

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207946Orig1s000

CHEMISTRY REVIEW(S)

NDA 207946

INVEGA TRINZA

Paliperidone palmitate extended release injectable suspension

Review #2

Updates from Review #1: Inclusion of Microbiology review (p.12), updated Facility review (p.9) and Executive Summary (p.4) and final recommendation (approval).

7 MAY 2015

Office of Pharmaceutical Quality Recommendation: [Approval](#)

Drug Name/Dosage Form	Paliperidone palmitate extended release injectable suspension
Strength	273 mg, 410mg, 546mg, 819mg
Route of Administration	Intramuscular Injection
Rx/OTC Dispensed	Rx
Applicant	Janssen
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original submission (# 0000)	1-Oct-14
Amendment # 0006 (DMEPA on container enclosure system)	27-Jan-15
Amendment # 0007 (CDRH on biocompatibility discussion, test report and risk assessment)	2-Feb-15
Amendment # 0008 (Response to 15 seconds shaking)	6-Feb-15

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Monica Cooper	
Drug Substance	Kasturi Srinivasachar (Secondary Reviewer)	
Drug Product	Wendy Wilson (Secondary Reviewer)	
Drug Product	Thomas Wong	
Drug Process	Sung Kim	
Drug Process	Lane Christensen (Secondary Reviewer)	
Microbiology	Vinayak Pawar	
Microbiology	Stephen Langille (Secondary Reviewer)	
Facility	Juandria Williams	
Facility	Grace McNally (Secondary Reviewer)	
Biopharmaceutics	Angelica Dorantes (Secondary Reviewer)	
Biopharmaceutics	Salaheldin Hamed	
Project/Business Process Manager	Dahlia Woody	
Application Technical Lead	David Claffey	
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Assessment (EA)	N/A	

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
20902	Type II	Janssen Pharmaceutica, N.V.	Paliperidone Palmitate drug substance	Adequate with IR	10-Mar-2015	By M. Cooper
18915	Type II	Janssen Pharmaceutica, N.V.	Paliperidone	Adequate	18-Feb-2015	By M. Cooper
(b) (4)	Type III	(b) (4)	(b) (4)	Adequate	20-Jul-2009	By D. Claffey
	Type II			Adequate	3-Jun-2008	By J. Metcalfe
	Type III			Adequate	25-Jun-2008	By Y. Sun
	Other					

¹ Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Referenced NDA	NDA 22264	Equivalent one-month product
	IND 76952	Supporting IND

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

Executive Summary

I. Recommendations

Recommend Approval.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues

N/A

2. Action letter language, related to critical issues such as expiration date

The proposed 24-month drug product expiry period with room temperature storage is acceptable.

3. Benefit/Risk Considerations

The most obvious risk associated with the proposed product is faster than expected in vivo release or dose-dumping of the three-month supply of drug. This potential risk is raised for this dosage form as it does not have a physical dissolution-rate controlling barrier like other extended release products (e.g. membrane, coating). Rather, it depends entirely on the intrinsic aqueous insolubility of the drug substance. The dissolution rate directly correlates with the (b) (4)

The in vivo performance of the product is assured through the drug substance and drug product manufacturing control strategy, (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Quality Assessments

Product Background: The proposed drug product is the third of a series of paliperidone products. Currently paliperidone is marketed as daily extended release tablets and as a monthly intramuscular extended release injectable suspension. This product was designed to extend drug release still further – so that it requires dosing every three months. As with the monthly product, the extended release characteristics for this product are achieved by use of a water-insoluble palmitate ester analogue of paliperidone. Product and manufacturing development of this product are based on the one-month product, with three main differences:

1. The dose is 3.5 times larger than the equivalent one-month product to achieve similar plasma profiles

2. (b) (4)

3. (b) (4)

Drug Product Description: The drug product was developed in four dosage strengths – 273, 410, 546 and 819 mg of paliperidone palmitate. The strengths are based on the quantity of paliperidone palmitate - the equivalent doses of the “active” paliperidone are listed below. Each strength is derived (b) (4)

Three different syringes sizes used to contain the four dosage strengths and each strength includes an overfill to ensure delivery of the complete labeled dose (table below).

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		

The following table lists the composition of the drug product suspension and their functions:

Component	Reference to Quality Standard	Function	Concentration (mg/mL)
Paliperidone palmitate (R092670) (b) (4)	Company Specifications ^b	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)

^b Reference is made to Module 1 where the letter authorizing the FDA to access the DMF (20902) is included.

Only paliperidone palmitate (b) (4). This product (b) (4) composition as the one-month product – just the quantities and concentrations of the components differ. The proposed commercial batch formula is identical to that used for the manufacture of the registration and clinical trial batches. The level of each excipient is within that found in other marketed products – with the exception of polyethylene glycol 4000. Its level was referred to the pharm/tox reviewer to ensure its acceptability.

Drug Substance: Paliperidone palmitate (R092670) drug substance is a “white to almost white” (b) (4) racemic mixture with a melting range of 114 -120 °C. (b) (4)

Studies demonstrated that the particle size distribution (PSD) of the incoming drug substance did not impact the PSD or the performance of the drug product. The drug substance specification also includes five specified impurities related to drug substance (b) (4)

Other drug substance tests critical to patient safety include the sterility and endotoxin tests. They were found adequate.

The majority of the drug substance information was referenced to DMFs 20902 and 18915. Both were found adequate to support this application. (b) (4) drug substance is synthesized at the Janssen, Cork, Ireland site. Both the Cork site and the Janssen, Beerse, Belgium site manufacture the final sterile-grade drug substance. Stability testing is carried out at the Beerse site and at J&J, Mumbai, India. These sites were found acceptable from a GMP perspective.

For the purposes of this application the drug substance is defined as being 'sterile grade' paliperidone. The drug substance specification included in the application was found to be acceptable in the evaluation of DMF 20902. A representative CoA from the Cork site found that it met specification with total impurities (b) (4) % and residual solvents well within their specified limit (both were (b) (4) ppm).

Drug Product Development: The drug product development built upon prior knowledge gained from the marketed one-month dosage form. Development centered on (b) (4)

(b) (4)

(b) (4)

Drug Product Manufacturing: The drug product is manufactured at Janssen Pharmaceutica NV, Beerse, Belgium. This site was found acceptable from a GMP perspective.

The manufacturing of the proposed product is similar to that of marketed one-month product. The process consists of (b) (4)

(b) (4)

(b) (4)

Data on all the batches manufactured to-date met specification. In addition, critical control points (CCP), CPPs and IPCs were identified as a control strategy at critical manufacturing steps to ensure sterility of the final drug product. Validation results of the three validation bulk batches demonstrated that the manufacturing process using the identified CCPs, CPPs and IPCs produced consistent quality of the drug product at the commercial manufacturing scale and all validation results met the pre-determined validation acceptable criteria.

This application was found acceptable from a microbiology perspective (review is included in this document).

Drug Product Specification: Drug product specification includes tests typical for a parental product. Release and stability test results were consistent and acceptable.

The particle size specification is discussed above. Other more immediately clinically-relevant tests specific for this dosage form include qualitative tests for resuspendability and injectability. These tests are critical as blocked syringes can result in incomplete injections and possibly months of suboptimal dosing for the patient. Considering that the proposed suspension is twice as concentrated as the marketed one-month product, data were requested to demonstrate that the labeled 15 seconds of shaking was sufficient to resuspend the product. These data also indicated adequate syringeability even after five seconds of “vigorous” shaking – which is critical as it may not be uncommon for the HCP to not shake for the entire 15 seconds. Data also supported the labeled five minute

in-use period after shaking – and also demonstrated adequate product performance after 90 minutes storage. No degradants specific to the drug product were detected.

The in vitro release method for the one-month product was selected for the proposed product due to the similarities of the formulations. The test and acceptance criteria were found adequate for assuring consistent bioavailability of the drug product. The applicant demonstrated that the dissolution method was able to detect fine changes in drug substance PSD (b) (4) that are within the proposed range.

Drug Product Stability: Stability data supported the quality and function of the product through the proposed 24 month expiry period when stored at room temperature. A slight weight loss ((b) (4) %) for all samples was observed at 6 and 12 month test time points – likely due to the known semi-permeable nature of the syringe system. However, this is not likely to impact product performance as the entire content of the syringe is administered. (b) (4)

A categorical exclusion from an environmental assessment was claimed under 21 CFR 25.31(b) (EIC = (b) (4) ppb). This is acceptable.

A. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Invega Trinza
Non Proprietary Name of the Drug Product	Paliperidone palmitate extended release injectable suspension
Non Proprietary Name of the Drug Substance	
Proposed Indication(s) including Intended Patient Population	Schizophrenia
Duration of Treatment	chronic
Maximum Dose	819 mg every three months
Alternative Methods of Administration	N/A

B. Novel Approaches N/A

C. Any Special Product Quality Labeling Recommendations? None

D. Process/Facility Quality Summary (see Attachment A)

E. Life Cycle Knowledge Information (see Attachment B)

Primary Quality Review

UPDATED ASSESSMENT OF FACILITIES

Drug Substance Manufacturing Facilities

The current NDA cross-references DMFs 18915 (b)(4) and 20902 (R092670 – paliperidone palmitate sterile grade drug substance). The DMFs supported the approved NDAs 21999 and 22264, applications which referenced INVEGA (extended-release tablet) and INVEGA SUSTENNA (1-month formulation of extended-release suspension for injection), respectively. As such, the drug substance manufacturers referenced in these applications are the same as those referenced in the current NDA.

Janssen Pharmaceutical, Cork, Ireland (FEI 3002807361)

The firm proposes to manufacture the (b)(4) (described in DMF 18915 which also supported approved NDAs 21999 and 22264) and the final R092670 sterile grade drug substance paliperidone palmitate (described in DMF 20902 which also supported NDA 22264). The most recent inspection ending 3/21/2014, which covered API manufacturing under 56002F, was classified NAI. A review of previous inspections indicate they have minimal GMP issues. A review of the facility's production load indicates it has steadily increased over the last few years as a drug substance manufacturer and tester. Given the firm's previous history and experience with a similar product, there is reasonable assurance the firm is capable of performing the proposed function. The district father recommends approval for this facility. It is therefore approved to support NDA 207946.

Janssen Pharmaceutica N.V., Beerse, Belgium (FEI 3002807336)

The firm proposes to manufacture and test the (b)(4) (described in DMF 18915 which also supported approved NDAs 21999 and 22264) and the final R092670 sterile grade drug substance, paliperidone palmitate (described in DMF 20902 which also supported NDA 22264). The firm further manufactures the "(b)(4)" grade of R092670 by (b)(4) produce the final sterile grade drug substance. The most recent inspection ending 5/14/2014, which covered the API manufacturing under 56002A, was classified VAI. The firm has primarily served as a release tester for manufacturers of various drug products, including their own. They are also the drug product manufacturer for a few liquid and suspension dosage forms. Given the firm's previous history and experience with the 1-month formulation product, there is reasonable assurance the firm is capable of performing the proposed function. The district recommends approval for this facility. It is therefore approved to support NDA 207946.

Johnson & Johnson Limited DBA APDC, Mumbai, India (FEI 3007543295)

The firm proposes to perform stability testing of the R092670 sterile grade drug substance. The firm currently performs stability testing of this drug substance to support NDA 22264. The most recent inspection ending 5/28/2014 resulted in an NAI. The inspection prior to that, dated 10/15/2010, was also NAI. The firm does not appear to test many products based on the number of applications that reference it; [REDACTED] (b) (4). The firm's inspectional history provides reasonable assurance that it is able to perform the responsibilities as described in the NDA. The facility is approved to support NDA 207946.

Drug Product Manufacturing Facilities

This NDA provides for a 3-month formulation of the currently marketed 1-month formulation approved under NDA 22264. The differences between the formulations include the particle size (3-month [REDACTED] (b) (4)), drug substance concentration, and fill volume.

Janssen Pharmaceutica N.V., Beerse, Belgium (FEI 3002807336)

The firm proposes to manufacture and test the [REDACTED] (b) (4) (described in DMF 18915 which also supported approved NDAs 21999 and 22264) and the final R092670 sterile grade drug substance, paliperidone palmitate (described in DMF 20902 which also supported NDA 22264). Additionally, it proposes to manufacture, test (release/stability), and package the finished drug product, including filling and stoppering the syringe. The firm currently manufactures the 1-month formulation of the drug product under the approved NDA 22264 as Invega Sustenna.

The most recent inspection ending 5/14/2014, which covered the 1-month formulation manufacturing under 56002A, was classified VAI. Refer to the summary review under the "Drug Substance Manufacturing Facilities" section.

The device constituent facility review of Janssen Pharmaceutica N.V. comprised a documentation review and facility inspectional history review. The facility is acceptable from a Quality System Regulation perspective. Please refer to the device constituent facility review memo (dated April 01, 2015). The facility is approved to support NDA 207946.

Phast, Homburg, Germany (FEI 3005909718)

The firm proposes to perform release and stability testing of the drug product. The most recent inspection ending 4/30/2013 resulted in NAI. The 2nd previous inspection was classified VAI for not requiring a validation or qualification when critical changes were made. The subsequent inspection in 2013 follow-up on this observation and determined

the firm had adequately addressed it. The product load does not appear to have increased over the last 6 years. As such, there is little concern about the firm's ability to control processes with varying degrees of complexity and risk. The firm's related experience and inspectional history provides reasonable assurance that it is able to perform the responsibilities described in the NDA. The facility is approved to support NDA 207946.

Janssen Pharmaceuticals, Inc., Titusville, New Jersey (2242843)

The firm proposes to perform stability testing of the drug product. The most recent inspection ending 6/8/2012 resulted in an NAI classification, as did the 2nd and 3rd previous inspection. Further review of the facility indicated that one lot of a product tested by the firm was recalled in August 2014 due to a sterility failure in a stability sample. As such, an inspection was requested to ensure their stability testing program was adequate. The inspection ended April 22, 2015 and was classified NAI; as such, the district recommended approval. There is reasonable assurance that the firm has adequate measures and controls in place to maintain a stability program. The firm's related experience and inspectional history provides reasonable assurance that it is able to perform the responsibilities described in the NDA. The facility is approved to support NDA 207946.

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

All facilities are found acceptable and are approved to support this NDA.

Juandria Williams
-S

Digitally signed by Juandria Williams -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=2000459158,
cn=Juandria Williams -S
Date: 2015.05.07 17:45:33 -04'00'

Supervisor Comments and Concurrence:

Grace E. McNally -S

Digitally signed by Grace E. McNally -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300042045, cn=Grace E. McNally -S
Date: 2015.05.07 17:39:58 -04'00'

ASSESSMENT OF MICROBIOLOGY

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 (b) (4)

(b) (4) 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 ^b	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)

^a (b) (4) paliperidone palmitate is equivalent to (b) (4) paliperidone active moiety.

^b Reference is made to Module 1 where the letter authorizing the FDA to access the DMF (20902) 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"> • 1 mL Long • 2.25 mL • 2.8 mL
Tip Cap	Bromobutyl rubber, dark gray
Plunger Stopper	(b) (4) bromobutyl rubber (b) (4) dark gray Sizes: <ul style="list-style-type: none"> • 1 mL Long used for 1-mL Long syringe • 1-3 mL used for 2.25-mL and 2.8-mL syringe

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 bacterial ingress study. This bacterial ingress 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

(b) (4)



The bacterial ingress study results met the acceptance criterion (i.e. no growth of *E. coli* in any of the test syringes); indicating that the container closure system maintains its integrity. The CCI testing is a stability requirement.

- Preservative Effectiveness – N/A
- Justification for not having a microbial limit specification for a non-sterile drug product – N/A

ADEQUATE

REVIEWER COMMENT – The applicant’s verification of container closure integrity is consistent with regulatory expectations for a pharmaceutical product.

P.3 Manufacture

P.3.1 Manufacturer: Janssen Pharmaceutica NV, Beerse, Belgium
FDA Site Registration: 3002807336

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

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY**Reviewer's Assessment and Signature: Adequate**

Digitally signed by Vinayak B. Pawar -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300151299, cn=Vinayak B. Pawar -A
Date: 2015.05.08 13:00:44 -04'00'

Supervisor Comments and Concurrence:

Stephen E.
Langille -A

Digitally signed by Stephen E. Langille -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People,
0.9.2342.19200300.100.1.1=1300151320,
cn=Stephen E. Langille -A
Date: 2015.05.08 12:49:34 -04'00'

I. Attachments

A. Facility

OVERALL RECOMMENDATION: Acceptable				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
Manufacture, Test	Janssen Pharmaceutical	3002807361	Sterile Operations	Acceptable
Manufacture, Test	Janssen Pharmaceutica NV	3002807336	Sterile Operations	Acceptable
Test	Johnson & Johnson Limited	3007543295	None	Acceptable
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
Manufacture, Test	Janssen Pharmaceutica NV	3002807336	Sterile Operations	Acceptable
Test (Release, Stability)		(b) (4)	None	Acceptable
Test (Stability)	Janssen Pharmaceuticals	2242843	2014 recall regarding stability failure – recommended GMP inspection	Acceptable

B. Lifecycle Knowledge Management

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking *	Risk Mitigation approach in control strategy	Risk Evaluation	Lifecycle Considerations/ Comments**
Sterility	Formulation Container closure Process Parameters Scale/Equipment/Site	H	Sterile processing and testing	Acceptable	None beyond typical expectations for a parenteral product.
Endotoxins	Formulation Container closure Process Parameters Scale/Equipment/Site	M	Controlled at drug substance release and in process	Acceptable	As above
Assay – Drug Substance	Formulation Container closure Raw Materials Process Parameters Scale/Equipment/Site	L	Controlled at drug product release	Acceptable	None. Drug substance is relatively robust, though it is an ester prone to hydrolysis.

<p>Assay – (b) (4)</p>	<p>Formulation Raw materials Process parameters Scale/Equipment/Site</p>	<p>L (release) H (stability)</p>	<p>Development studies shown that the level used limits (b) (4) on stability</p>	<p>Acceptable</p>	<p>(b) (4) limits (b) (4) levels were found to be stable in the registration batches but are not part of the regular stability protocol. Testing should be considered if any changes to the quantities of (b) (4) are proposed.</p>
<p>Physical Stability</p>	<p>Formulation Container closure Raw materials Process Parameters Scale/Equipment/Site</p>	<p>L</p>	<p>Drug substance shown to be (b) (4)</p>	<p>Acceptable</p>	<p>Any changes to (b) (4)</p>
<p>Dose Uniformity</p>	<p>Formulation Container closure Raw materials Process Parameters Scale/Equipment/Site</p>	<p>L</p>	<p>(b) (4) Release test.</p>	<p>Acceptable</p>	
<p>Content Uniformity</p>	<p>Formulation Container closure Process Parameters Scale/Equipment/Site</p>	<p>M</p>	<p>See above + release test</p>	<p>Acceptable</p>	<p>Will require close examination after changes to process especially the (b) (4) operation.</p>
<p>Osmolality</p>	<p>Formulation Container closure Raw materials Process</p>	<p>L</p>	<p>pH adjusting agents to obtain an (b) (4)</p>	<p>Acceptable</p>	<p>None.</p>

	Parameters Scale/Equipment/Site		formulation. Although it is not mentioned in the submission, it is expected that the osmotic pressure is about 290 mOsm/kg, like the 1-month formulation.		
pH	Formulation Container closure Raw materials Process Parameters Scale/Equipment/Site	L	No tests employed, but buffer used and development studies shown to be consistent during manufacturing and storage.	Acceptable	Buffers appear robust, but ensure that pH remains within specified range.
Particle Size Distribution	Formulation Container closure Raw materials Process Parameters Scale/Equipment/Site	M	Critical. ^(b) ₍₄₎	Acceptable	This is a critical parameter. ^(b) ₍₄₎
Particulate Matter	Formulation Container closure Raw materials Process Parameters Scale/Equipment/Site	M	Controlled at release and stability	Acceptable	None beyond typical expectations for a parenteral product.
Leachables/Extractables	Formulation Container closure Raw materials Process Parameters Scale/Equipment/Site	L	Studies found to be acceptable	Acceptable	Three extractables were found. Ensure that the levels remain within

					acceptable levels if changes to (b) (4) are proposed.
Re-dispersability	Formulation Process Parameters Scale/Equipment/Site	M (release) H(stability)	Tested at release and stability. In use tests support the labeled shake times and in-use period after shaking	Acceptable	This is part Test #1 in the drug product specification. Ensure that resuspendability and especially injectability are acceptable. Especially when changes are (b) (4) The current test is qualitative, but quantitative syringeability data may need to be requested and compared to those in NDA review #1.
Appearance	Formulation Container closure Raw materials Process Parameters Scale/Equipment/Site	L	Tested at release and stability. No changes noted	Acceptable	Critical that the suspension remains 'white to off-white' for user acceptability.
<i>In vitro</i> Release	Formulation Process Parameters Scale/Equipment/Site	H	Test and acceptance criteria found adequate. Used at release and stability.	Acceptable	It is critical that manufacturing changes be supported by in vitro release data.

Application Technical Lead Signature:

David J.
Claffey -S



Digitally signed by David J. Claffey -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300225565,
cn=David J. Claffey -S
Date: 2015.05.08 14:28:36 -04'00'

APPEARS THIS WAY ON ORIGINAL.

NDA 207946

INVEGA TRINZA

Paliperidone palmitate extended release injectable suspension

Review #1

21 April 2015

Office of Pharmaceutical Quality Recommendation: The final recommendation will be captured in a subsequent review document. An approval recommendation will be made on receipt of an acceptable recommendation from the facilities reviewer regarding the manufacturing sites and on receipt of a review and an acceptable recommendation from the microbiology reviewer.

Drug Name/Dosage Form	Paliperidone palmitate extended release injectable suspension
Strength	273 mg, 410mg, 546mg, 819mg
Route of Administration	Intramuscular Injection
Rx/OTC Dispensed	Rx
Applicant	Janssen
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original submission (# 0000)	1-Oct-14
Amendment # 0006 (DMEPA on container enclosure system)	27-Jan-15
Amendment # 0007 (CDRH on biocompatibility discussion, test report and risk assessment)	2-Feb-15
Amendment # 0008 (Response to 15 seconds shaking)	6-Feb-15

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Monica Cooper	
Drug Substance	Kasturi Srinivasachar (Secondary Reviewer)	
Drug Product	Wendy Wilson (Secondary Reviewer)	
Drug Product	Thomas Wong	
Drug Process	Sung Kim	
Drug Process	Lane Christensen (Secondary Reviewer)	
Microbiology	Vinayak Pawar	
Microbiology	Stephen Langille (Secondary Reviewer)	
Facility	Juandria Williams	
Facility	Grace McNally (Secondary Reviewer)	
Biopharmaceutics	Angelica Dorantes (Secondary Reviewer)	
Biopharmaceutics	Salaheldin Hamed	
Project/Business Process Manager	Dahlia Woody	
Application Technical Lead	David Claffey	
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Assessment (EA)	N/A	

Table of Contents

Table of Contents	3
Quality Review Data Sheet	4
Executive Summary	5
Primary Quality Review	10
ASSESSMENT OF THE DRUG SUBSTANCE	10
2.3.S DRUG SUBSTANCE	10
ASSESSMENT OF THE DRUG PRODUCT	17
2.3.P DRUG PRODUCT	17
R.2 Comparability Protocols.....	48
ASSESSMENT OF THE PROCESS.....	49
2.3.P DRUG PRODUCT	49
R.2 Comparability Protocols.....	67
ASSESSMENT OF THE FACILITIES	67
2.3.S DRUG SUBSTANCE	67
2.3.P DRUG PRODUCT	69
ASSESSMENT OF THE BIOPHARMACUETICS	73
ASSESSMENT OF MICROBIOLOGY	83
A APPENDICES	83
A.2 Adventitious Agents Safety Evaluation	83
I. Review of Common Technical Document-Quality (Ctd-Q) Module 1	84
Labeling & Package Insert.....	84
II. List of Deficiencies To Be Communicated.....	93
III. Attachments	94
Administrative.....	98

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
20902	Type II	Janssen Pharmaceutica, N.V.	Paliperidone Palmitate drug substance	Adequate with IR	10-Mar-2015	By M. Cooper
18915	Type II	Janssen Pharmaceutica, N.V.	Paliperidone	Adequate	18-Feb-2015	By M. Cooper
(b) (4)	Type III	(b) (4)	(b) (4)	Adequate	20-Jul-2009	By D. Claffey
	Type II			Adequate	3-Jun-2008	By J. Metcalfe
	Type III			Adequate	25-Jun-2008	By Y. Sun
	Other					

¹ Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Referenced NDA	NDA 22264	Equivalent one-month product
	IND 76952	Supporting IND

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

Executive Summary

I. Recommendations

An OPQ approval recommendation will be made on receipt of an acceptable recommendation from the facilities reviewer regarding the manufacturing sites and on receipt of a review and an acceptable recommendation from the microbiology reviewer.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues

N/A

2. Action letter language, related to critical issues such as expiration date

The proposed 24-month drug product expiry period with room temperature storage is acceptable.

3. Benefit/Risk Considerations

The most obvious risk associated with the proposed product is faster than expected in vivo release or dose-dumping of the three-month supply of drug. This potential risk is raised for this dosage form as it does not have a physical dissolution-rate controlling barrier like other extended release products (e.g. membrane, coating). Rather, it depends entirely on the intrinsic aqueous insolubility of the drug substance. The dissolution rate directly correlates with the (b) (4)

The in vivo performance of the product is assured through the drug substance and drug product manufacturing control strategy, (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Quality Assessments

Product Background: The proposed drug product is the third of a series of paliperidone products. Currently paliperidone is marketed as daily extended release tablets and as a monthly intramuscular extended release injectable suspension. This product was designed to extend drug release still further – so that it requires dosing every three months. As with the monthly product, the extended release characteristics for this product are achieved by use of a water-insoluble palmitate ester analogue of paliperidone. Product and manufacturing development of this product are based on the one-month product, with three main differences:

1. The dose is 3.5 times larger than the equivalent one-month product to achieve similar plasma profiles

2. (b) (4)

3. [Redacted] (b) (4)

Drug Product Description: The drug product was developed in four dosage strengths – 273, 410, 546 and 819 mg of paliperidone palmitate. The strengths are based on the quantity of paliperidone palmitate - the equivalent doses of the “active” paliperidone are listed below. Each strength is derived [Redacted] (b) (4)

[Redacted] Three different syringes sizes used to contain the four dosage strengths and each strength includes an overfill to ensure delivery of the complete labeled dose (table below).

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	[Redacted]	[Redacted] (b) (4)
410	263	2.25 mL	1.315	[Redacted]	[Redacted]
546	350	2.25 mL	1.750	[Redacted]	[Redacted]
819	525	2.8 mL	2.625	[Redacted]	[Redacted]

The following table lists the composition of the drug product suspension:

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

^b Reference is made to Module 1 where the letter authorizing the FDA to access the DMF (20902) is included.

Only paliperidone palmitate [Redacted] (b) (4)

[Redacted] This product [Redacted] (b) (4) composition as the one-month product – just the quantities and concentrations of the components differ. The proposed commercial batch formula is identical to that used for the manufacture of the registration and clinical trial batches. The level of each excipient is within that found in other marketed products – with the exception of polyethylene glycol 4000. Its level was referred to the pharm/tox reviewer to ensure its acceptability.

Drug Substance: Paliperidone palmitate (R092670) drug substance is a “white to almost white” [Redacted] (b) (4), racemic mixture with a melting range of 114 -120 °C. [Redacted] (b) (4)

[Redacted] Studies demonstrated that the particle size distribution (PSD) of the incoming drug substance did not impact the PSD or the performance of the drug product.

The drug substance specification also includes five specified impurities related to drug substance [Redacted] (b) (4)

Other drug substance tests critical to patient safety include the sterility and endotoxin tests. They were found adequate.

The majority of the drug substance information was referenced to DMFs 20902 and 18915. Both were found adequate to support this application. (b) (4) drug substance is synthesized at the Janssen, Cork, Ireland site. Both the Cork site and the Janssen, Beerse, Belgium site manufacture the final sterile-grade drug substance. Stability testing is carried out at the Beerse site and at J&J, Mumbai, India. A GMP recommendation from these sites is pending at this time.

For the purposes of this application the drug substance is defined as being 'sterile grade' paliperidone. The drug substance specification included in the application was found to be acceptable in the evaluation of DMF 20902. A representative CoA from the Cork site found that it met specification with total impurities (b) (4) % and residual solvents well within their specified limit (both were (b) (4) ppm).

Drug Product Development: The drug product development built upon prior knowledge gained from the marketed one-month dosage form. Development centered on

(b) (4)

(b) (4)

Drug Product Manufacturing: The drug product is manufactured at Janssen Pharmaceutica NV, Beerse, Belgium. A final GMP recommendation is pending at time of completion of this review.

The manufacturing of the proposed product is similar to that of marketed one-month product. The process consists of (b) (4)

(b) (4)

(b) (4)

Data on all the batches manufactured to-date met specification. In addition, critical control points (CCP), CPPs and IPCs were identified as a control strategy at critical manufacturing steps to ensure sterility of the final drug product. Validation results of the three validation bulk batches demonstrated that the manufacturing process using the identified CCPs, CPPs and IPCs produced consistent quality of the drug product at the commercial manufacturing scale and all validation results met the pre-determined validation acceptable criteria.

A microbiology review of this application was not available by the time this document was finalized. It will be part of a subsequent review document.

Drug Product Specification: Drug product specification includes tests typical for a parental product. Release and stability test results were consistent and acceptable.

The particle size specification is discussed above. Other more immediately clinically-relevant tests specific for this dosage form include qualitative tests for resuspendability and injectability. These tests are critical as blocked syringes can result in incomplete injections and possibly months of suboptimal dosing for the patient. Considering that the proposed suspension is twice as concentrated as the marketed one-month product, data were requested to demonstrate that the labeled 15 seconds of shaking was sufficient to resuspend the product. These data also indicated adequate syringeability even after five seconds of “vigorous” shaking – which is critical as it may not be uncommon for the

HCP to not shake for the entire 15 seconds. Data also supported the labeled five minute in-use period after shaking – and also demonstrated adequate product performance after 90 minutes storage. No degradants specific to the drug product were detected.

The in vitro release method for the one-month product was selected for the proposed product due to the similarities of the formulations. The test and acceptance criteria were found adequate for assuring consistent bioavailability of the drug product. The applicant demonstrated that the dissolution method was able to detect fine changes in drug substance PSD (b) (4) that are within the proposed range.

Drug Product Stability: Stability data supported the quality and function of the product through the proposed 24 month expiry period when stored at room temperature. A slight weight loss ((b) (4) %) for all samples was observed at 6 and 12 month test time points – likely due to the known semi-permeable nature of the syringe system. However, this is not likely to impact product performance as the entire content of the syringe is administered. (b) (4)

A categorical exclusion from an environmental assessment was claimed under 21 CFR 25.31(b) (EIC = (b) (4) ppb).

A. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Invega Trinza
Non Proprietary Name of the Drug Product	Paliperidone palmitate extended release injectable suspension
Non Proprietary Name of the Drug Substance	
Proposed Indication(s) including Intended Patient Population	Schizophrenia
Duration of Treatment	chronic
Maximum Dose	819 mg every three months
Alternative Methods of Administration	N/A

B. Novel Approaches N/A

C. Any Special Product Quality Labeling Recommendations? None

D. Process/Facility Quality Summary (see Attachment A)

E. Life Cycle Knowledge Information (see Attachment B)

88 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application Technical Lead Signature:

David J.
Claffey -S

Digitally signed by David J. Claffey -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300225
565, cn=David J. Claffey -S
Date: 2015.04.21 09:50:00 -04'00'