

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207946Orig1s000**

**MICROBIOLOGY / VIROLOGY REVIEW(S)**

# Product Quality Microbiology Review

APRIL 24, 2015

**NDA:** 207946

**Drug Product Name**

**Proprietary:** INVEGA TRINZA

**Non-proprietary:** paliperidone palmitate injection

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

<b>Submit</b>	<b>Received</b>	<b>Review Request</b>	<b>Assigned to Reviewer</b>
November 18, 2014	November 18, 2014	November 18, 2014	December 22, 1014

**Submission History (for 2<sup>nd</sup> Reviews or higher) – N/A**

**Applicant/Sponsor**

**Name:** Janssen Pharmaceuticals, Inc.

**Address:** 1125 Trenton-Harbourton Rd., Titusville, NJ  
08560

**Representative:** Beth Geter-Douglass, Ph.D., Assoc. Director  
Global Regulatory Affairs  
TEL: 609-730-4409

**Name of Reviewer:** Vinayak B. Pawar, Ph.D.

**Conclusion:** Recommend Approval

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## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original NDA
  2. **SUBMISSION PROVIDES FOR:** Paliperidone palmitate, extended-release injectable suspension.
  3. **MANUFACTURING SITE:** Janssen Pharmaceutica NV  
FDA Site Registration: 3002807336  
Turnhoutseweg 30, B-2340 Beerse  
Belgium
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 273 mg, 410mg, 546mg, 819mg/mL extended release suspension for intramuscular Injection.
  5. **METHOD(S) OF STERILIZATION:** (b) (4)
  6. **PHARMACOLOGICAL CATEGORY:** Treatment of Schizophrenia.
- B. **SUPPORTING/RELATED DOCUMENTS:** DMF 20902 (sterile drug substance), DMF (b) (4) and DMF (b) (4)
- C. **REMARKS:** Janssen Pharmaceuticals, Inc. has submitted an original New Drug Application (NDA 207946) for paliperidone palmitate, extended-release injectable suspension for the treatment of schizophrenia in adult patients. This is an electronic submission.

**filename:** N207946R1

**Executive Summary**

**I. Recommendations**

- A. **Recommendation on Approvability** – Recommend Approval.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

**II. Summary of Microbiology Assessments**

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The drug product is manufactured by (b) (4). To assure sterility of the drug product, a series of successful validation tests were performed.
- B. **Brief Description of Microbiology Deficiencies** – None.
- C. **Contains Potential Precedent Decision(s)** -  Yes  No

**III. Product Quality Microbiology Risk Assessment**

**A. Initial Product Quality Microbiology Risk Assessment**

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O <sup>(3, 4, 5)</sup>	Severity of Effect (S)	Detect. (D)	Risk Priority Number <sup>6</sup> (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	(b) (4)	9		5	5	225	(b) (4)
Endo		4		4	4	64	(b) (4)

6 = RPN = O (after modification when applicable) × S × D

RPN < 50 = Low Risk; RPN 50-120 = Moderate Risk; RPN > 120 = High Risk

- B. Final Risk Assessment** – The safety risk associated with the microbiology deficiencies is considered High.

**III. Administrative**

- A. Reviewer's Signature** See electronic signature on the last page  
Vinayak B. Pawar, Ph.D., Sr. Review Microbiologist,  
CDER/OPQ/OPF/DMA
- B. Endorsement Block** See electronic signature on the last page  
Stephen E. Langille, Ph.D., Acting Chief, Branch III/OPQ/DMA
- C. CC Block**  
N/A

**Product Quality Microbiology Assessment**

**1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q), MODULE 3.2: BODY OF DATA**

**S DRUG SUBSTANCE -**

**S.2 Manufacture**

**S.2.1 Manufacturers -** Janssen Pharmaceutical, Cork, Ireland

**S.2.2 Description of the Manufacturing Process and Process Controls**

The manufacturing process for the drug substance was found adequate per OPS Microbiology Review of DMF 20902 dated July 2013 (a letter of authorization dated October 16, 2014 was provided in Section 1.4.2) and there are no major changes in the manufacturing process since approval, except for the reduction in (b)(4)

(b)(4) location was found acceptable in a recent OPQ Microbiology Review of this DMF 20902 on March 23, 2015.

**S.2.5 Process Validation and/or Evaluation**

**Sterilization Validation –** Adequate per DMF 20902 review, July 2013

**S.4 Control of Drug Substance –** No change since DMF approval, July 2013.

**S.4.1 Specification:** No change since DMF approval, July 2013.

**S.4.2 Analytical Procedures –** No change since DMF approval, July 2013.

**S.6 Container Closure System –** No change since DMF approval, July 2013.

**S.7 Stability –** No change since DMF approval, July 2013.

**P DRUG PRODUCT**

**P.1 Description of the Composition of the Drug Product**

- Description of drug product – Paliperidone palmitate (R092670) eq. to (b)(4) paliperidone extended release suspension for injection (F015) is intended for intramuscular (IM) injection, and is also referred to throughout this dossier as the 3-month formulation (F015).
- Drug product composition – The composition of paliperidone palmitate eq (b)(4) extended release suspension for injection is provided in Table 1 (copied from Table 1, Section 3.2.P.1).

**Table 1. Composition of Paliperidone palmitate eq. (b)(4) Extended Release Suspension for Injection.**

Component	Reference to Quality Standard	Function	Concentration (mg/mL)
Paliperidone palmitate (R092670) (b)(4)	Company Specifications <sup>a</sup>	Active drug substance	(b)(4)
Polysorbate 20	NF	(b)(4)	10
Polyethylene glycol 4000	NF	(b)(4)	75
Citric acid monohydrate	USP	(b)(4)	7.5
Sodium dihydrogen phosphate monohydrate	USP	(b)(4)	(b)(4)
Sodium hydroxide	NF	(b)(4)	(b)(4)
Water for Injection	USP	(b)(4)	(b)(4)

<sup>a</sup> (b)(4) paliperidone active moiety

<sup>b</sup> Reference is made to Module 1 where the letter authorizing the FDA to access the DMF (b)(4) is included.

Table 2 (copied from Table 2, Section 3.2.P.1) presents the different dosage strengths, including the syringe size, the nominal fill volume, the overfill volume, and the effective fill volume.

**Table 2. Different Dosage Strengths with their Syringe Size and Fill Volumes**

Dose as paliperidone palmitate (mg)	Dose equivalent as paliperidone (mg)	Syringe Size	Nominal Fill Volume (mL)	Overfill (mL)	Effective Fill Volume (mL)
273	175	1 mL Long	0.875		(b) (4)
410	263	2.25 mL	1.315		
546	350	2.25 mL	1.750		
819	525	2.8 mL	2.625		

- Description of container closure system – The syringe components are described in Table 3 (copied from Table 3, Section 3.2.P.1).

**Table 3. Syringe Components**

Component	Description
Syringe Barrel	Transparent Cyclic Olefin Copolymer (COC) with integrated luer lock Sizes: <ul style="list-style-type: none"> <li>• 1 mL Long</li> <li>• 2.25 mL</li> <li>• 2.8 mL</li> </ul>
Tip Cap	Bromobutyl rubber, dark gray
Plunger Stopper	(b) (4) bromobutyl rubber (b) (4), dark gray Sizes: <ul style="list-style-type: none"> <li>• 1 mL Long used for 1-mL Long syringe</li> <li>• 1-3 mL used for 2.25-mL and 2.8-mL syringe</li> </ul>

The 2.25-mL and 2.8-mL syringes are different only in syringe barrel length. They have the same inner syringe diameter and the same plunger stopper (1-3mL is used). Therefore, the largest syringes (2.25-mL and 2.8-mL) were considered worst case considering the largest internal neck opening.

**P.2 Pharmaceutical Development**

**P.2.5 Microbiological Attributes**

- Container-Closure and Package integrity – The integrity of the container closure system has been demonstrated through a (b) (4) study. This (b) (4) study covered the full range of internal diameters of the syringes used for the paliperidone palmitate 3-month formulation as summarized in Table 4 (copied from Table 10, Section 3.2.P.2.4.2.3).

**Table 4. Syringes- Internal Diameter**

Internal Diameter	F013 syringes	F015 syringes
6.4-6.5 mm	0.5-mL syringe	1-mL Long syringe
8.6-8.8 mm	2.25-mL syringe	2.25-mL syringe and 2.8-mL syringe

The marketed product stability program will be conducted to confirm the continued compliance of routine production batches with the applicable specifications over the shelf life period.

Specifications and testing schedule for post-approval stability program.

- Container Closure Integrity – At initial, 12, 24 and 36 months.
- Endotoxin – At initial, 12 and 24 month
- Microbial Limits – N/A

**P.8.3 Stability Data** –See Review Section P.8.1.

**ADEQUATE**

**REVIEWER COMMENT** – The applicant meets the regulatory expectations with regard to the design of the stability program to support the drug product’s microbiological quality throughout its shelf life

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

**A. PACKAGE INSERT**

INVEGA TRINZA is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in dose strengths of 273 mg, 410 mg, 546 mg, and 819 mg paliperidone palmitate. The drug product hydrolyzes to the active moiety, paliperidone, resulting in dose strengths of 175 mg, 263 mg, 350 mg, and 525 mg of paliperidone, respectively. Final package insert language will be finalized with other review disciplines during labeling meetings.

**ADEQUATE**

**REVIEWER COMMENT** – None

**3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS: None.**

Digitally signed by Vinayak B. Pawar -A  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,  
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Date: 2015.05.07 11:35:50 -04'00'

Stephen E. Langille -A

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