CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213586Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

NDA 213586 Executive Summary Assessment 2

1. Application/Product Information

NDA Number.	213586		
Applicant Name	Teva Neuroscience		
Drug Product Name	Risperidone extended-release injectable suspension		
Dosage Form.	Suspension, extended release		
Proposed Strength(s)	50, 75, 100, or 125 mg (q1m) or 100, 150, 200, or 250 mg (q2m)		
Route of Administration	Subcutaneous		
Maximum Daily Dose	125 mg once monthly; 250 mg every two months		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of schizophrenia		
Drug Product Description	Risperidone (TV-46000) extended-release injectable suspension for subcutaneous (sc) administration. TV-46000 contains risperidone and 2 biocompatible block copolymers as excipients that form a depot under the skin to deliver therapeutic levels of risperidone over periods of 1 month (q1m) and 2 months (q2m). TV-46000 is presented as a ready to use suspension in a prefilled syringe.		
Co-packaged product information	N/A		
Device information:	Pre-filled syringe		
Storage Temperature/ Conditions	2-8 °C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	N/A	N/A
	Drug Product/ Labeling	Mariappan Chelliah	Julia Pinto

	Manufacturing	Sureshbabu Dadiboyena	Kamal Tiwari
	Biopharmaceutics	Assadollah Noory	Tapash Ghosh
	Microbiology	N/A	N/A
	Other (specify):	N/A	N/A
	RBPM	Teshara Bouie	
	ATL	Valerie Amspacher	
Consults	N/A		

2. Final Overall Recommendation - Approval with QPA(s)

3. Action Letter Information

a. Expiration Dating: The proposed shelf-life of 24 months is acceptable when stored between 2° and 8°C (36° and 46° F).

b. Additional Comments for Action

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The CMC recommendation for this review cycle remains approval with QPA's. The CMC recommendation during the last review cycle was for approval with PMC's from (b) (4) biopharm. The CMC IQA dated 17 Mar 2022 recommended approval with a PMC from (b) (4) (b) (4) biopharm. The PMC's from the last review cycle remain in place and the due dates for the PMC's have been revised with this resubmission. The facilities have been reviewed and remain adequate.

This resubmission was submitted 28 Oct 2022. This resubmission is a response to a complete response letter sent 15 Apr 2022. The complete response was the action taken on the original NDA submitted 17 Jun 2021.

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: Choose an item.
Comments:

Comparability Protocols (PACMP): Choose an item.
Comments:

Additional Lifecycle Comments: N/A

(b) (4)

[redacted]

Biopharm QPA

PMC - 4237-2 - We acknowledge that you submitted an IVIVC report. However, there are deficiencies in your IVIVC report. Therefore, your provided IVIVC report is not reviewed at this time because the report is not in the right format. We are accepting your dissolution method and acceptance criteria on an interim basis. We will make final decision on the dissolution method and acceptance criterion once you submit document addressing the following deficiencies within 6-months (180

[redacted]

days) post-action. Finalization of the dissolution method and acceptance criteria will be made upon review of these documents within one-year post-action. Consider this as a Post-Marketing Commitment:

(b) (4)

To aid in the regulatory decision making in terms of acceptability of the proposed IVIVC model, submit the following information/data in a prior-approval supplement (PAS):

- **A modeling summary report, which provides an overview of the modeling strategy and details of the modeling procedures, including model development, model verification/modification, and model application in a step-by-step process. Inclusion of a flow chart, decision tree, or other similar representation is preferred for clarity.**
- **Generally, for the IVIVC development of immediate release drug products, at least 3 batches of the proposed drug product that differ in the in vivo PK and in vitro dissolution profiles should be used. As part of the validation steps, follow the "leave-one out" cross validation approach in the construction and validation of your model to challenge its robustness.**
- **Submit the executable project files (e.g., .phxproj, .xlsx or .xls, .sas) for the IVIVC model development and internal/external validation. Provide all relevant input including complete in vitro and in vivo data (i.e., individual, mean, % CV, profiles, in .csv, .xlsx or .xls, or .xpt format) and output files used in the construction and validation of the IVIVC model.**
- **Provide definition file(s) listing all input and output files, and the use or purpose of each of this files in an appropriate format (e.g., .pdf, .xpt, .xls). In addition, provide the hyperlinks for each data file and instructions for extracting these files.**
- **Provide the IVIVC predictions including the output files and summary table supporting your proposed dissolution acceptance criterion.**

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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
03/24/2023 11:49:57 AM

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RECOMMENDATION

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

NDA 213586
Assessment 1

Drug Product Name	risperidone (TV-46000) extended-release injectable suspension
Dosage Form	injectable suspension
Strength	50, 75, 100, or 125 mg (q1m) or 100, 150, 200, or 250 mg (q2m)
Route of Administration	subcutaneous (sc)
Rx/OTC Dispensed	Rx
Applicant	Teva Neuroscience, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 1; eCTD 0001	16 Jun 21	All; original submission
Supporting document 15; eCTD 0015	19 Nov 21	Process
Supporting document 17; eCTD 0017	8 Dec 21	Microbiology
Supporting document 21; eCTD 0021	6 Jan 22	Drug product
Supporting document 24; eCTD 0024	13 Jan 22	Drug product
Supporting document 28; eCTD 0028	15 Feb 22	Drug product
Supporting document 31; eCTD 0031	10 Mar 22	Biopharmaceutics
Supporting document 34; eCTD 0034	15 Mar 22	Biopharmaceutics and drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Zhixing Shan	Donna Christner
Drug Product	Mariappan Chelliah	Julia Pinto
Manufacturing	Sureshbabu Dadiboyena	Kamal Tiwari
Microbiology	Hemlata Tamta	Denise Miller
Biopharmaceutics	Assadollah Noory	Tapash Ghosh
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Mariappan Chelliah	Julia Pinto

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)	1	-11 Feb 22 by Hemlata Tamta for micro -26 Oct 21 by Zhixing Shan for drug substance	
	IV			1	4 Mar 22	reviewed by Mari Chelliah
	V			4		
	V			4		
	III			4		

(b) (4)	III	(b) (4)	1	11 Feb 22	Reviewed by Hemlata Tamta for micro

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
NDA	020272	LD - Risperdal
IND	124384	

2. CONSULTS

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

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends approval of the application with several post-marketing commitments (PMC's). (b) (4) biopharmaceutics will require PMC's (see individual reviews for details). All disciplines recommend approval.

The proposed shelf-life of 24 months is acceptable when stored between 2° and 8°C (36° and 46° F).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Teva has developed a new formulation of risperidone (TV-46000) as an extended-release injectable suspension for subcutaneous (sc) administration. TV-46000 contains risperidone and 2 biocompatible block copolymers as excipients that form a depot under the skin to deliver therapeutic levels of risperidone over periods of 1 month (q1m) and 2 months (q2m).
TV-46000 is presented as a ready to use suspension in a prefilled syringe (PFS) and delivered by sc injection at dosages of 50, 75, 100, or 125 mg (q1m) or 100, 150, 200, or 250 mg (q2m).

Risperidone Extended-Release Injectable Suspension (TV-46000) in pre-filled syringe (PFS) is a sterile, white to off white opaque suspensionfor subcutaneous (SC) use. The product is manufactured and filled in a single use 1 mL clear glass syringe by (b) (4).
The PFS is assembled with a plunger rod and (b) (4)
At the proposed storage condition of 2°C–8°C the product is a white to off white opaque solid.

The proposed shelf-life of 24 months is acceptable when stored between 2° and 8°C (36° and 46° F).

Proposed Indication(s) including Intended Patient Population	treatment of schizophrenia
Duration of Treatment	1 month or 2 months; chronic
Maximum Daily Dose	125 mg once monthly; 250 mg every two months
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The CMC information for the drug substance, Risperidone Sterile, is cross-referenced to Type II DMF 035434. Risperidone Sterile is manufactured by the Holder of the referenced DMF – Teva Pharmaceutical Industries Ltd.
The DMF was originally submitted on 14-APR-2021. Since then, the DMF has been reviewed 1 time by the Agency with the conclusion of "Adequate"; Zhixing Shan, Ph.D., 26-OCT-2021.
The Applicant refers to the DMF and provides a brief description of the general properties, specification, analytical methods, batch analyses, stability, etc. for the drug substance. All the information is adequate.
Based upon the information submitted in the DMF, there were no potentially genotoxic impurities detected in the drug substance; therefore,

the drug substance is not likely to pose any potential genotoxicity concerns.
Based upon stability data in DMF 035434, the DMF Holder currently has a retest period of (b) (4) months for the drug substance when stored in the container closure system at (b) (4)

Drug Product: Adequate

Both the copolymers are novel and they play a critical role in the formation of the depot and the controlled release of risperidone. The 50, 75, 100, and 125 mg strengths are intended for once a month administration and the 100, 150, 200, and 250 mg strengths are intended for once every two months administration.
The proposed specification and controls for the novel diblock and triblock copolymers are aligned with their respective specifications in DMF (b) (4) This reviewer assessed DMF (b) (4) and found it adequate (see DMF (b) (4) Chemistry Review #1).

The specification is adequate to control the quality of the drug product through the shelf-life. The impurity controls meet the ICH Q3B Guideline. The proposed criteria for risperidone particle size distribution and copolymer molecular weight are supported by the pharmaceutical development and stability data.
The proposed criteria for the syringe functionality tests are reasonable. Except for the 50 mg strength, the proposed acceptance range for the delivered volumes for individual syringes are ± (b) (4)% of their respective labeled volumes. For the 50 mg strength, the Applicant proposed a slightly wider criterion of (b) (4)% to (b) (4)% of the labeled volume, which is acceptable from a risk perspective.

The Applicant provided stability batch data using a bracketed approach. Data for 3 batches per strength were provided for the lowest and highest strengths, but only 1 or 2 batches for the intervening strengths. The data demonstrate that the Applicant can manufacture the drug product in consistent quality.
Six (6) months of accelerated data (25°C/60% RH) and 18 to 24 months of long-term data (5°C) are provided. No trending was noted for any of the tested attributes. The proposed shelf-life of 24 months when stored in refrigerator is acceptable. The thermal excursion data supports the statement that unopened package may be stored for up to 90 days then returned to the refrigerator.

The components of the primary container closure systems are suitable for packaging the drug product and they meet the appropriate USP chapters. The glass barrel of the syringe has low risk for glass delamination. All the primary components have been adequately characterized for extractables. The Applicant conducted only a simulated leachable study

using syringes filled with dimethyl sulfoxide, which showed the leachables did not exceed the acceptable daily intake. (b) (4)

(b) (4)

Labeling: Adequate

Manufacturing: Adequate

Manufacturing Process (b) (4)

xhibit batch size is (b) (4) Kg for 50 mg, 75 mg, 100 mg, 125 mg and 150 mg strengths and (b) (4) kg for 200 mg and 250 strengths. (b) (4)

(b) (4)

Process validation has been performed and the information provided ensures that the proposed commercial manufacturing facility, produces sterile drug product consistently.

Facilities: All the listed manufacturing facilities are approvable (from OPMA standpoint, concurred by ORA) based on the firm's inspection history and manufacturing experience

Biopharmaceutics: Adequate

TEVA requested a biowaiver for prefiled syringes (PFS) 50, 75, 125, 150, 200, and 250 mg dose strengths based on formulation proportionality to the 100 mg PFS used in the clinical study. (b) (4)

USP apparatus II (paddle) was chosen for product release and QC for this NDA. The USP Apparatus II IVR method is discriminating and sensitive to changes in critical quality attributes. The proposed dissolution method and the acceptance criteria are shown below.

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criteria

2 With Vessel cover	75	Phosphate buffer pH 6.0 at 37±0.5°C	1000	2 h: NMT (b) (4)% 24 h: (b) (4) 216 h: NLT (b) (4)

PMC 4237: We acknowledge that you submitted an IVIVC report. However, there are deficiencies in your IVIVC report. Therefore, your provided IVIVC report is not reviewed at this time because the report is not in the right format. We are accepting your dissolution method and acceptance criteria on an interim basis. We will make final decision on the dissolution method and acceptance criterion once you submit document addressing the following deficiencies within 6-months (180 days) post-action. Finalization of the dissolution method and acceptance criteria will be made upon review of these documents within one-year post-action. Consider this as a Post-Marketing Commitment:

(b) (4)

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•Generally, for the IVIVC development of immediate release drug products, at least 3 batches of the proposed drug product that differ in the in vivo PK and in vitro dissolution profiles should be used. As part of the validation steps, follow the “leave-one out” cross validation approach in the construction and validation of your model to challenge its robustness.

•Submit the executable project files (e.g., .phxproj, .xlsx or .xls, .sas) for the IVIVC model development and internal/external validation. Provide all relevant input including complete in vitro and in vivo data (i.e., individual, mean, % CV, profiles, in .csv, .xlsx or .xls, or .xpt format) and output files used in the construction and validation of the IVIVC model.

•Provide definition file(s) listing all input and output files, and the use or purpose of each of this files in an appropriate format (e.g., .pdf, .xpt, .xls). In addition, provide the hyperlinks for each data file and instructions for extracting these files.

•Provide the IVIVC predictions including the output files and summary table supporting your proposed dissolution acceptance criterion.

Microbiology (if applicable): Adequate

Risperidone extended-release injectable suspension (50, 75, 100, 125, 150, 200, 250 mg/ PFS) involves (b) (4)

(b) (4)

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L	(b) (4)	Acceptable or Not Acceptable	
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H		Acceptable	
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M		Acceptable	
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Uniformity of Dose (Fill Volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		Acceptable	
Content uniformity (suspension)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	

Particle size distribution (suspension)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M	(b) (4)	Acceptable	
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable (b) (4)	
***In vitro* release (ER)-Depot forming**	• Formulation • Process parameters • Scale/equipments • Site	H		Acceptable (with PMC)	
Appearance (Color/ turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	

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

7. Microbiology Deficiencies

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

Facilities screenshot showing approval (taken 17 Mar 22)

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(b) (4)

R REGIONAL INFORMATION

Environmental

The Applicant claims categorical exclusion under 21 CFR 25.31(b) and states that, in accordance with 21 CFR 25.15(d), there is no extraordinary circumstance that would warrant a report.

Assessment: *Adequate*

The Applicant has provided calculation to demonstrate that at the estimated peak sale of (b) (4) kg/year of risperidone, the expected introduction concentration (EIC) in aquatic environment is (b) (4) ppb, which is well below 1 ppb limit that would warrant an environmental assessment. Claim of categorical exclusion is acceptable.

Methods Validation or Verification Package

Assessment: *Not Applicable*

Comparability Protocols

Assessment: Not Applicable

Post-Approval Commitments

Assessment: *Adequate*

(b) (4)

(b) (4)

Lifecycle Management Considerations

None

DRUG PRODUCT LIST OF DEFICIENCIES

None

Primary Drug Product Assessor: Mariappan V. Chelliah

Secondary Assessor: Julia Pinto

Mariappan Chelliah

Digitally signed by Mariappan Chelliah
Date: 3/04/2022 08:38:43AM
GUID: 5399cb2c00032b7c21877aa0d4d5f794

Julia Pinto

Digitally signed by Julia Pinto
Date: 3/04/2022 10:52:24AM
GUID: 5050dbcb00001294a888a4bdc20a3a58

CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active	N/A	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another	N/A	

section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Adequate	

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	Adequate	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	Prefilled syringe intended for administration by healthcare providers

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information): Not Applicable

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Choose an item.	
Special preparation instructions (if applicable)	Choose an item.	
Storage and handling information (if applicable)	Choose an item.	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	Choose an item.	
Active ingredient(s) (if applicable)	Choose an item.	
Alphabetical listing of inactive ingredients (if applicable)	Choose an item.	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Choose an item.	

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

(Copy/paste or refer to a representative example of a proposed container)

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Inadequate	Quantities of each copolymer should be listed (b) (4) (b) (4)
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: *Adequate*

(b) (4)

(b) (4) This will be addressed during the labeling negotiation.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor: Mariappan V. Chelliah

Secondary Assessor: Julia Pinto

Mariappan Chelliah

Digitally signed by Mariappan Chelliah
Date: 3/04/2022 08:39:50AM
GUID: 5399cb2c00032b7c21877aa0d4d5f794

Julia Pinto

Digitally signed by Julia Pinto
Date: 3/04/2022 10:52:05AM
GUID: 5050dbcb00001294a888a4bdc20a3a58

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BIOPHARMACEUTICS

Product Background:

NDA: NDA-213586 – ORIG -1

Drug Product Name / Strength: Risperidone extended-release injectable suspension, 50,75,100,125,150,200,250 mg/prefilled syringe

Route of Administration: Subcutaneous injection

Applicant Name: Teva Neuroscience, Inc.

Review recommendation:

The Division of Biopharmaceutics recommends approval of this NDA at this time with a post marketing commitment (PMC 4237-2).

The following dissolution method and acceptance criteria are approved on an interim basis until the requirements on the PMC 4237-2 and further justification/documentation are received within 6-months (180 days) post-approval. Finalization of the dissolution method and acceptance criteria will be made upon review of these documents within one-year post approval.

Agency approved Interim Dissolution Method and Accpetance Criteria

USP Apparatus	Speed (rpm)	Medium/Temp	Vol (mL)	In vitro Drug Release	Release and Shelf-life Acceptance Criteria
2 With Vessel cover	75	Phosphate buffer pH 6.0 at 37+0.5°C	1000	After 2 h After 24 h After 216 h	Per USP <711>, Acceptance Table 2 (b) (4) Not less than (b) (4)%

Biopharmaceutics Comment:

The proposed IVR method shows discriminatory power to detect changes in different critical quality attributes among batches. However, the revised proposed dissolution acceptance range for 24 hours (b) (4) is permissive and needs further review based on your statistical/IVIVC analyses. An interim acceptance of the proposed method and acceptance criteria is issued with a post-marketing commitment (PMC 4237-2). In revising the acceptance criteria for the current

approval, Teva agreed on 3/15/2022 to comply with the format/principle in Acceptance Table 2 (USP <711>).

Post Marketing Commitment (PMC 4237-2)

We acknowledge that you submitted an IVIVC report. However, there are deficiencies in your IVIVC report. Therefore, your provided IVIVC report is not reviewed at this time because the report is not in the right format. We are approving your dissolution method and acceptance criteria on an interim basis. We will make final decision on the dissolution method and acceptance criterion once you submit document addressing the following deficiencies within 6-months (180 days) post-approval. Finalization of the dissolution method and acceptance criteria will be made upon review of these documents within one-year post approval. Consider this as a Post Marketing Commitment (PMC 4237-2).

(b) (4)

To aid in the regulatory decision making in terms of acceptability of the proposed IVIVC model, the applicant needs to submit the following information/data in a post-approval supplement (PAS):

- A modeling summary report, which provides an overview of the modeling strategy and details of the modeling procedures, including model development, model verification/modification, and model application in a step-by-step process. Inclusion of a flow chart, decision tree, or other similar representation is preferred for clarity.
- Generally, for the IVIVC development of immediate release drug products, at least 3 batches of the proposed drug product that differ in the in vivo PK and in vitro dissolution profiles should be used. As part of the validation steps, follow the “leave-one out” cross validation approach in the construction and validation of your model to challenge its robustness.
- Submit the executable project files (e.g., .phxproj, .xlsx or .xls, .sas) for the IVIVC model development and internal/external validation. Provide all relevant input including complete in vitro and in vivo data (i.e., individual, mean, % CV, profiles, in .csv, .xlsx or .xls, or .xpt format) and output files used in the construction and validation of the IVIVC model.

- Provide definition file(s) listing all input and output files, and the use or purpose of each of this files in an appropriate format (e.g., .pdf, .xpt, .xls). In addition, provide the hyperlinks for each data file and instructions for extracting these files.
- Provide the IVIVC predictions including the output files and summary table supporting your proposed dissolution acceptance criterion.

The applicant will provide an IVIVC development and validation report addressing the issues described above for the regulatory purpose of proving that the developed IVR method and acceptance criteria are clinically relevant within 180 days following approval of the proposed product. The Division of Biopharmaceutics, ONDP, OPQ may be contacted for further guidance. Note that FDA's final decision regarding the acceptability of the IVIVC model will be made based on the totality of the supportive data and relevant information provided in the submission, which should include demonstration of robust model predictability.

Applicant's Response to PMC 4237-2 :
On 3/15/2022 the Applicant indicated "Teva concurs with the Post-Marketing Commitment as proposed by the Agency."

Review Summary:
Teva submitted this original NDA under the 505(b)(2) NDA pathway relying on the Agency's previous findings of efficacy and safety on the listed drug (LD), RISPERDAL®, NDA 020272. Risperidone (TV-46000) is an extended-release injectable suspension for sub-cutaneous (sc) administration. TV-46000 contains risperidone and 2 biocompatible block copolymers that forms a depot under the skin to deliver risperidone over a periods of 1 month or 2 months. TEVA has developed 7 different strengths (50, 75, 100, 125, 150, 200 and 250 mg) of Risperidone Suspension for 1-month and 2-month dose regimen. All strengths have the same qualitative and quantitative composition, but differ in the suspension amount (i.e. fill weight) which is subcutaneously administered via prefilled syringe. In early development, Risperidone Suspension was in a vial and later into development in prefilled syringes (PFS).

TEVA requested a biowaiver for prefiled syrnges (PFS) 50, 75, 125, 150, 200, and 250 mg dose strengths based on formulation proportionality to the 100 mg PFS used in the clinical study. (b) (4)

USP apparatus II (paddle) was chosen for product release and QC for this NDA. The USP Apparatus II IVR method is discriminating and sensitive to changes in critical quality attributes. The proposed dissolution method and the acceptance criteria are shown below.

Applicant Proposed dissolution test method and acceptance criteria:

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criteria
2 With Vessel cover	75	Phosphate buffer pH 6.0 at 37±0.5°C	1000	2 h: NMT (b) (4)% 24 h: (b) (4) 216 h: NLT (b) (4)%

The following information request (IR) was sent to the applicant to get their response before finalizing this review:

You need to restate your proposed acceptance criteria (described below) as per the format/principle in Acceptnce Table 2 (USP <711>) on an interim basis and update your submission accordingly:

Applicant's Response to IR:
In response to requested information request (IR), the Applicant proposed a revised dissolution acceptance criteria for their product, shown below.

Reviewer's Assessment:

(b) (4)

(b) (4) however, the division of biopharmaceutics will accept this revised dissolution acceptance criteria as interim specification pending the review of the PMC.

(b) (4) the interim Agency Accepted dissolution acceptance criteria are shown as the "Newly Proposed" in the following Table:

Table: Revised Release and Shelf-life Acceptance Criteria for In vitro Drug Release

Previously Proposed		Newly Proposed	
In vitro Drug Release	**Release and Shelf-life Acceptance Criteria**	**In vitro Drug Release**	**Release and Shelf-life Acceptance Criteria**
(b) (4)		After 2 hours After 24 hours After 216 hours	Per USP <711>, Acceptance Table 2 (b) (4) Not less than (b) %

NMT Not more than; NLT Not less than

Module 2.3.P.5, Module 3.2.P.5.1, Module 3.2.P.5.4 and Module 3.2.P.5.6 are revised to reflect this change in acceptance criteria.

List of Submissions being reviewed:

ORIGINAL	06/17/2021
Response to Information Request	03/07/2022

Highlight Key Outstanding Issues from Last Cycle: **NA**

Concise Description Outstanding Issues Remaining: NA

BCS Designation : **NA**

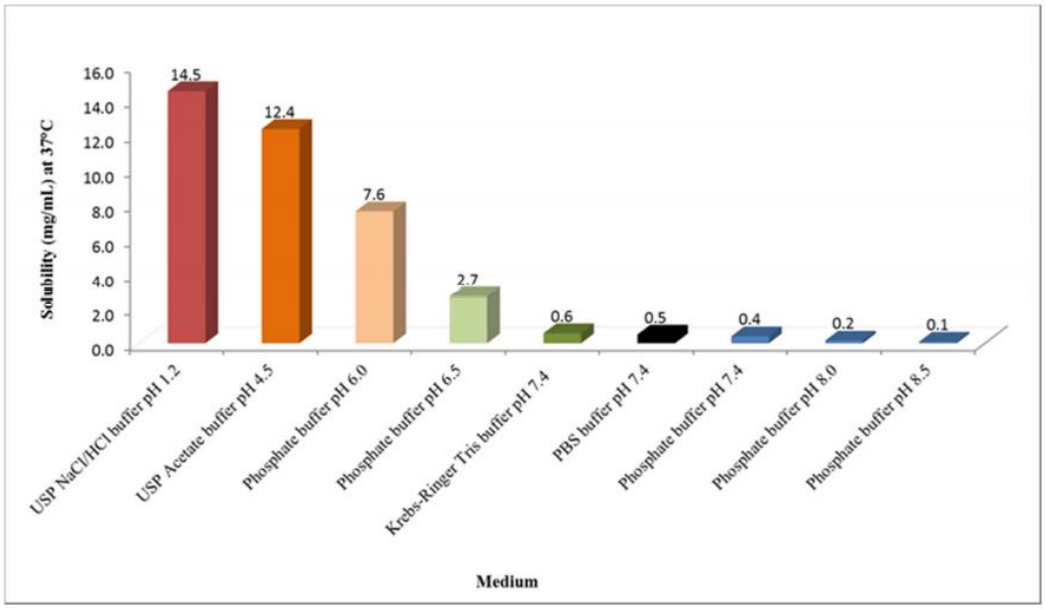
Solubility:

Risperidone drug substance shows pH dependent solubility profile that decreases with increasing pH of the medium shown below.

Table 2: Risperidone Drug Substance Solubility in Different pH Media at 37°C

Medium	Solubility
USP NaCl/HCl buffer pH 1.2	14.5 mg/mL
USP Acetate buffer pH 4.5	12.4 mg/mL
Phosphate buffer pH 6.0	7.6 mg/mL
Phosphate buffer pH 6.5	2.7 mg/mL
Krebs-Ringer Tris buffer pH 7.4	0.6 mg/mL
Phosphate-buffered saline (PBS) pH 7.4	0.5 mg/mL
Phosphate buffer pH 7.4	0.4 mg/mL
Phosphate buffer pH 8.0	0.2 mg/mL
Phosphate buffer pH 8.5	0.1 mg/mL

Figure 2: Risperidone Drug Substance Solubility in Different pH Media at 37°C



Permeability: No permeability data is provided

Mechanism of Drug Release From Depot: Risperidone Extended-Release Injectable Suspension (TV-46000), referred to as Risperidone Suspension, contains biodegradable polymeric mixture of triblock and diblock copolymers made of methoxy-poly (ethylene glycol) and poly (lactide) dissolved in the biocompatible, organic and water-soluble solvent dimethyl sulfoxide (DMSO) in which risperidone drug substance is suspended. Following subcutaneous administration of the Risperidone Suspension, DMSO diffuses out of the formulation while water penetrates. This

leads to phase inversion and precipitation of water insoluble polymers that form a depot and entrap the drug substance. Risperidone is then slowly released from this depot, providing sustained pharmacological action as a result of gradual diffusion of the drug and copolymer degradation. The copolymers degrade through hydrolytic scission of the ester bonds of the polylactide part of the chains and form products that are eliminated via renal excretion.

(b) (4)

(b) (4) At the beginning of the development, the sample was placed directly to the release medium using syringes of different needle size (21, 22 and 23G). Depot formed this way had (b) (4) shown below (b) (4)

Figure 2: Depots Formed by 21G (left), 22G (middle) and 23G (right) Needle Size

(b) (4)

(b) (4) the cap of gelatin capsule was used as a mold for sample placement. Suspension was weighted centrally into capsule cap placed on a metal carrier ensuring that no air bubbles was present and filled capsule cap was transferred into dissolution medium.

As medium diffuses through the capsule (b) (4) depot is formed while capsule cap quickly dissolves at 37°C shown below.

(b) (4)

To evaluate release mechanism of risperidone from the depot, in vitro study was performed and real-time in vitro release (IVR) method was used.

Overview of IVR Method Development

(b) (4)

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Discriminatory Power of the (b) (4) USP II Method

The discriminatory power of the (b) (4) USP II method was evaluated using samples with variations in: critical material attributes (b) (4)), critical formulation variables ((b) (4) and critical process parameters ((b) (4) (b) (4)). The following samples with the above mentioned variations were tested:

- Samples with a (b) (4) of the drug substance in comparison to target sample with no other changes in formulation or copolymers properties.
- Samples with differences in formulation variables ((b) (4) (b) (4)
- Samples simulating potential (b) (4) (b) (4) in comparison to the target sample.

IVR analyses were conducted on the lowest (50 mg) and highest (250 mg) strengths of the drug product. IVR results demonstrate that the newly-developed (b) (4) USP II IVR method is discriminative and sensitive to changes in critical quality attributes. This demonstrates that the newly-developed USP II method shows discriminatory power for both the lowest and the highest strength.

Considering all presented data obtained using the newly-developed (b) (4) USP II IVR method, additional IVR experiments were conducted to explore possibility of using the same sample size in QC IVR testing for all 7 proposed Risperidone Suspension strengths. The proposed sample preparation procedure for routine QC IVR analysis of all strengths would include weighing the same amount of suspension (167 mg) that corresponds to 50 mg of risperidone into gelatin capsule cap. To verify the proposed sample preparation procedure, following IVR analyses were conducted:

1) Five equal depots corresponding to 50 mg risperidone strength each, prepared from one 250 mg pre-filled syringe, analyzed in the same vessel so that total amount of risperidone in each vessel equals 250 mg

2) Five equal depots corresponding to 50 mg risperidone strength each, prepared from one 250 mg pre-filled syringe, tested in 5 separate vessels

The presented IVR results confirm that risperidone release rate is not limited by sink conditions and that sink conditions are ensured during the IVR analysis of the highest strength as well. Therefore, using the same sample weight of 167 mg for all strengths (which corresponds to the sample size of a full deliverable volume of the lowest - 50 mg strength) is considered justified as

(b) (4) for routine QC IVR testing of all strengths. (b) (4)

Using this newly-developed (b) (4) USP II IVR method and clinical PK data from the Phase 1 study (TV46000-SAD-10055), Level A IVIVC model has been developed and presented in the IVIVC report for validation. As per the applicant, the established Level A IVIVC demonstrates clinical relevance of the newly-developed (b) (4) IVR method and suitability of the developed IVR method for QC IVR testing. The applicant claims that the newly-developed (b) (4) IVR method using USP Apparatus II is discriminative for critical quality attributes for both the lowest (50 mg) and the highest (250 mg) strength and for all drug product strengths when using the same testing sample size.

Validation of QC method for IVR

The developed (b) (4) IVR USP Apparatus II method was found to be simple, robust and discriminative and therefore was selected as quality control (QC) method.

Parameters of the final (b) (4) in vitro release method are:

- Apparatus: USP Apparatus II (Paddle Apparatus) with (b) (4) vessel covers
- Medium: 0.1 M Phosphate buffer pH 6.0
- Volume: 1000 mL
- Rotation speed: 75 rpm
- Temperature: 37°C±0.5°C
- Sample preparation for all strengths: 167 mg of the suspension (corresponds to 50 mg of risperidone) is weighed into gelatin capsule cap (b) (4)

Released risperidone in IVR samples is quantified by reversed phase HPLC at (b) (4) nm wavelength.

Method Comparison – Between (b) (4) Sample And Separate And Newly-Developed (b) (4) USP II Method

The IVR method parameters of the (b) (4) sample and separate QC IVR method and the newly-developed QC IVR method (USP Apparatus II) are compared in Table 40.

Table 40: Comparison of IVR Method Parameters of Current and Newly-Developed QC IVR Method

IVR parameters	Current QC[a] IVR[b] Method- Sample and Separate Method	Newly-Developed QC IVR Method - USP[c] Apparatus II
Tested samples	(b) (4)	From 24 months time point stability of TV-46000 (suspension in PFS) used in Phase 3 study
Apparatus		USP Apparatus II
IVR medium	Phosphate buffer pH 6.0	
IVR medium volume	(b) (4)	1000 mL
Rotation speed		75 rpm

IVR parameters	Current QC[a] IVR[b] Method- Sample and Separate Method	Newly-Developed QC IVR Method - USP[c] Apparatus II
Temperature	37°C±0.5°C	
Sample preparation	Depot containing 167 mg of drug product, corresponding to 50 mg of risperidone, is prepared by use of gelatin capsule cap (b) (4)	
Sampling	Specification: 2 hours, 24 hours and 216 hours Note: additional time points were collected for sample characterization	
Quantification	Reversed phase HPLC with UV detection	

[a] QC - Quality Control, [b] IVR - In Vitro Release, [c] USP - United States Pharmacopeia

Method comparison analyses were performed on the following samples:

- Risperidone Extended-Release Injectable Suspension (TV-46000) in PFS, 50 mg, Batch No. GE8666
- Risperidone Extended-Release Injectable Suspension (TV-46000) in PFS, 250 mg, Batch No. GE8520
- Risperidone Extended Release Injectable Suspension (TV-46000) in vials, Batch No. GE7305

The summary reslts are as follows:

1. Similarity factor calculated for IVR profiles of Risperidone Extended-Release Injectable Suspension (TV-46000), 50 mg in PFS, Batch No. GE8666 obtained using USP II Method and Sample and Separate Method is 72, therefore the profiles obtained by two evaluated methods are considered to be similar.

2. Similarity factor calculated for IVR profiles of Risperidone Extended-Release Injectable Suspension (TV-46000), 250 mg in PFS, Batch No. GE8520 obtained using USP II Method and Sample and Separate Method is 56, therefore the profiles are considered similar.

3. Since the variability on six units is very low (≤ 6%) and similarity factor calculated for information purpose for IVR profiles of Risperidone Extended-Release Injectable Suspension (TV-46000), in vials, Batch No. GE7305 obtained using USP II Method and Sample and Separate Method is 82, profiles are considered to be similar.

Overall, the IVR results obtained using both (b) (4) methods (USP II vs. Sample and Separate) are similar which suggests that (b) (4) did not affect in vitro release profiles of risperidone from the depot. Similar IVR profiles indicate that both methods are also comparable in mechanism of in vitro release of the risperidone from the depot; therefore, same specification was set for both tests as follows.

SPECIFICATION PROPOSAL AND JUSTIFICATION

For setting the IVR Specification, statistical analysis of tolerance intervals at selected specification time points was done using SAS JMP® 13.2.1 software for obtained IVR data. Three time points were chosen since they adequately describe critical stages of the profile – 2 hours as it adresses (b) (4) risperidone; 24 hours time point as it (b) (4) (b) (4) and last time point at 216 hours as it is (b) (4).

A tolerance interval is an interval in which a given proportion p of the population falls, with a given confidence level 1− α. A one-sided tolerance interval which contains 99.9% of the population (p=0.999) with 99.9% confidence (α = 0.001) is constructed. The upper limit (for 2h time point) and the lower limit (for 216h time point) is computed as follows:

$$\bar{X} \pm \frac{t(1-\alpha, n-1, \Phi^{-1}(p)\cdot\sqrt{n})}{\sqrt{n}} \cdot s$$

Where:

- $\bar{X}$ is the mean IVR value
- $t()$ is the $1-\alpha$ quantile from the non-central t-distribution with $n-1$ degrees of freedom and non-centrality parameter $\Phi^{-1}(p)\cdot\sqrt{n}$
- $\Phi^{-1}(p)$ is the standard normal quantile
- s is the standard deviation of IVR values

Similarly, a two-sided tolerance interval which contains 99.9% of the population (p=0.999) with 99.9% confidence ($\alpha = 0.001$) was constructed (for 24h time point).

Results are presented in Figure 48 and in Table 49.

Figure 48: Statistical Analysis of Tolerance Intervals for in Vitro Release Test at 2h, 24h and 216h Time Points

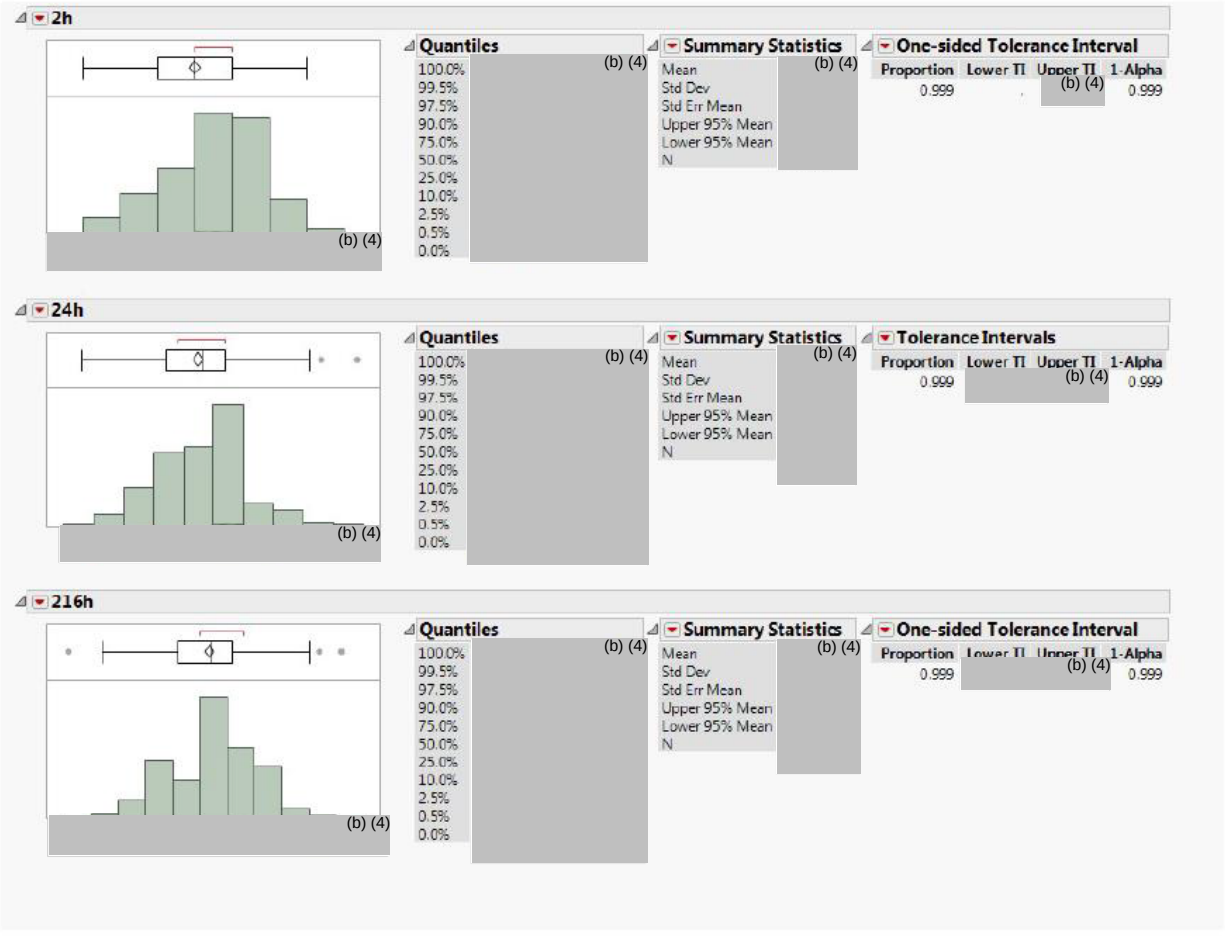

Table 49: Statistical Analysis of Tolerance Intervals for in Vitro Release Test at 2h, 24h and 216h Time Points

Time point	Proportion	Lower TI	Upper TI	1-Alpha
2 hours	0.999		(b) (4)	0.999
24 hours	0.999			0.999
216 hours	0.999			0.999

Statistical analysis showed with 99.9% confidence that:

- The upper one-sided tolerance interval for population of 99.9% at time point 2 hours is (b) (4) %
- The two-sided tolerance interval for population of 99.9% at time point 24 hours is ((b) (4) A range from (b) (4) based on the statistical analysis, is set to be a limit for 24 hours time point. (b) (4) % is chosen as the upper specification limit with the aim of covering the remaining 0.001% of the population, for which there is no statistical guarantee and may arise from specific IVR experimental particularities.
- The lower one-sided tolerance interval for population of 99.9% at time point 216 hours is (b) (4) %

Based on the statistical analysis performed using all IVR data obtained for all clinical and primary stability batches and having in mind specific particularites of IVR set up (manual preparation of the depot, extended drug release) and complex drug release mechanism, current drug product specification for in vitro release test with acceptance criteria described in Table 50 was set as release and shelf life control.

Table 50: In Vitro Release Test Release and Shelf-Life Specification

Attribute	Release and Shelf-Life Acceptance Criteria
In vitro Drug Release	
Stage 1 (6 units)	
After 2 hours	Average value not more than (b) (4) %
After 24 hours	Average value (b) (4)
After 216 hours	Average value not less than (b) (4) %
Stage 2 (12 units)	
After 2 hours	Average value not more than (b) (4) %
After 24 hours	Average value (b) (4)
After 216 hours	Average value not less than (b) (4) %

As it can be seen from the Table 50, testing times and acceptance criteria were set to address crucial stages of the risperidone IVR profile with adequate control strategy determined by statistical analysis. Testing at the 2 hours time point, with acceptance criteria of not more than (b) (4)% risperidone released, assures (b) (4). Middle point testing at 24 hours with the range of (b) (4) of the IVR profile.Testing point at 216 hours with requirement of not less than (b) (4)% covers the (b) (4) (b) (4)

Reviewer's Assessment: The Applicant provided a lot of information for IVR method development. The proposed method shows discriminatory power to detect among batches. However, the proposed dissolution acceptance criteria for 24 hours of (b) (4) is permissive and needs further review based on your statistical/IVIVC analysis. An interim acceptance with a post-marketing comminment (PMC) will be issued. However, the principle as per the following Table (USP Chapetr <711>) should be followed:

Acceptance Table 2

Level	Number Tested	Criteria
L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units (L_1 + L_2) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time.
L_3	12	The average value of the 24 units (L_1 + L_2 + L_3) lies within each of the stated ranges, and is not less than the stated amount at the final test time; not more than 2 of the 24 units are more than 10% of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10% of labeled content below the stated amount at the final test time; and none of the units is more than 20% of labeled content outside each of the stated ranges or more than 20% of labeled content below the stated amount at the final test time.

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: The Applicant provided an IVIVC report indicating that the proposed model is able to predict the in vivo performance of the PFS administered subcutainiously based on percent predictability. The IVIVC report, as it stands, appears incomplete.

Bridging of Formulations:

Investigational drug product for the Phase 1 study RISPE1ZG15EU was manufactured on a (b) (4) (b) (4)

(b) (4) Primary packaging changed from vial to a PFS during the clinical program. Comparison of TV-46000 dosing from vial and PFS is presented in Table below:

Table 1: Formulation composition of Risperidone Extended-Release Injectable Suspension (TV-46000) in Vials and PFS

(b) (4)

Table 2: Final Formulation Composition of Risperidone Extended-Release Injectable Suspension (TV-46000)

Ingredient	Quantity		Function
	%, w/w	mg/g	
Risperidone sterile	30.00	300.0	Drug substance
Triblock PDL-PEG-PDL copolymer [a]	10.00	100.0	(b) (4)
Diblock mPEG-PDL copolymer [b]	15.00	150.0	
Dimethyl sulfoxide (DMSO)	45.00	450.0	Solvent
(b) (4)			
Total	**100.00**	**1000.0**	Not applicable

[a] Poly(D,L-lactide)-*co*-poly(ethylene glycol)-*co*-poly(D,L-lactide).
[b] Methoxy-poly(ethylene glycol)-*co*-poly(D,L-lactide).

(b) (4)

Reviewer's Assessment: The commercial formulation is same as the formulation used in clinical studies vial or prefilled syringe (PFS). This establishes the bridging of formlation from clinical to commercial.

Biowaiver Request:

Teva has developed the injectable suspension in pre-filled syringe (PFS) to be used as the to-be-marketed product presentation of TV-46000, to replace the glass vial and plastic syringe (vial) presentation used throughout most of the TV-46000 clinical development program. The TV-46000 vial presentation has been used in Phase 1 studies (Study 10055, and Study 10148) and in the pivotal Phase 3 study (Study 30072). The TV-46000 PFS presentation has been used in the ongoing Phase 3, long-term safety study (Study 30078) and in Phase 1 study (Study 10148).

For both Prefilled Syringe and Vial Product presentations, the qualitative and quantitative formulation is unchanged, while the primary packaging differs. Teva performed a relative bioavailability (rBA) study (Study 10148) with TV-46000 100 mg dose of the proposed to-be-marketed drug-device combination product (in PFS presentation) to strengthen the comparability data package between the 2 product presentations and to bridge between TV-46000 (100 mg) and the reference listed drug (RLD) (US-approved RISPERDAL® 4 mg tablet, NDA 20272). The purpose of the biowaiver request, is to provide supporting justification for the comparability of the lower and higher drug product doses of the proposed to-be-marketed drug-device combination product (TV-46000 prefilled glass syringe, PFS, presentation) that were not evaluated in Study 10148.

Teva requests a biowaiver for the lower (50 and 75 mg) and higher (125, 150, 200, and 250 mg) dose strengths of TV-46000 for the PFS product presentation which were not evaluated in the relative BA study, based on the following factors:

Similarity of the Prefilled Syringe and Vial Product Presentations: For both presentations, the qualitative and quantitative formulation is unchanged, while the primary packaging differs. TV-46000 is filled into either (b) (4) (b) (4) (vial presentation) or into a single-use 1 mL long Luer lock clear glass syringe closed with a rubber tip cap and plunger stopper (PFS presentation).

Compositionally Proportional Dosage Strengths of TV-46000: TV-46000 was used in 7 different strengths: 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 200 mg, and 250 mg. The different product strengths have the same qualitative and quantitative composition, and they differ only in the amount of injected suspension. Therefore, all strengths of TV-46000 used in the vial and PFS product presentations are compositionally proportional.

The table below shows the composition proportionality of all presentations.

Composition

Table 1: Risperidone Extended-Release Injectable Suspension (TV-46000) in PFS - Composition

Ingredient	Quantity									Function	Quality Standard
	%, w/w	mg/g	mg/syringe, label claim								
			50 mg	75 mg	100 mg	125 mg	150 mg	200 mg	250 mg		
Risperidone Sterile	30.00	300.0	50.0	75.0	100.0	125.0	150.0	200.0	250.0	(b) (4)	USP
Triblock PDL-PEG-PDL Copolymer[a]	10.00	100.0	16.7	25.0	33.3	41.7	50.0	66.7	83.3		In-House
Diblock mPEG-PDL Copolymer[b]	15.00	150.0	25.0	37.5	50.0	62.5	75.0	100.0	125.0		In-House
Dimethyl Sulfoxide	45.00	450.0	75.0	112.5	150.0	187.5	225.0	300.0	375.0	Solvent	USP
(b) (4)											
Total:	**100.00**	**1000.0**	**166.7**	**250.0**	**333.3**	**416.7**	**500.0**	**666.7**	**833.3**		

[a] Poly(D,L-lactide)-*co*-poly(ethylene glycol)-*co*-poly(D,L-lactide)
[b] Methoxy-poly(ethylene glycol)-*co*-poly(D,L-lactide)
(b) (4)

Dose Proportionality of TV-46000: Overall, the PopPK analysis indicated that 50, 75, 100, and 125 mg of TV-46000 administered q1m and 100, 150, 200, and 250 mg of TV-46000 administered q2m resulted in a proportional increase in the steady-state exposure levels, including Ctrough,ss, AUC,ss, and Cmax of TAM (Total active moiety the sum of the plasma concentrations of risperidone and 9-hydroxyrisperidone [9-OH-risperidone]), (Module 2.7.2, Section 3.6).

In-Vitro In-Vivo Correlation (IVIVC) Analysis: Comparability between the two product presentations was also established in vitro. The drug product batches of TV-46000 used in study TV46000-BA-10148 (delivered in vials or PFS) were compared according to the release specification and acceptance criteria, and results showed that physicochemical attributes were comparable between the tested batches (Module 2.7.1, Section 2.3.2). The in vitro drug release of the 2 drug product batches of TV 46000 in vials and PFS was analyzed using the newly-developed USP II IVR method. The USP II IVR method was claimed to be clinically relevant by establishing Level A IVIVC using the PK data of five dosage strengths of TV-46000 (50, 75, 100, 150, and (b) (4) mg). The population PK (PopPK) analysis of in-vivo risperidone data obtained following administration of the same dosage strengths of TV-46000 evaluated in Study TV46000-SAD-10055 in vials. The Level A IVIVC model allows to predict accurately and precisely the expected bioavailability characteristics from the dissolution profile characteristics.

The in-vitro component of the IVIVC model is presentation-agnostic, as the tested doses were pre-weighted before testing and vials and syringes or PFS are not used in this method. Therefore, based on the in-vivo bridge established between vials and PFS in study TV46000-BA-10148, and since the TV-46000 formulation contained in vials and PFS is identical, it is the Sponsor's position that the established model can be adequately applied to predict in-vivo performance of TV-46000 in PFS, and that model application would result in similar in-vivo performance of TV-46000 contained in vials or PFS.

The secondary endpoint of Study 10148 was to establish a PK bridge between TV-46000 and RLD (Risperdal®, oral risperidone). To compare TV-46000 versus oral risperidone, $AUC_{0-\infty}$ of TAM was used as a variable for TV-46000 PFS and vials and TAM calculated area under the

plasma concentration-time curve over the 28-day dosing interval ($AUC_{0–28d}$ calculated) for oral risperidone, both of which reflect the steady-state AUC over the 1-month dosing interval. The study results supported the PK bridge, demonstrating a similar exposure range between the two products. TAM exposure range of individual patients following 100 mg TV-46000 administered from the PFS and vial combined, and PFS and vial presentations, was within the range of exposure of individual patients following oral risperidone administration of 4 mg/day over 28 days.

Dose proportionality of oral risperidone has been previously established in the dose range of 1-16 mg/day (RISPERDAL® US Prescribing Information 2021). Given the dose proportionality demonstrated for TV-46000 at all dose strengths (see Sections 1.2.2 to 1.2.4 above), the PK bridge established between TV-46000 100 mg and oral Risperidone 4 mg can be extrapolated to the entire proposed dose range of TV-46000 (50-250 mg), which corresponds to an oral risperidone dose range of 2-5 mg/day.

In conclusion, on the basis of compositional proportionality of TV-46000 across all strengths, linear pharmacokinetics across the proposed dose range and comparability of the PK profile as well as the qualitative and quantitative formulation similarity between the PFS and vial product presentations in the100 mg mid-range strength, the sponsor concludes that the in vivo performance of the to-be-marketed PFS product presentation would be similar to that of the vial product presentation across all doses and dose regimens of TV-46000.

Therefore, the sponsor requests a waiver from in vivo bioavailability studies for the remaining 50, 75, 125, 150, 200, and 250 mg strengths of TV-46000 in the to-be-marketed PFS product presentation. Additionally, it is the sponsor's position that the PK bridge established between TV-46000 and the RLD at 100 mg and 4 mg doses, respectively, can be extrapolated to the entire TV-46000 dose range.

Reviewer's Assessment:

The provided information is adequate; a biowaiver for 50, 75, 125, 150, 200 and 250 mg dose strengths is granted.

IVIVC

(b) (4)

(b) (4)

However, to aid in the regulatory decision making in terms of the acceptability of the proposed IVIVC model, please submit the following information/data:

- A modeling summary report, which provides an overview of the modeling strategy and details of the modeling procedures, including model development, model verification/modification, and model application in a step-by-step process. Inclusion of a flow chart, decision tree, or other similar representation is preferred for clarity.
- Generally, for the IVIVC development of immediate release drug products, at least 3 batches of the proposed drug product that differ in the in vivo PK and in vitro dissolution profiles should be used. As part of the validation steps, follow the "leave-one out" cross validation approach in the construction and validation of your model to challenge its robustness.
- Submit the executable project files (e.g., .phxproj, .xlsx or .xls, .sas) for the IVIVC model development and internal/external validation. Provide all relevant input including complete in vitro and in vivo data (i.e., individual, mean, % CV, profiles, in .csv, .xlsx or .xls, or .xpt format) and output files used in the construction and validation of the IVIVC model.
- Provide definition file(s) listing all input and output files, and the use or purpose of each of this files in an appropriate format (e.g., .pdf, .xpt, .xls). In addition, provide the hyperlinks for each data file and instructions for extracting these files.
- Provide the IVIVC predictions including the output files and summary table supporting your proposed dissolution acceptance criterion.
- A PMC agreement ***(PMC 4237-2)*** to address the issues above was obtained from the applicant on 3/15/2022. The applicant agreed to provide an IVIVC development and validation report addressing the issues described above for the regulatory purpose of proving that the developed IVR method and acceptance criteria are clinically relevant within 180 days following approval of the proposed product. The Division of Biopharmaceutics, ONDP, OPQ may be contacted for further guidance. Note that FDA's final decision regarding the acceptability of the IVIVC model will be made based on the totality of the supportive data and relevant information provided in the submission, which should include demonstration of robust model predictability.

Links to documents

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R Regional Information

Comparability Protocols

Reviewer's Assessment: **NA**

Post-Approval Commitments

Reviewer's Assessment: **NA**

Lifecycle Management Considerations

List of Deficiencies:

Primary Biopharmaceutics Reviewer Name and Date:

Assadollah Noory, Ph. D.

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

Tapash Ghosh, Ph. D.

Assadollah Noory

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Tapash Ghosh

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CHAPTER VII: MICROBIOLOGY

Product Information	Indicated for treatment of schizophrenia
NDA Number	213586
Assessment Cycle Number	1
Drug Product Name/ Strength	Risperidone extended-release injectable suspension/ 50, 75, 100, 125, 150, 200, 250 mg/ PFS
Route of Administration	Subcutaneous
Applicant Name	Teva Neuroscience, Inc.
Therapeutic Classification/ OND Division	OND/ON/DP
Manufacturing Site	Teva Pharmaceutical Industries Ltd. 8, Eli Hurvitz street, Industrial zone 4410202 Kfar Saba, Israel FEI # 3002721084
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:
Risperidone extended-release injectable suspension (50, 75, 100, 125, 150, 200, 250 mg/ PFS) involves (b) (4)

(b) (4)

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0001 (1)	**06/17/2021**
0017 (17)	**12/18/2021**

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: This is an eCTD submission.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): None

Supporting Documents:

D3543M01R01.docx dated 02/01/2022 (adequate)	Manufacturing process for Risperidone (Sterile) drug substance

(b) (4)

S DRUG SUBSTANCE

The drug substance is received sterile from the API manufacturer. A Letter of authorization dated 02/25/2021 from Teva Api was provided authorizing access to Type II DMF 035434 for information pertaining to drug substance (Risperidone sterile) manufacturing process and process controls, control of materials, critical steps and intermediates, process validation and evaluation, and manufacturing process development.

Note to reviewer: DMF 35434 was reviewed and deemed adequate in microbiology review D3543M01R01.docx dated 02/01/2022.

Assessment: *{Adequate}*
DMF 35434 is adequate.

S.2. MANUFACTURE

S.2.1 MANUFACTURERS

API (Risperidone- (b) (4) manufacturing and testing:
(b) (4)

API (Risperidone- (b) (4)) manufacturing and testing:
(b) (4)

Drug substance stability testing:
Teva API India Ltd. (gajraula site)
Plot Nos. A-2, A-2/1, A-2/2, UPSIDC Industrial Area,
Bijnor Road, Distt. Amroha, Gajraula, Uttar Pradesh, India 244235

Assessment: *{Adequate}*

P DRUG PRODUCT

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product- Risperidone Extended-Release Injectable Suspension in single-use pre-filled syringe (PFS) is a sterile, white to off white opaque suspension for subcutaneous administration.

Drug product composition- Risperidone Extended-Release Injectable Suspension, 50, 75, 100, 125, 150, 200, 250 mg/ PFS:

Ingredients	Grade	Function	Quantity							
			% w/w	mg/g	mg/syringe					
					50 mg	75 mg	100 mg	125 mg	150 mg	200 mg	250 mg
Risperidone sterile	USP	Drug substance	30.0	300.0	50.0	75.0	100.0	125.0	150.0	200.0	250.0
Triblock PDL-PEG-PDL Copolymer[a]	In-house	(b) (4)	10.0	100.0	16.7	25.0	33.3	41.7	50.0	66.7	83.3
Diblock mPEG-PDL Copolymer[b]			15.0	150.0	25.0	37.5	50.0	62.5	75.0	100.0	125.0
Dimethyl Sulfoxide	USP	Solvent	45.0	450.0	75.0	112.5	150.0	187.5	225.0	300.0	375.0
(b) (4)											
Total			100.0	1000.0	166.7	250.0	333.3	416.7	500.0	666.7	833.3

[a] Poly(D,L-lactide)-*co*-poly(ethylene glycol)-*co*-poly(D,L-lactide)

[b] Methoxy-poly(ethylene glycol)-*co*-poly(D,L-lactide)

(b) (4)

Description of container closure system

(3.2.P.7 container-closure-system.pdf)

Primary container closure system components:

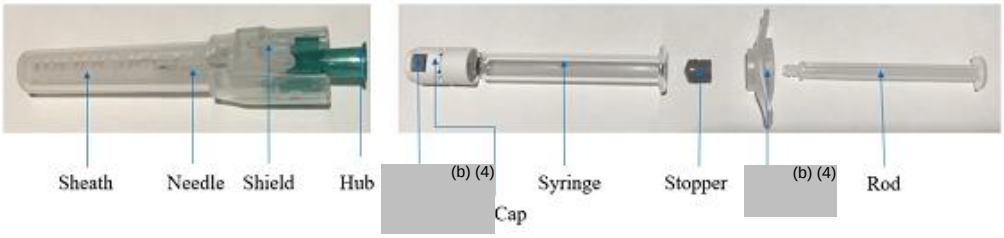
Component	Description	Manufacturer	DMF
1 mL long Luer Lock (b) (4) (b) (4) Syringe barrel and tip closure	(b) (4)		
Plunger stopper			

Secondary components:

Component	Description	Manufacturer
Plunger rod	(b) (4)	

The pre-filled syringe (assembled with rod, (b) (4) syringe label and syringe tag) and a sterile pouched 21G x 5/8’ length safety needle is placed in the tray. The tray and prescribing information leaflet are placed in the carton.

A photographic illustration of the single-use syringe is included below for review convenience.



Primary and secondary container closure components of single-use syringe and safety needle (picture taken directly from the submission)

Exhibit Batch size:

Batch No.	Composition	Batch size
GE8666	50 mg/PFS	(b) (4) kg
GE8671		
GE8838		
GE8683	75 mg/PFS	
GE8519	100 mg/PFS	
GE8839		
GE8668	125 mg/PFS	
GE8669	150 mg/PFS	
GE8670	200 mg/PFS	(b) (4) kg
GE8520	250 mg/PFS	
GE8521		
GE8522		

Proposed Commercial Batch Size:

- (b) (4) kg (50 mg, 75 mg, 100 mg, 125 mg, and 150 mg/ PFS)
- (b) (4) kg (200 mg, and 250 mg/ PFS)

Assessment: *{Adequate}*
The applicant provided an adequate description of the drug product composition and the primary container closure system designed to maintain product sterility.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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Hemlata Tamta

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Denise Miller

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Date: 2/11/2022 11:36:06AM
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Valerie Amspacher

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Date: 3/17/2022 09:36:59AM
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/s/

VALERIE R AMSPACHER
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