage was observed and the luer connection was interconnected for all samples for both vial adapter and needle. Details are shown in microsphere section 3.2.P.2.4	
Shipping Study	Distribution simulation testing was performed per ASTM D4169-16: Standard Practice for Performance Testing of Shipping Containers and Systems.	ASTM-D4169	During the distribution simulation testing, no critical observations were noted upon completion of the distribution simulation testing; some minor damages were observed on the shippers, such as scuffing and creasing. Details are shown in microsphere section 3.2.P.2.4	
Container Closure Integrity	Helium Leak analysis (Selbly-12) was performed on the lyophilized sample vials after a shipping study following ASTM-D4169 had been completed.	ASTM-D4169 Selbly-12	All samples tested passed acceptance criteria. Details are shown in microsphere section 3.2.P.2.4	
The Luer Connectivity	Using fluid path connectors used in the clients PFS system	ISO11040-8 Section 6.6 ISO 80369-7	All test results conform to the acceptance criteria. Details are shown in diluent section 3.2.P.2.4 .	

Validation Testing (Demonstrated in traceability matrix):

Table 15: Traceability Matrix

User Need	Design Input	Design Output	Design Verification	Design Validation	Shelf Life	Shipping	Lot Release
Suspend risperidone microspheres	The syringe must contain sufficient volume diluent to suspend the risperidone microspheres.	The syringe must hold (b) (4) uL.	Filling volume of diluent in diluent Section 3.2.P.2.3.	In-use stability data in microspheres Section 3.2.P.8.3.	NA.	NA.	NA.
Administer constituted drug	The syringe must deliver the required volume.	Deliverable volume is (b) (4) mL when tested by USP <697>.	Deliverable volume study in Table 14.	In-use stability data in microspheres Section 3.2.P.8.3.	Stability data in microspheres section 3.2.P.8.3.	NA.	Tested on all batches.
Drug purity	Materials must be compatible with diluent solution.	(b) (4) stability required.	Package compatibility studies in microspheres section 3.2.P.2.4.	Stability study in microspheres section 3.2.P.8.1.	NA.	NA.	NA.
Safe for skin contact	Materials must be biocompatible.	Passes ISO-10993 for transient contact, cytotoxicity, irritation, sensitization.	Refer to (b) (4) ISO 10993 compliance statement in Figure 8 Figure 9 Figure 10 Figure 11.	Refer to (b) (4) ISO 10993 compliance statement in Figure 9 Figure 10 Figure 11.	NA.	NA.	NA.

User Need	Design Input	Design Output	Design Verification	Design Validation	Shelf Life	Shipping	Lot Release
	Meets compendial requirements for glass.	Meets USP <660>.	Quality statement in Figure 5.	Quality statement in Figure 5.	NA.	NA.	NA.
	Meets compendial requirements for rubber.	Meets USP <381>.	Quality statement from supplier in Figure 7.	Quality statement in Figure 7.	NA.	NA.	NA.
No mechanical aid	Can be administered with hand pressure.	Break free glide force N, ISO 11940-4 (b) (4).	Break free and glide force study in Table 14.	NA.	NA.	NA.	NA.
Sterility	Maintains seal integrity for sterility.	Container closure integrity test for diluent shows no leak.	Diluent section 3.2.P.2.5.	Components are provided from (b) (4) to be used as a syringe.	Diluent section 3.2.P.8.1.	Kit transport studies in microspheres section 3.2.P.2.4.	Tested on all batches.
Distributed product meets specifications	Provides 2 year product stability.	Stability protocol diluent section 3.2.P.8.1.	Stability data diluent section 3.2.P.8.3.	Performance with the drug product is confirmed on stability.	NA.	NA.	NA.
Distribution	Can be shipped.	Passes ASTM D4169-16.	Kit transport studies in microspheres section 3.2.P.2.4.	NA.	NA.	NA.	NA.

NA = column are not applicable unless an essential performance requirement.

Shipping studies:

Distribution Simulation Testing

Distribution simulation testing was performed per ASTM D4169-16. The following table describes the cycles for distribution simulation testing:

Test Interval	Sample Numbers	Test Schedules
Initial Test	001 - 002	ASTM D4169-16, DC 13, Assurance Level I Schedules: A, C, F, I, E and A.

Table 4: Distribution simulation cycle summary

During the distribution simulation testing, some observations were noted as follows:

- No critical observations were noted upon completion of the distribution simulation testing; some minor damages were observed on the shippers, such as scuffing and creasing.

Reviewer's Note: Risperidone Extended-release Microspheres used in-use stability study was stored at 2 - 8°C and taken out of storage condition to be reconstituted with diluent after 12 months and 24 months. The reconstituted sample was stored at room temperature and tested at 0h, 1h, 3h, 6h, and 24h. Extractable/deliverable volume and break loose/glide force for the reconstituted drug product was studied and all results complied with the specification. Results demonstrate that the risperidone microspheres could be successfully reconstituted and delivered. Shipping studies were conducted and met acceptance criteria. I have no additional questions.

6.1.3. Stability Review Summary

Storage condition	Accelerated Aging	Long term stability
Storage conditions	25°C ± 2°C/ 60% ± 5% RH, in upright and inverted position	5°C ± 3°C, in upright and inverted position
Packaging (drug stored in vial prior to drawing up in syringe)	(b) (4) glass vial with 20 mm (b) (4) rubber stopper, sealed with 20 mm aluminum-plastic cap	
Time schedule	0, 1, 2, 3, 6 m	0, 3, 6, 9, 12, 18, 24, 36 m
Time completed	0, 1, 2, 3, 6 m*	0, 3, 6, 9, 12 m

Stability studies under accelerated (25°C ± 2°C/ 60% RH ± 5% RH), long-term (5°C ± 3°C) have been conducted. Up to 6 months accelerated stability data and 12 months long-term stability data are available prior to submission and included in this application.

Table 30: Data Summary for In-use Stability Study

Stability Test	Batch No.	Storage Condition	Study Time Point	Results Evaluation	Conclusion
In-use stability	U61706031 U61707021	Room temperature	0 h, 1 h, 3 h, 6 h, 24 h	No obvious change trend	The reconstituted suspension is stable within 24 h at room temperature.

Reviewer Comments: Stability testing has been conducted for both accelerated and real time. The sponsor has provided a post approval stability protocol to provide additional real time testing. Based on the information provided up to this point, the sponsor's results showed that the reconstituted suspension was stable within 24 h at room temperature. The sponsor has proposed a recommendation in the drug product label that states: "Do not store suspension after reconstitution. Administer dose as soon as possible after reconstitution to avoid settling". As this is directly related to the drug product stability and its use, I will defer this to CDER.

6.1.4. Biocompatibility Evaluation

- Biocompatibility was **evaluated** [e.g. co-packaged syringes, co-packaged components outside of primary container closure]
- Biocompatibility was not evaluated **because**: as this is a prefilled syringe, biocompatibility is deferred to CDER

Reviewer's Note: The biocompatibility studies have been performed on the (b) (4) syringes in compliance with ISO 10993-1:2009 standard for surface contacting devices in contact with skin for a limited exposure for the glass syringe, plunger stopper, plunger rod, and backstop. Certificates of compliance have been provided for the testing conducted. As the syringe is prefilled, biocompatibility will be deferred to CDER.

6.1.5. Sterility Evaluation

- Sterility **Evaluated** (e.g. co-packaged syringes, co-packaged components outside of primary container closure)
- Sterility not evaluated (syringe, including needle are part of primary container closure, sterility evaluation is under the purview of CDER)

Reviewer's Note: The (b) (4) syringe barrels with luer tip (b) (4) (b) (4) products meet 10-6 sterility assurance level (SAL). (b) (4) (b) (4). The Syringe Barrel with Luer tip has a certificate of conformance to validate sterility. The needle is cleared (b) (4) and sterility has been conducted in the cleared device. As the device is part of the container closure, sterility will be deferred to CDER.

6.2. Device Performance Review Conclusion

DEVICE PERFORMANCE REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
Reviewer Comments: None		
CDRH sent Device Performance Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

7. LABELING

General Labeling Review



(b) (4)

The labeling, including the device constituent labeling and prescriber information were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors			X
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
<u>MRI</u> Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments

The sponsor has provided all necessary information for the combination product labeling. Instructions for use are located in 0000(1) 03/28/2019 section 1.14.3.

Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☒ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
Reviewer Comments The request for the step by step instructions for use has been noted above.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: Yes No		

8. CONTROL STRATEGY REVIEW

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or <u>release testing</u> activities:	Acceptable (Y/N/NA)
Dose Accuracy	≥ 0.1mL tested by USP 697	Y

Break loose Force, minimum glide force, maximum glide force	Diluent only: the range of break-loose force, maximum glide force and minimum glide force are (b) (4) respectively. Reconstituted drug: (b) (4) respectively	Y

Reviewer Comments

The sponsor has provided the control strategy for both dose accuracy and breakthrough/glide force per request. EPRs are provided in the stability testing.

Table 17: Data of Break-Loose and Glide Force of the Reconstituted Product for Registration Batches

Batch No.	No .	Break -loose force (N)	Maximu m glide force (N)	Minimu m glide force (N)	Batch No.	No .	Break -loose force (N)	Maximu m glide force (N)	Minimu m glide force (N)
U6170601 1	1	(b) (4)			U61708021	1	(b) (4)		
	2					2			
	3					3			
	4					4			

Batch No.	No.	Break-loose force (N)	Maximum glide force (N)	Minimum glide force (N)	Batch No.	No.	Break-loose force (N)	Maximum glide force (N)	Minimum glide force (N)
	5			(b) (4)		5			(b) (4)
	6					6			
	7					7			
	8					8			
	9					9			
	10					10			
U61706021	1				U61709011	1			
	2					2			
	3					3			
	4					4			
	5					5			
	6					6			
	7					7			
	8					8			
	9					9			
	10					10			
U61706031	1				071901012C O	1			
	2					2			
	3					3			
	4					4			
	5					5			
	6					6			
	7					7			
	8					8			
	9					9			
	10					10			
U61706041	1				071901022C O	1			
	2					2			
	3					3			
	4					4			
	5					5			
	6					6			
	7					7			
	8					8			
	9					9			
	10					10			
U61707011	1				071901042C O	1			
	2					2			
	3					3			
	4					4			
	5					5			
	6					6			
	7					7			

Batch No.	No.	Break loose force (N)	Maximum glide force (N)	Minimum glide force (N)	Batch No.	No.	Break loose force (N)	Maximum glide force (N)	Minimum glide force (N)
	8	(b) (4)					(b) (4)		
	9								
	10								
U6170702 1	1								
	2								
	3								
	4								
	5				071902012C				
	6				O				
	7								
	8								
	9								
	10								
U6170703 1	1								
	2								
	3								
	4								
	5				071902022C				
	6				O				
	7								
	8								
	9								
	10								
U6170704 1	1								
	2								
	3								
	4								
	5				071902032C				
	6				O				
	7								
	8								
	9								
	10								
U6170801 1	1								
	2								
	3								
	4								
	5				071903012C				
	6				O				
	7								
	8								
	9								
	10								

Reviewer's Note: The range of break-loose force, maximum glide force and minimum glide force of the reconstituted product for registration batches are (b) (4), respectively. This force is reasonable for the patient population.

Review comment for CDER: Review of the reconstituted drug batches in the stability section for break loose and glide force, it appears they have met reliability (appear to have tested 160 devices over the 16 batches), but there is question regarding the effectiveness of reconstitution that will be deferred to CDER.

Control Strategy Conclusion

The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.

Yes

No

8.1. Control Strategy Review Conclusion

v05.02.2019

CONTROL STRATEGY REVIEW CONCLUSION

Filing Deficiencies:

Yes No N/A

Mid-Cycle Deficiencies:

Yes No N/A

Final Deficiencies:

Yes No N/A

Reviewer Comments

We are unable to locate the control strategy for essential performance requirements. The sponsor will need to provide us the location of this information or provide the information itself.

CDRH sent Control Strategy Deficiency or Interactive Review Questions to the Sponsor: Yes No

Please provide the location of the your control strategy that ensures that the final finished combination product maintains its essential performance requirements. The control strategy may consist of, but is not limited to, lot release, in-process, control of incoming materials, purchasing controls, etc.	Date Sent: 7/31/2019	Date/Sequence Received: Click or tap to enter a date.
Information Request #	4	
Sponsor Response	Specific deficiency was not provided to sponsor	
Reviewer Comments	Based on conversation with CDER, the amount of drug delivered does not seem to be adequately controlled in the combination product. The problem is not the syringe but that fact that this is a suspension, not a solution. The syringe does indeed meet the specification but the reconstituted product may not (which really is a clinical issue). If it were a solution mass/volume delivered might be able to be a surrogate for what we are more interested in, the amount of drug delivered. As this is a suspension that is harder to control, as it can be inhomogeneous due to the settling of the solids from the liquid. However, the break loose and glide force was not addressed adequately in the stability plan and as a result, an IR was sent to the sponsor requesting that the sponsor provide all available data on the break loose and glide force of the drug product syringe both before reconstitution and after reconstitution. Additionally, they will need to add these tests to the drug product release and stability specification or justify their absence. Based on the response, the range of break-loose force, maximum glide force and minimum glide force of the reconstituted product for registration batches are (b) (4) respectively. While the force is reasonable for the patient population, the range is wide.	
Response Adequate:	☐ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

7 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/

DAVID J CLAFFEY
12/09/2019 08:44:34 PM