CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207946Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs—ODE IV
Center for Drug Evaluation and Research
Food and Drug Administration
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Pediatric and Maternal Health Staff Memorandum

From:	Hari Cheryl Sachs, MD, Team Leader Office of New Drugs - ODE IV Division of Pediatric and Maternal Health (DPMH)
Through:	Lynne Yao, MD, OND Acting Director, DPMH
To:	Division of Psychiatric Products
Drug:	NDA 207946/IND 076952
Applicant:	Janssen Research & Development, LLC
Therapeutic Class:	Antipsychotic
Dosage Forms:	3-month extended-release injectable suspension
Proposed Indication:	(b) (4) treatment (b) (4) in adult subjects with schizophrenia who have been adequately treated with Invega Sustenna for at least four months (17 weeks).
Consult Question:	"We would like [DPMH] input on the label. We would especially appreciate your recommendations with respect to labeling this product with respect to pregnancy and nursing given that plasma levels has been detected for up to 18 months after a single dose. Should there be a statement about this in HIGHLIGHTS?" Note: input on the pediatric use section was also requested given the persistence of detectable levels of paliperidone.

Materials Reviewed:

- Division of Psychiatric Products Consult dated January 27, 2015.
- Draft Guidance for Industry and Review Staff: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling dated February 2013.
- Information available in the sponsor's submission dated November 18, 2014, including the Sponsor's Waiver Requests

- Approval Letter and Labeling (approved 4/27/2007) for NDA 022043 Paliperidone Tablet, Extended Release
- Approval Letters and Labeling (approved 4/27/2007) for NDA 021999 Invega (paliperidone) Extended Release
- Approval Letters and Labeling (4/18/2014) for NDA 020272 Risperdal (risperidone)
- Applicant's proposed labeling
- Biometrics review (Reference ID 3714202) dated March 16, 2015
- European Medicines Agency Decision dated July 04, 2011 for modification of an agreed pediatric investigation plan for paliperidone/paliperidone palmitate

Trinza® Drug Development Program

The applicant has submitted a NDA application for Invega Trinza, (PP3M, paliperidone palmitate) for use as (b) (4) treatment (b) (4) in adult subjects with schizophrenia who have been adequately treated with Invega Sustenna for at least four months (17 weeks). The differences between these formulations of paliperidone are described in detail below.

Drug Information

Paliperidone is the major active metabolite of risperidone, a second generation atypical antipsychotic. Both paliperidone and risperidone are approved for indications related to the treatment of schizophrenia. In addition, risperidone is approved for bipolar disorder (10 years and older) and autism (5 years and older). The applicant has developed three formulations of paliperidone: an oral extended-release formulation (Invega® Extended Release [ER] tablets), and two long-acting injectable formulations (Invega® Sustenna [paliperidone palmitate, a 1-month formulation [PP1M]] and the newly proposed Invega® Trinza). The new Invega® Trinza (PP3M) is an extended-release formulation of paliperidone palmitate designed for administration every 3 months.

The oral formulation of paliperidone (Invega tablets) was initially approved by the FDA for the acute treatment of schizophrenia December 19, 2006, under NDA 21999. Subsequently, paliperidone was approved for the maintenance treatment of schizophrenia in April, 2007, and for the treatment of schizoaffective disorder in July, 2009. As a result of studies conducted to meet PREA requirements and in response to a WR, the schizophrenia indication was extended down to adolescents ages 12 to 17 years in April, 2011. PREA requirements for pediatric patients with schizoaffective disorder and less than 12 years of age for schizophrenia were waived (because studies were considered to be impossible or highly impracticable).

The PP1M injectable formulation (Invega Sustenna) was approved by the FDA for the acute and maintenance treatment of schizophrenia in adults in July, 2009, (NDA 22264), and for the treatment of schizoaffective disorder in November, 2014. PREA requirements related to the injectable formulations were ultimately waived (see reviewer comment below).

Reviewer Comment:
Initially, PREA requirements were put in place for Invega Sustenna. However, after oral paliperidone (i.e., Invega tablet) was approved for use in pediatric patients, the applicant was released from these requirements on the grounds that the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients 13-17 years of age.

According to the applicant, paliperidone palmitate is an aqueous suspension for intramuscular injection with low water solubility allowing the drug to dissolve slowly before being hydrolyzed to paliperidone which enters the circulation. By slowly releasing the drug from the injection site, the paliperidone palmitate formulation enables a dosing interval that reaches potentially therapeutic plasma concentrations for 3 months. Compared to the once-monthly formulation, the every 3-months formulation has (b) (4) and larger injection volume. The proposed dose levels of the every 3-months formulation are 273, 410, 546, and 819 mg which correspond to a 3.5 fold multiple of the marketed 1-month formulations doses of 78, 117, 156, and 234mg respectively. The proposed indication for PP3M is (b) (4) treatment (b) (4) in adult subjects with schizophrenia who have been adequately treated with PP1M (Invega Sustenna) for at least four months (17 weeks). PP3M is not approved or marketed in any other country and is not intended to be used for initiation of treatment in acutely symptomatic patients or patients who are immediately transitioning from oral to long-acting antipsychotic therapy. The applicant posits that the every 3-months formulation offers "great ease of use and increased medication adherence."

Summary of Trials Submitted with NDA to Support Proposed Claim.
According to the applicant, clinical development for Invega Trinza began in 2008. Three clinical trials were conducted in adults to support FDA approval

- Trial R092670-PSY-1005: a multi-panel Phase 1 pharmacokinetic (PK), safety, and tolerability study
- Trial R092670-PSY-3011: a Phase 3, randomized, double-blind, noninferiority study comparing PP3M (Invega Trinza) with the PP1M (Invega Sustenna)
- Trial R092670-PSY-3012: a Phase 3, randomized, double-blind, placebo-controlled relapse prevention study in adults with schizophrenia

Trial R092670-PSY-3012 is considered the single "pivotal" trial used to support effectiveness for the proposed indication. (The reader should refer to the protocol and primary review for details regarding the study design and outcomes).

Safety Concerns for Paliperidone

Known safety concerns of Paliperidone

In adults, multiple safety concerns are outlined in Warnings and Precautions. Several of these are relevant to pediatric patients including cerebrovascular (stroke), cardiac (QT prolongation, orthostatic hypotension/syncope) , neuroleptic malignant syndrome, neurologic adverse events (tardive dyskinesia, cognitive and motor impairment, seizures), metabolic changes (hyperglycemia, Diabetes Mellitus, dyslipidemia and weight gain) endocrine (hyperprolactinemia), cytopenias (leukopenia/neutropenia, and agranulocytosis), gastrointestional (obstructive symptoms, dysphagia, antiemetic effects), genitourinary (priapism) and psychiatric (suicide) adverse events. Notably, with respect to hyperprolactinemia, the following is noted in current labeling (italics added for emphasis).

> "Like other drugs that antagonize dopamine D2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a

prolactin-elevating effect similar to that seen with risperidone, a drug *that is associated with higher levels of prolactin than other antipsychotic drugs:*

Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevated compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects*"*

With the exception of the warning related to GI obstruction that does not appear in risperidone labeling, similar warnings are in labeling for the parent compound, risperidone.

There are no available clinical data for use of the injectable forms of paliperidone in pediatric patients. However, the oral formulations of both risperidone and paliperidone are approved for pediatric use. Paliperidone labeling includes descriptions of the following commonly observed adverse reaction in adolescents during the 6 week trial: somnolence, akathisia, tremor, dystonia, cogwheel rigidity, anxiety, weight increased and tachycardia. Dose related increases appear to be present for changes in fasting glucose (see Table 1b) as well as tachycardia, akathisia, extrapyramidal symptoms, somnolence and headache.

Reviewer comment: The pediatric trial of paliperidone was only 6 weeks in duration; and therefore, likely underestimates identification of safety concerns that require longer monitoring (e.g., growth) or longer exposure (galactorrhea, amenorrhea). Even in this shorter pediatric trial, per labeling, "there were notably higher incidences of dystonia, hyperkinesia, tremor and parkinsonism in the adolescent population as compared to the adult studies."

The labeling for risperidone contains pediatric specific adverse reactions about tardive dyskinesia, weight gain, somnolence, and hyperprolactinemia. In particular, relatively high rates of hyperprolactinemia were observed (up to 80-87% of risperidone treated bipolar or schizophrenia patients compared to 3-7% placebo).

Adverse Event Profile of PP3M

In adults, the primary reviewer states that the adverse event profile for this product in adults is similar to that which has been observed with other atypical antipsychotics.

Reviewer comment: Limited information is available regarding persistent exposure to long-acting injectables. However, a high rate of prolactin related adverse events were observed in a small study of monthly injections of paliperidone compared with multiple oral antipsychotics, including oral paliperidone (NDA 22,264s14 Effectiveness vs. Efficacy: Should Effectiveness Data be Included in Psychiatric Drug labeling? Tiffany Farchione, regulatory briefing, March 13, 2015). The incidence rates of prolactin-related events in the paliperidone palmitate group were higher than observed during clinical trials for paliperidone (25% of patients in the paliperidone injection group vs 5% of patients in the oral antipsychotic group experienced a prolactin-related event.). In addition, at the final visit, a larger proportion of study participants in the injection group had a prolactin level above the upper limit of normal (70% of women and

65% of men in the paliperidone palmitate injection group vs 15% of women and 17% of men in the oral group). Galactorrhea was also reported more frequently in the injectable group. Other adverse events reported more frequently in paliperidone group relative to the oral group (>2% difference) included:

- *injection site pain*
- *weight increased*
- *anxiety*
- *fatigue*
- *libido decreased*
- *abnormal weight gain*
- *nasal congestion*
- *oropharyngeal pain*
- *insomnia*
- *akathisia*
- *erectile dysfunction*
- *increased appetite*
- *back pain*
- *salivary hypersecretion*
- *semen volume decreased*

The reason for the increases in prolactin –related adverse events seen with longer exposures to the injectable formulation is unclear. Nonetheless, information related to hyperprolactinemia is already present in the applicant's proposed "Warnings and Precautions" and "Highlights". Labeling notes that paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs.

Paliperidone use is associated with a number of serious adverse events, including QT prolongation, metabolic changes and dystonia as well as hyperprolactinemia. Hyperprolactinemia is associated with a number of adverse side effects including abnormal carbohydrate and lipid metabolism, osteopenia, gynecomastia, oligomenorrhea, pituitary tumors, infertility, growth and pubertal delay in pediatric patients. Because children and adolescents are still growing and there are no clinical data regarding use of any extended form for paliperidone, DPMH recommends that the pediatric use section include language to discourage use of this longer-acting injectable (see below)

Review of Labeling and DPMH Recommendations

Pediatric Use Labeling

The Pediatric Use subsection should provide useful information that is clear and accessible to health care providers and should describe what is known and unknown about use of the drug in the pediatric population (e.g., if studies have been done or not, explanation of why the available evidence does not support a pediatric approval) and must highlight any differences in effectiveness or safety in the pediatric population versus the adult population (21CFR 201.57(c)(9)(iv)(B))

As is the case with the current application, when a pediatric indication is not supported by available data because there no studies available in any pediatric population and/or extrapolation of adult effectiveness data to the pediatric population is not possible, the Pediatric Use subsection must contain a statement explaining that safety and effectiveness have not been established in the relevant pediatric population(s)(21 CFR 201.57(c)(9)(iv)(F). An example statement is "Safety and effectiveness in pediatric patients have not been established." The basis for this statement should be provided (e.g. stating that studies have not been conducted or

providing an explanation of why the available evidence does not support a pediatric approval in those patients).

Sections 505A(j) and 505B(g)(2) of the Food, Drug and Cosmetic Act (FDCA) require that data submitted in response to a PREA study requirement be described in the labeling whether the findings are positive, negative, or inconclusive. The applicant has not submitted the pediatric assessment that is required under PREA. However, the applicant has submitted a request for a full waiver of the PREA requirement (discussed below). When pediatric studies under PREA are fully or partially waived by the FDA because there is evidence that a drug would be ineffective or unsafe in a pediatric population or pediatric subpopulation, the safety concern or lack of efficacy must be described in labeling (section 505B(a)(4)(D) and 505B(b)(2)(D) of the FD&CAct (21 U.S.C. 355(c)).

If a specific risk has been identified for pediatric patients or in a pediatric subpopulation, this risk information must be described in the Pediatric Use subsection and, if appropriate, placed in the "Contraindications" section or "Warnings and Precautions" section. In such cases, the Pediatric Use subsection must refer to the risk information in the "Contraindications" or "Warnings and Precautions" section, as required by regulation(21 CFR 201.57(c)(9)(iv)(B),(E),and (F)) Similarly, If a drug contains one or more inactive ingredients that present an increased safety risk (toxic effects) to a pediatric population, a special note of the risk must be provided in labeling. A special note of the risk must be placed in the "Contraindications" section (21CFR201.57(c)(5)) and/or "Warnings and Precautions" section (21 CFR201.57(c)(6)), and also briefly summarized in the Pediatric Use subsection (21 CFR201.57(c)(9)(iv)).

If nonclinical toxicology studies in a juvenile animal model have been conducted to support clinical pediatric trials, these studies should be noted in the Pediatric Use subsection. A concise summary of the juvenile animal data, including the human dose exposure equivalents used in the study as well as pertinent study endpoints, should be described.

Reviewer Comment: DMPH recommendations are based on the "draft annotated labeling" provided in the applicant's original submission dated November 18, 2014. Additionally DPMH participated in the orientation, team, and labeling meetings for this application.

Applicant proposed labeling:

8.4 Pediatric Use
Safety and effectiveness of TRADENAME in patients < 18 years of age have not been established.

(b) (4) juvenile rats (b) (4) paliperidone from days 24 to 73 of age, a reversible impairment of performance in a test of learning and memory (b) (4), in females only, (b) (4) no-effect dose of 0.63 mg/kg/day, (b) (4) produced plasma levels (AUC) (b) (4) paliperidone similar to those in adolescents. No other consistent effects on neurobehavioral or reproductive development were seen up to the highest dose tested (b) (4) which produced plasma (b) (4) paliperidone 2-3 times those in adolescents.

Juvenile dogs (b) (4) for 40 weeks (b) (4) oral risperidone, which is extensively metabolized to paliperidone in animals and humans, at (b) (4) 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density (b) (4) with a no-effect dose of 0.31 mg/kg/day, which produced plasma levels (AUC) of risperidone plus paliperidone (b) (4) similar to those in children and adolescents receiving the maximum recommended human dose of risperidone. In addition, (b) (4) delay (b) (4) sexual maturation was seen at all doses in both males and females. (b) (4) effects showed little or no reversibility in females after a 12-week drug-free recovery period.

The long-term effects of paliperidone on growth and sexual maturation have not been fully evaluated in children and adolescents.

DPMH Comments and Recommended Labeling Changes
DPMH requires additional input from the nonclinical team in order to validate the applicant's proposed language in Section 8.4 of the labeling. The language appears to be (b) (4)

Approximately 2% of the PP3M drug product remains detectable after 3 months. Given the persistence of this extended injectable and the known safety concerns for paliperidone, particularly QT prolongation, metabolic effects and hyperprolactinemia, DPMH recommends that the pediatric use section include additional language to alert prescribers to discourage use of this specific long-acting injectable.

Additionally DPMH suggests replacing the symbol "<" with the words "less than" and recommends adding a subtitle to clearly delineate the juvenile animal data from the clinical data. Consequently Section 8.4 should read as follows:

> ***8.4 Pediatric Use***
>
> Safety and effectiveness of TRADENAME in patients **less than** 18 years of age have not been established. Use of TRADENAME is not recommended in pediatric patients because of the potential longer duration of an adverse event compared to shorter-acting products.
>
> **Juvenile Animal Data**
>
> In a study in which juvenile rats were treated with oral paliperidone from days 24 to 73 of age, a reversible impairment of performance in a test of learning and memory was seen, in females only, with a no-effect dose of 0.63 mg/kg/day, which produced plasma levels (AUC) of paliperidone similar to those in adolescents. No other consistent effects on neurobehavioral or reproductive development were seen up to the highest dose tested (2.5 mg/kg/day), which produced plasma levels of paliperidone 2-3 times those in adolescents.
>
> Juvenile dogs were treated for 40 weeks with oral risperidone, which is extensively metabolized to paliperidone in animals and humans, at doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were seen with a no-effect dose of 0.31 mg/kg/day, which produced plasma levels (AUC) of risperidone plus paliperidone which were similar to those in children and adolescents receiving the maximum recommended human dose of risperidone. In addition, a delay in sexual maturation was seen at all doses

in both males and females. The above effects showed little or no reversibility in females after a 12-week drug-free recovery period.

V. Summary and Conclusions:

1) DPMH suggests that the "Indications" and "Dosage and Administrations" sections of the labeling clearly reflect that the proposed product is to be used in "adults only" because of the potential longer duration of any serious adverse events associated with use of this 3-month injectable and the availability of shorter-acting antipsychotics, including oral paliperidone.

2) Additional language should be added to "8.4 Pediatric Use" to convey that use of this particular long-acting formulation is not recommended because of the potential longer duration of any serious adverse event compared to shorter-acting products.

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/s/

HARI C SACHS
05/13/2015

LYNNE P YAO
05/18/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 11, 2015
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 207946
Product Name and Strength:	Invega Trinza (paliperidone palmitate) Extended-Release Injectable Suspension 273 mg, 410 mg, 546 mg, and 819 mg
Submission Date:	December 18, 2014
Applicant/Sponsor Name:	Janssen Pharmaceuticals, Inc.
OSE RCM #:	2014-2560
DMEPA Primary Reviewer:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Psychiatry Products (DPP) requested that we review the revised Label (syringe) and labeling (Prescribing Information (PI), Information for Use (IFU) and carton labeling) (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSIONS

[1] Myers, D. Human Factors Usability Study Protocol, Label and Labeling Review for Invega Trinza (NDA 207946). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015APR16. 36 p. OSE RCM No.: 2014-2572 and 2014-2560.

The revised label (syringe) and labeling (PI, IFU and carton labeling) is acceptable from a medication error perspective.

APPENDIX A: LABEL AND LABELING SUBMITTED ON MAY 4, 2015

- **Prescribing Information (no image)**
- **Information for Use (no image)**
- **Carton labeling (not to scale)**

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

DEBORAH E MYERS
05/11/2015

DANIELLE M HARRIS
05/11/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
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Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: 4-17-2015

From: Leyla Sahin, MD
Medical Officer,
Division of Pediatric and Maternal Health, Maternal Health Team

Through: Tamara Johnson, M.D., M.S.
Acting Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, MD
Acting Director,
Division of Pediatric and Maternal Health

To: Division of Psychiatry Products

Drugs: Invega Trinza (paliperidone palmitate) extended release injectable suspension for intramuscular use; NDA 207946

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Applicant: Janssen

Materials Reviewed:
- Applicant's proposed labeling
- Approved labeling for Invega Sustenna, Invega, and Risperdal

Consult Question: Please advise regarding Pregnancy and Lactation Labeling Rule (PLLR) Conversion

INTRODUCTION

The applicant submitted a new drug application for Invega Trinza, a new extended release formulation of intramuscular paliperidone palmitate for the treatment of schizophrenia, on November 18, 2014. The Division of Psychiatry Products (DPP) designated this application a priority review as it has the advantage of administration every 3 months instead of monthly. DPP consulted the Division of Pediatric and Maternal Health (DPMH) on January 27, 2015, to assist with reviewing the Pregnancy and Nursing Mothers subsections of labeling.

BACKGROUND

Product Background

Invega (paliperidone) is an atypical antipsychotic indicated for treatment of schizophrenia and schizoaffective disorder. Invega was approved as an oral tablet in 2006, and as a monthly intramuscular injection in 2009, under the trade name Invega Sustenna. Paliperidone is the active metabolite of risperidone (Risperdal), which was approved in 1993 for schizophrenia and is manufactured by the same company.

Currently approved Invega Sustenna' s pregnancy labeling is in a hybrid format modeled after the proposed Pregnancy and Lactation Labeling Rule, and includes developmental toxicity data in rats and rabbits at doses up to 8 times the maximum recommended oral dose, based on body surface area. Pregnancy labeling for Invega and Invega Sustenna also include class labeling for antipsychotics regarding third trimester use and extrapyramidal and/or withdrawal symptoms in the neonate, which was implemented by DPP in 2011.[1]

Pregnancy and Lactation Labeling Rule (PLLR)

On December 4, 2014, the Food and Drug Administration (FDA) published the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*," also known as the Pregnancy and Lactation Labeling Rule (PLLR).[2] The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and a new subsection for information with regard to females and males of reproductive potential (if applicable). Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule, to include information about the risks and benefits of using these products during pregnancy and lactation. The PLLR will officially take effect on June 30, 2015; however, at this time applicants may voluntarily convert labeling to the PLLR format. The recommendations in this review are consistent with the PLLR format.

[1] http://www.fda.gov/Drugs/DrugSafety/ucm243903.htm
[2] Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

DISCUSSION

The applicant's proposed labeling for Invega Trinza is modeled after the approved labeling for Invega Sustenna, with the addition of language regarding risk in pregnancy and breastfeeding due to the detection of drug 18 months after administration. DPMH was concerned that additional information in the labeling may be needed if this product continues to be detectable in plasma longer than the currently approved products. The actual amount detected at 18 months was not quantified in the applicant's proposed labeling, in either section 8 Specific Populations or section 12 Clinical Pharmacology. DPMH requested input from the Office of Clinical Pharmacology's Clinical Pharmacology reviewers regarding the amount of drug that is present in plasma up to 18 months after administration and the potential for accumulation in plasma or other body compartments. Based on the assessment of Clinical Pharmacology reviewers, K. Kumi, in the Division of Clinical Pharmacology 1, and D. Rekic, in the Division of Clinical Pharmacometrics, drug exposures following Invega Trinza administration are similar to those following Invega Sustenna administration (monthly intramuscular injection) and Invega (the daily oral administration). In addition, there appears to be no accumulation after administration. DPMH discussed these issues at a meeting with Clinical Pharmacology on April 15, 2015, and there was agreement that it may be reasonable to modify the applicant's proposed statement in Pregnancy and Lactation labeling to include a statement that paliperidone has been detected in plasma at low levels up to 18 months after administration and that the clinical significance is not known. This statement will cross reference the Clinical Pharmacology section where additional information will be included.

There are three published case reports of paliperidone levels in milk following administration of risperidone.[3,4,5] Based on a review of these publications by the National Library of Medicine's LactMed database, an exclusively breastfed infant would receive an average of about 1% of the maternal weight-adjusted dosage, which is substantially less than the limit of 10% of the maternal weight adjusted dose that is commonly used as the acceptable level.[6] No adverse reactions were observed in these infants. Therefore, DPMH recommends that the following statement be included in the lactation section of labeling, "The development and health benefits of breastfeeding should be considered along with the mother's clinical need for INVEGA TRINZA and any potential adverse effects on the breastfed infant from INVEGA TRINZA or from the underlying maternal condition."

DPP agreed to defer a search of published literature on the safety of paliperidone and risperidone in pregnancy and lactation for consideration of inclusion in labeling to after the effective date of PLLR.

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[3] Hill RC, McIvor RJ, Wojnar-Horton RE et al. Risperidone distribution and excretion into human milk: case report and estimated infant exposure during breast-feeding. J Clin Psychopharmacol. 2000;20:285-6. Letter

[4] Ilett KF, Hackett LP, Kristensen JH et al. Transfer of risperidone and 9-hydroxyrisperidone into human milk. Ann Pharmacother. 2004;38:273-6.

[5] Aichhorn W, Stuppaeck C, Whitworth AB. Risperidone and breast-feeding. J Psychopharmacol. 2005;19: 211-213.

[6] United States National Library of Medicine. TOXNET Toxicology Data Network. *Drugs and Lactation Database (LactMed*). http://www.toxnet.nlm.nih.gov/cgi-bin/sis/search2

CONCLUSION
The Pregnancy and Lactation subsections of labeling were structured to be consistent with the PLLR.

Because the applicant has voluntarily complied with the PLLR requirements prior to the June 30, 2015 effective date, language waiving the current labeling requirements should be included in the approval letter. The following approval letter language is suggested.

"WAIVER OF PREGNANCY, LABOR AND DELIVERY, AND NURSING MOTHERS SUBSECTIONS

We are waiving the current requirements of 21CFR 201.56(d)(1) and 201.57(c)(9)(i) through (iii), regarding the content and format of labeling for subsections 8.1 Pregnancy, 8.2 Labor and Delivery, and 8.3 Nursing Mothers of prescribing information. Your approved labeling for subsections 8.1, 8.2, and 8.3 reflects the content and format requirements of the Pregnancy and Lactation Labeling Rule (79 FR 72063, December 4, 2014) which implements on June 30, 2015."

DPMH LABELING RECOMMENDATIONS
DPMH discussed our labeling recommendations with DPP at a meeting on April 1, 2015. DPMH recommendations are below and reflect the discussions with DPP at that meeting.
See final labeling for all of the labeling revisions negotiated with the applicant.

HIGHLIGHTS OF PRESCRIBING INFORMATION
USE IN SPECIFIC POPULATIONS
Reviewer Comments: The purpose of Highlights is to highlight important information for the safe and effective use of a product. Because of potential for neonatal extrapyramidal/withdrawal symptoms following administration in the third trimester of pregnancy, DPMH recommends adding the following concise statement:

- Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)

8.1 Pregnancy
Reviewer comment:
Pregnancy Category and Regulatory Language
Under PLLR, the pregnancy category should be removed and the accompanying standard regulatory language is not needed.

Pregnancy Exposure Registry

Reviewer comment:
The National Pregnancy Registry for Atypical Antipsychotics collects data and monitors pregnancy outcomes in women exposed to atypical antipsychotics during pregnancy. The contact information for this registry should be added.

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to

INVEGA TRINZA during pregnancy. For more information contact the National Pregnancy Registry Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-andresearch-programs/pregnancyregistry/.

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There are no available data on INVEGA TRINZA use in pregnant women to inform any drug-associated risks for birth defects or miscarriage. Paliperidone has been detected in plasma at very low levels up to 18 months after a single-dose administration of INVEGA TRINZA™, and the clinical significance of INVEGA TRINZA™ administered maternally before pregnancy or anytime during pregnancy is not known *[see Clinical Pharmacology (12.3)]*. No teratogenicity was observed in pregnant rats injected intramuscularly with the 1-month paliperidone palmitate suspension during organogenesis at doses up to 3 times the maximum recommended human dose (MRHD) of 819 mg of the 3-month paliperidone palmitate injectable suspension on mg/m^2 basis *[see Data]*. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recover within hours or days without specific treatment; others may require prolonged hospitalization.

Data

Animal Data

No developmental toxicity studies were conducted with the 3-month paliperidone palmitate intramuscular injection.

No treatment-related effects on the offspring were observed when pregnant rats were injected intramuscularly with 1-month paliperidone palmitate during the period of organogenesis at doses up to 3 times the MRHD of 819 mg of the 3-month paliperidone palmitate injectable suspension on mg/m2 basis.

No increases in fetal abnormalities were observed when paliperidone was administered orally to pregnant rats and rabbits during the period of organogenesis at doses up to 8 times the MRHD of 12 mg/day of oral paliperidone on mg/m2 basis.

In rat reproduction studies with risperidone, which is extensively converted to paliperidone in rats and humans, pup deaths increased at oral doses which are less than the MRHD of risperidone on a mg/m2 body surface area basis (see RISPERDAL® package insert).

8.2 Lactation

Reviewer comment:
Under PLLR this subsection is renamed "Lactation" and renumbered 8.2.

Risk Summary

Paliperidone is present in human breast milk; however there are insufficient data to assess the amount in human milk, the effects on the breastfed infant, or the effects on milk production. Paliperidone has been detected in plasma at very low levels up to 18 months after a single-dose administration of INVEGA TRINZA™, and the clinical significance on the breastfed infant is not known [see Clinical Pharmacology (12.3)]. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for INVEGA TRINZA and any potential adverse effects on the breastfed infant from INVEGA TRINZA or from the underlying maternal condition.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise patients to notify their physician if they become pregnant or intend to become pregnant during treatment with INVEGA TRINZA™. Advise patients that INVEGA TRINZA may cause extrapyramidal and/or withdrawal symptoms in a neonate. Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to INVEGA TRINZA during pregnancy [see Use in Specific Populations (8.1)].

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TAMARA N JOHNSON
04/28/2015

LYNNE P YAO
04/29/2015

HUMAN FACTORS USABILITY STUDY PROTOCOL, LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 16, 2015
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 207946
Product Name and Strength:	Invega Trinza (paliperidone palmitate) Extended-Release Injectable Suspension 273 mg, 410 mg, 546 mg, and 819 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Janssen Pharmaceuticals, Inc.
Submission Date:	December 18, 2014
OSE RCM #:	2014-2572 and 2014-2560
DMEPA Primary Reviewer:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Danielle Harris, PharmD, BCPS
DMEPA Associate Director	Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

Janssen Pharmaceuticals, Inc. submitted a Class 2 resubmission on December 18, 2014 for Invega Trinza Extended-Release Injectable Suspension. This review is in response to a consultation request from the Division of Psychiatry Products (DPP) to evaluate the human factors validation studies to determine the usability of this product. DPP is especially interested in whether there were any problems with adequately shaking the syringe vigorously for at least 15 seconds.

This review also responds to an additional consultation request from DPP to review the package insert, instructions for use (IFU), and carton/container labeling, for areas of vulnerabilities that can lead to medication errors. DPP asked DMEPA to make certain that the carton/container is sufficiently different from the 1-month formulation (Invega Sustenna) such that there will be no confusion between the two products.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C
Human Factors Study	D
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Assessment of the Human Factors Studies:

There were two needle selection errors that occurred during the validation study. The root cause analysis suggested that the participants that committed the use errors overlooked key instructions in the needle selection chart.

To use this product the correct needle must be selected based on the patient's weight and site of administration. As a result of the use errors, the Applicant has made improvements to the Instructions For Use (IFU), specifically to the needle selection table. We note the Applicant has

not validated the changes made to the user interface; however, we determined the changes will minimize the risk for needle selection errors without introducing new risks to the system. Thus, in this circumstance we will not require the Applicant to conduct another human factors validation study.

We have reviewed the human factors formative and summative studies for paliperidone palmitate extended-release injectable suspension (3-month injection) submitted on February 6, 2015, and determined that the Applicant has provided sufficient data to support that the product can be used safely and effectively.

With regards to DPP's concern regarding adequately shaking the product for 15 seconds prior to administration, we note that 15/15 users in the Human Factors Validation (Summative) study completed the task successfully. We believe the shaking requirements are clear and prominent within the IFU, as well as on the carton labels.

Assessment of Labels and Labeling:

DPP requested that we ensure the Invega Trinza carton/container is sufficiently different from the 1-month formulation (Invega Sustenna) to minimize the risk for selection errors between the two products. Our evaluation determined there is adequate differentiation between the two products' container labels and carton labeling. However, we identified areas of the labels and labeling that can be revised to increase clarity, improve readability, and add important critical information to mitigate medication errors. We provide recommendations in Section 4 below, and we believe these recommendations can be implemented without requiring additional human factors validation.

4 CONCLUSION & RECOMMENDATIONS

We conclude there is sufficient data to support the safe and effective use of Invega Trinza by intended users, for intended uses and use environments. Additionally, we conclude that the Sponsor's proposed product labels and labeling adequately differentiates the 3-month formulation from the currently marketed 1-month formulation of paliperidone Extended-Release Injectable Suspension.

We identified areas of the labels and labeling that can be revised to increase clarity, improve readability, and add important critical information to mitigate medication errors. We provide recommendations in Section 4.1 below. We advise the following recommendations are implemented prior to the approval of this NDA.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
   1. *Highlights of Prescribing Information* and *Full Prescribing Information*
      a. Currently nowhere in the *Highlights of Prescribing Information* or *Full Prescribing Information*; 2. *Dosage and Administration* is it clearly stated to dose this

product once every 3 months. (Under *Highlights of Prescribing Information; Indications and Usage*, next to Invega Trinza it is stated that this is a 3-month injection.) Therefore, we recommend adding the dosing frequency to these two areas. To maintain clarity, simplicity, and consistency consider using language similar to what appears in the *Instructions for Use; Dosing*: "This medication should be administered once every 3 months."

b. Under *Highlights of Prescribing Information; Dosage and Administration*, by bullet four, we recommend changing the order of this sentence, to begin with the patient weight since this is the differentiating factor. This is consistent with *Full Prescribing Information*; 2.1 *Administration Instructions* and the *Instructions for Use*, as well as how this information is presented, per DMEPA's previous safety recommendations for Invega® Sustenna™, under Section 2.1 *Administration Instructions*. E.g., "For deltoid injection: for patients weighing less than 90 kg use the 1-inch 22G thin wall needle or for patients weighing 90 kg or more use the 1 ½-inch 22G thin wall needle. For gluteal injection: regardless of patient weight use the 1 ½-inch 22G thin wall needle."

c. The symbols '<', '≤', '>', and '≥' are dangerous abbreviations that appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations because these symbols are often mistaken and used as opposite of intended.[1] As a part of a national campaign to reduce medication errors related to error-prone medical abbreviations, symbols, and dose designations, the FDA agreed not to approve labels and labeling that include error-prone abbreviations, symbols, and dose designations. Thus, we recommend revising all instances of the symbol '<', '≤', '>', and '≥' to read "less than", "less than or equal to", "greater than", or 'greater than or equal to" respectively where used in the dosing information. These symbols appear three times in last two bullets under *Highlights of Prescribing Information*; Dosage and Administration, three times following the words "Missed Dose" in Section 2.3 *Missed Doses*, once in the title of Table 2, three times within Section 2.5 *Dosage Adjustments*, and five times within Table 3 displayed within Section 2.8 *Switching Invega Trinza to Oral Paliperidone Extended-Release Tablets*.

d. The symbol →appears in the conversion chart under *Highlights of Prescribing Information; Dosage and Administration*, as well as Tables 1 and 2 in the *Full Prescribing Information*. This symbol is not defined. We recommend the replacement of this symbol with its intended meaning to prevent misinterpretation and confusion.

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[1] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2015 Mar 3]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

2. Section 2.1, *Administration Instructions; Dosage and Administration*
    a. "Inject slowly" appears in the third paragraph. We recommend providing further clarification by defining "slowly" (e.g., over 10 seconds).
3. Section 16. *How Supplied/Storage and Handling*
    a. We recommend switching the current order of the syringe sizes to be consistent with the Carton Labeling, Principal Display and Back Panels to read "The kit contains a prefilled syringe and 2 safety needles (a thin walled 22G, 1-inch safety needle and a thin walled 22G, 1 ½-inch safety needle)."

4. *Instructions for Use (IFU)*
    a. Text prior immediately prior to and following the header *Important*
        1. Revise the statement, that appears twice, both immediately prior the header *Important*, as well as immediately prior to the header *Dose pack contents;* (b) (4) to read "Do not administer by any other route." This is in alignment with DMEPA's previous safety recommendations specific to Invega Sustenna, as well as statements in Section 2.1 *Administration Instructions* in the Invega Trinza *Full Prescribing Information*. Negative statements such as (b) (4) may have an opposite of the intended effect and inadvertently encourage the wrong route of administration. Thus, revising this statement to omit the incorrect route of administration such as "Do not administer by any other route" may help minimize the potential for wrong route of administration errors.
        2. To eliminate potential confusion, we recommend removing the statement, (b) (4) which appears under the headers *Important*; *Dosing*. Negative statements such as (b) (4) may have an opposite of the intended effect and inadvertently encourage the frequency of administration. Thus, deleting this statement to omit the frequency and leaving only "This medication should be administered once every 3 months" may help minimize the potential for wrong frequency of administration errors.
        3. The first sentence under the header *Important* currently reads, "Invega Trinza should be administered by a healthcare professional…" We recommend changing this to read, "Invega Trinza must be administered only by a healthcare professional…" This language is consistent with the wording in *Highlights of Prescribing Information*; *Dosage and Administration*, as well as *Full Prescribing Information*; 2.1 *Administration Instructions*.
        4. Consider changing the negative sentence "Do not divide dose into multiple injections", under the header *Important*, to align with the positive language statement used in fourth paragraph under *Full Prescribing Information*; 2.1 *Administration Instructions* that states, "Administer the dose in a single injection; do not administer in divided injections. Inject slowly, deep into the deltoid or gluteal muscle taking care to avoid injecting into the blood vessel."
        5. Under the sub-header *Thin Wall safety*; *Needle Section*, we recommend removing the negative sentence (b) (4)

(b) (4) Negative statements such as (b) (4) may have an opposite of the intended effect and inadvertently encourage the incorrect frequency of administration. (b) (4) and leaving the previous two statements "Thin wall safety needles are designed to be used with Invega Trinza. Therefore, it is important to only use the needles provided in the Invega Trinza kit" may help minimize the potential for the needle selection or wrong frequency of administration errors.

b. *Select Needle*
   1. We recommend the removal of all non-metric references to weight; (b) (4) Having the weight specified in both lbs and kg can be confusing. Having the weight specified in kg alone is consistent with the *Full Prescribing Information*; 2.1 *Administration Instructions*.
   2. Please add a space between the four weight expressions (90 kg). These currently lack adequate space between the Arabic number (90) and the unit of measure (kg). Please place adequate space between the number and unit of measure to improve legibility.

b. *Inject*
   1. Revise the statement that appears under the sub-header Inject dose, (b) (4) to read "Do not administer by any other route." This is in alignment with DMEPA's previous safety recommendations specific to Invega® Sustenna™, as well as statements in Section 2.1 *Administration Instructions* in the Invega Trinza *Full Prescribing Information*. Negative statements such as (b) (4) may have an opposite of the intended effect and inadvertently encourage the wrong route of administration. Thus, revising this statement to omit the incorrect route of administration such as "Do not administer by any other route" may help minimize the potential for wrong route of administration errors.

4.2 RECOMMENDATIONS FOR JANSSEN PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA 207946:

A. Carton Labeling
   1. Principal Display Panel
      a. DMEPA identified several cases involving patients self-administering Invega Sustenna. In an effort to further mitigate medication errors that have been reported resulting from Invega Sustenna being self-administered by patients, we recommend adding the statement "Each injection must be administered only by a health care professional." to the carton's principal display panel.
      b. Currently two of the three strength expressions (these are the two most prominent) on the Principal Display Panel lack adequate space between the

Arabic numeral and the unit of measure. Please place adequate space between the numerical dose and unit of measure (e.g., 10 mg instead of 10mg) because the "m" is sometimes mistaken as a zero or two zeros, risking a 10- to 100-fold overdose.

c. Our post-marketing experience indicates that sequential numbering of the NDC product code (middle 3 digits) has led to selecting and dispensing of the wrong strength and wrong drug and is not an effective differentiating feature (e.g., 606, 607, 608, and 609). These middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, we recommend changing these numbers or increasing the font size of the middle digits of the NDC product code.[2]

B. Syringe Label

1. Lot number and expiration date

a. The syringe labels currently submitted do not contain notation of where the lot number and expiration date are intended to be printed. The lot number statement is required on the immediate container per 21 CFR 201.10(i)(1) and the expiration date is required on the immediate container per 21 CFR 201.17. When determining this placement, please ensure that there are no other numbers located in close proximity to the lot number/expiration date where it can be mistaken as the lot number/expiration date.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

[2] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

Table 2 presents relevant product information for Invega Trinza that Janssen Pharmaceuticals, Inc. submitted on November 18, 2014.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Invega Trinza</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>paliperidone palmitate</td></tr>
<tr><td>Indication</td><td>treatment of schizophrenia in adult patients who have been adequately treated with the 1-month paliperidone palmitate injectable product for at least 4 months</td></tr>
<tr><td>Route of Administration</td><td>intramuscular injection</td></tr>
<tr><td>Dosage Form</td><td>extended-release injectable suspension</td></tr>
<tr><td>Strength</td><td>273 mg, 410 mg, 546 mg, and 819 mg</td></tr>
<tr><td>Dose and Frequency</td><td>Use only after patients have been adequately treated with the 1-month paliperidone palmitate injectable product for at least 4 months. Initiate Invega Trinza at the time when the next 1-month paliperidone palmitate dose was to be scheduled with an Invega Trinza dose based on the previous 1-month injection dose as shown:
Conversion Between the Last Paliperidone Palmitate 1-Month Injectable Product (INVEGA® SUSTENNA®) and Paliperidone Palmitate 3-Month Injectable Product (INVEGA® TRINZA™) Doses Using 3.5 as a Multiplier
<table>
<tr><th>If the last INVEGA® SUSTENNA® dose is:</th><th>Initiate INVEGA® TRINZA™ at the following dose:</th></tr>
<tr><td>78 mg →</td><td>273 mg</td></tr>
<tr><td>117 mg →</td><td>410 mg</td></tr>
<tr><td>156 mg →</td><td>546 mg</td></tr>
<tr><td>234 mg →</td><td>819 mg</td></tr>
</table>
Conversion from the 39 mg 1-month paliperidone palmitate injectable product was not studied.
For intramuscular injection only. Each injection must be administered only by a health care professional. For deltoid injection, use the 1-inch 22G thin wall needle for patients weighing less than 90 kg or the 1 ½-inch 22G thin wall needle for patients weighing 90 kg or more. For gluteal injection, use the 1 ½-inch 22G thin wall needle regardless of the patient weight.
Prior to administration, shake the prefilled syringe vigorously for at least 15 seconds within 5 minutes prior to administration to ensure a homogeneous suspension.</td></tr>
<tr><td>How Supplied</td><td>The kit contains a prefilled syringe and 2 safety needles (a thin walled 22G, 1 ½-inch safety needle and a thin walled 22G, 1-inch safety needle).</td></tr>
<tr><td>Storage</td><td>Store at room temperature (25°C, 77°F): excursions between 15°C and 30°C (between 59° and 86°F) are</td></tr>
</table>

	permitted.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on February 26, 2015 using the terms, Invega to identify reviews previously performed by DMEPA.

C.2 Results

Our search did not identify any previous Label and Labeling Reviews for Invega Trinza. Although, for this review for Invega Trinza, recent previous Label and Labeling Reviews (Memos)[3] [4], as well as Postmarket Medication Error Review[5] for Invega Sustenna were reviewed and are referenced. Previous recommendations have been implemented or considered for Invega Sustenna. Some of these previous recommendations are reinforced in this review and recommendations for Invega Trinza.

APPENDIX D. HUMAN FACTORS STUDY

On January 30, 2015, DMEPA (along with CMC) submitted an Information Request (IR) to Janssen Pharmaceuticals, Inc. to clarify if a summative human factors study was conducted for the paliperidone palmitate extended-release injectable suspension (3-month injection) product. If so, DMEPA requested a summary of the findings from the formative human factors work, updated use risk analysis, and summative study results be submitted for our review. In addition we requested that Janssen submit a detailed summary of all use errors identified during their clinical development program as well as the training and other risk mitigation strategies that were implemented and specify how this was used to inform the use risk analysis and commercial product interface design. Finally, we requested that Janssen provide their rationale for why they believe all use-related risks associated with their product have been mitigated to an acceptable level and this product can be used safely and effectively if marketed.

Janssen's response dated February 6, 2015, included; responses to our questions from our IR dated January 30, 2015, Human Factors Summary Report, Human Factors Validation Report,

[3] Holmes L. Label and Labeling Review for INVEGA SUSTENNA (NDA 022264). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014OCT23. 10 p. OSE RCM No.: 2014-1014.

[4] Holmes L. Review of Revised Label and Labeling Review MEMO for INVEGA SUSTENNA (NDA 022264). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014NOV12. 4 p. OSE RCM No.: 2014-1014.

[5] Neupauer D. Postmarket Medication Error Review for INVEGA SUSTENNA (NDA 022264). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014OCT15. 28 p. OSE RCM No.: 2014-368.

Hazard Identification Report, Technical Document Risk Management, and Instructions for Use. This data, studies, and reports submitted were analyzed for this review.

D.1 Study Design

The Human factors engineering was performed in two stages:

Formative Study (July 2014) – conducted during the development phase to evaluate packaging and labeling options to optimize the differentiation of the new 3-month kits from the existing 1-month kits and to communicate the need for shaking of the syringe prior to injection. Usability of the product was evaluated by having healthcare (HCPs) prepare and administer the injections under simulated conditions. Effectiveness of the Instructions for Use (IFU) was also assessed in these studies.

Summative Study (October 2014) – performed on the optimized final design to assure all usability objectives have been met and that end users can safely and effectively select the proper kit, select the correct needle, and prepare and administer the injection in the appropriate injection site.

The development of the study protocol was guided by:

- FDA Draft Guidance for Industry and Food and Drug Administration Staff - Applying Human Factors and Usability Engineering to Optimize Medical Device Design (2011)
- Janssen experience with Invega Sustenna (1-month), a product that uses a highly similar pre-filled syringe ([redacted] (b) (4) suspension) kitted with two prepackaged hypodermic needles, and;
- Input from Human Factor experts at [redacted] (b) (4) who conducted the study on Janssen's behalf and have significant experience assessing prefilled syringes.

Formative Studies:

Design improvements were focused on assuring that the 3-month Kit can be readily distinguished from the 1-month kit by users. A comprehensive formative study was conducted with 24 healthcare providers (HCPs). HCPs were not trained on how to select and use the syringe prior to the study. They were tested for their ability to:

- Distinguish various cartons from the 1-month version of the product
- Select the proper needle size
- Prepare to inject patients of different weight at gluteal or deltoid areas.

In addition they were allowed to review the IFU and were probed on the clarity of the instructions. The study design is shown in Table 1:

Table 1 – Pal Pal 3M Formative Study Design

Study Factor	*HCPs*							
N-Value	N=24							
Training Condition	Untrained (N=24)							
Carton Label Design	Carton A (N=4)	Carton B (N=4)	Carton C (N=4)	Carton A (N=4)	Carton B (N=4)	Carton C (N=4)		
Syringe Label Design	Syringe Label A (N=12)			Syringe Label B (N=12)				
Injection Site	Deltoid (N=8)		Gluteal (N=4)		Deltoid (N=8)		Gluteal (N=4)	
Patient Weight	Under 200lbs (N=4)	Over 200lbs (N=4)	Under 200lbs (N=2)	Over 200lbs (N=2)	Under 200lbs (N=4)	Over 200lbs (N=4)	Under 200lbs (N=2)	Over 200lbs (N=2)
Needle Assignment	1" Pink (N=4)	1½" Yellow (N=8)			1" Pink (N=4)	1½" Yellow (N=8)		

In order to determine which carton design best allowed for recognition and differentiation of the product from the existing 1-month dose, three product cartons were produced and evaluated in the formative studies. These designs alternatives are shown below:

(b) (4)

Carton A **Carton B** **Carton C**

The study showed carton design C best allows the use to differentiate the 3-month kit from the 1-month kit and most effectively communicated the syringe need to be vigorously shaken for 15 seconds. This design was implemented for the final design.

In order to determine the best syringe label design that allows for effective preparation and mixing of the syringe, two syringe designs were produced and evaluated. These design

alternatives are shown below:

(b) (4)

Syringe Label A

(b) (4)

Syringe Label B

(b) (4)

The formative study showed that syringe B had the most effective icon related to the shaking of the syringe. During this study it was determined that none of the syringe label designs effectively communicate that the syringe is to be administered once every 3 months or the need to shake for the required 15 seconds. Label B was selected for the final design and (b) (4) was added to the syringe label.

Additionally the formative study tested participants' ability to prepare and inject the patients and 96% (23/24) of the participants were able to successfully administer the full dose of the drug using the 3-month kit (one participant accidentally expelled some of the syringe content prior to injection). Also the study evaluated the readability and effectiveness of the IFU. Several recommended changes were implemented to further optimize the readability of the IFU.

Human Factors Validation (Summative) Study

Validation of the Paliperidone Palmitate 2-Month Kit was performed after completion of design changes to address all issues uncovered during the formative studies. Below is the final design:

The validation study was performed by recruiting 15 HCP participants with 3 to 20 years of experience with Schizophrenic patient care from hospitals and care units around the San Francisco Bay Area. Participants had prior experience with the Invega Sustenna 1-month kit, but no experience with the new 3-month kit and were not provided any training on how to use the 3-month kits. The rationale for selecting HCPs with prior experience with Invega Sustenna1-month kit was the 3-month will be prescribed almost exclusively to patients who have been stabilized on the Invega Sustenna 1-month product and the 3-month dose would be administered by the same HCPs who were familiar with the Invega Sustenna 1-month kit (i.e., participants naïve to any Invega Sustenna use are not representative users).

The validation served two objectives:

1. Demonstrate that the 3-month kit, associated IFU, packaging and labeling can be safely and effectively prepared and used by intended users without patterns of preventable errors that would result in harm to a patient or user.
2. Demonstrate that the 3-month kit can be differentiated from the Invega Sustenna 1-month kit without difficulty by the intended user.

All critical tasks including selection of appropriate package, unpacking, review of IFU, selection of appropriate needle, preparation/mixing, injection of the dose and disposal were performed by each participant under simulated conditions. The Summative Validation Study Design is as follows:

Study Factor	HCPs			
N-Value	N=15			
Training Condition	Untrained (N=15)			
Study Sessions	Single 1/1 Session (N=15)			
Unaided Injections	Single Unaided Injection (N=15)			
Injection Site	Deltoid (N=10)		Gluteal (N=5)	
Patient Weight	135lbs (N=5)	260lbs (N=5)	135lbs (N=3)	260lbs (N=2)
Needle Assignment	1" Pink (N=5)	1½" Yellow (N=5)	1½" Yellow (N=8)	

The results of the Summative Validation Study (observed actions and knowledge probes) are as follows:

Tasks/Questions	HCPs (N=15)
Failure to Identify the Pal Pal 3M Kit	**0/15 (0%)**
Failure to separate Pal Pal 3M image cards from Invega Sustenna image cards	**0/15 (0%)**
Failure to Shake Syringe Vigorously	**0/15 (0%)**
Failure to Remove Rubber Cap From Syringe	**0/15 (0%)**
Failure to Select Correct Needle	**2/15 (13%)**
Failure to Attach Needle to Syringe	**0/15 (0%)**
Failure to Remove Needle Sheath	**0/15 (0%)**
Failure to Remove Air From Syringe	**0/15 (0%)**
Failure to Administer Full Dose of Drug	**0/15 (0%)**
Failure to Inject Within 5 Minutes of Shaking Syringe	**0/15 (0%)**
Failure to Secure Needle	**0/15 (0%)**
Failure to Dispose of Syringe Properly	**0/15 (0%)**
Needle Prick	**0/15 (0%)**
Bent Needle	**0/15 (0%)**
Syringe Tampering	**0/15 (0%)**
Failure state how long one must shake at minimum before injecting	**0/15 (0%)**
Failure to identify how many minutes one has to administer an injection after drug is shaken	**0/15 (0%)**
Failure to state proper disposal of unused needle	**0/15 (0%)**

100% (15/15) of the HCP participants were observed to have successfully prepared, mixed, and administered the full dose of the drug without hesitation or complication. No participants (0%, 0/15) stated that had any difficulty with any part of the preparation or injection process. In particular, participants notices and successfully executed the important step of mixing the drug by shaking vigorously.

Two of the fifteen participants selected the 1" needle instead on the 1 ½" needle when asked to inject a thin patient in the gluteus area. The risk level associated with this category of error is "medium" with the potential clinical consequence of a less effective dose than ideal. The actual clinical risk is even lower given that the assumed patient was slender and weighed 135 pounds. In this case, the selected 1" needle very likely would reach the same therapeutic area as intended by the 1 ½" needle. Yet, neither participant was referring to the IFU when choosing their needle and it was presumed that both relied on their normal clinical judgment and practice regarding the appropriate needle length for the patient weight and build provided to them. Accordingly, neither the kit components nor the labeling were directly implicated as a root cause. This use error was determined to have an acceptable residual risk based on the delivery of required dose, the low probability of potential injury, and the lack of feasible design changes to address this risk.

D.2 Results

A comprehensive formative study with 25 healthcare professionals validated improvements to the product package design, the syringe label and the IFU readability. The Sponsor determined that the final summative study showed that the user requirements for the 3-month kit were met and the product can safely and effectively identified, prepared and administered by the healthcare professionals to a patient's gluteal or deltoid muscles. The Instruction for Use for the 3-month kit was validated in this study as readable and easy to follow based on observations performed by Human Factors experts and in participant knowledge probes.

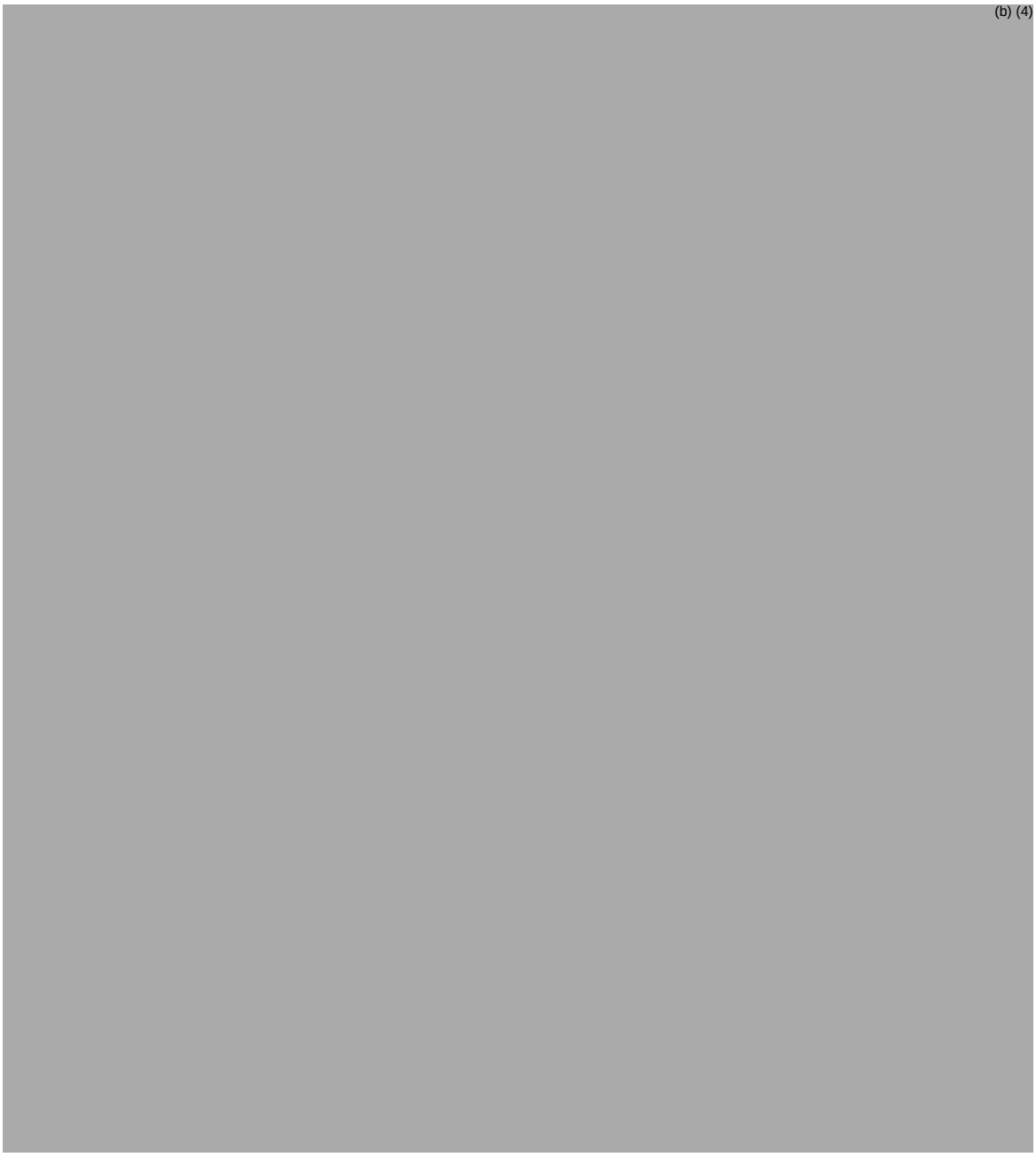
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[6] along with postmarket medication error data, we reviewed the following Invega Trinza labels and labeling submitted by Janssen Pharmaceuticals, Inc. on December 18, 2014 and February 13, 2015 (specific submission dates associated with each label are notated below in italics).

- Syringe labels (not to scale) *submitted December 18, 2014*

(b) (4)



[6] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

20 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEBORAH E MYERS
04/16/2015

DANIELLE M HARRIS
04/17/2015

IRENE Z CHAN
04/20/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: April 17, 2015
From: Kathleen FitzGerald, Nurse consultant WO66, RM2510
CDRH/ODE/DAGRID/GHDB
To: Christina Burkhart CDER/OND/ODEI
Subject: CDRH/ODE Device review for NDA 207946

1. Issue/Request from CDER:

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH) regarding NDA 207946. CDER states the 3-month paliperidone palmitate product will be 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 kit will contain a prefilled syringe and 2 safety needles (a thin walled 22G, 1 ½ inch safety needle and a thin walled 22G, 1-inch safety needle).The 3-month paliperidone palmitate formulation (PP3M) differs from the approved 1-month formulation (Invega Sustenna) in its (b) (4) and higher fill volume in order "to ensure a physically and chemically stable 3-month formulation that is easily resuspendable and minimizes injection force." (b) (4) for the 3-month formulation compared to the 1-month formulation, safety needles with a wider inner diameter (a 22G thin wall needle) were selected. Please evaluate proposed kit. CDRH has been consulted to review and provide feedback for the 3-month formulation container closure system.

2. Device Description:

DESCRIPTION OF THE DOSAGE FORM

Indication: Treatment of Schizophrenia in adult patients who have been adequately treated with the 1-month paliperidone palmitate injectable product for at least four months.

Paliperidone palmitate (R092670) eq. to (b) (4) mg/mL 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).

For commercial use, the paliperidone palmitate eq. (b) (4) mg/mL extended release suspension for injection (F015) will be provided in a prefilled syringe. Dosage strengths ranging from eq. 175 mg to eq. 525 mg are obtained by filling the syringes with

different volumes of the eq. (b) (4) mg/mL bulk suspension. A separate overfill has been determined for each dosage strength (refer to Drug Product Formulation Development section).

Table 2 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		

CONTAINER CLOSURE SYSTEM

The primary packaging system (plastic syringe with rubber plunger stopper) is selected based on the requirements that the container closure system needs to provide satisfactory protection for the drug product during storage, maintain product microbiological, chemical, and physical properties throughout its shelf life, and enable safe and accurate product delivery for human administration.

SYSTEM DESCRIPTION

For commercial distribution, the drug product will be packaged in a prefilled syringe.

The syringe will consist of the following packaging components:

- Transparent COC (Cyclic Olefin Copolymer) plastic syringe with integrated luer lock
- Dark gray bromobutyl rubber tip cap (connected to the syringe)
- Coated bromobutyl rubber plunger stopper

Three different sizes of syringes and 2 different sizes of rubber plunger stoppers will be used to package the different dosage strengths. The 1-mL Long syringe will be closed with a 1-mL Long plunger stopper, while the 2.25-mL and the 2.8-mL syringe will be closed with a 1-3-mL plunger stopper as outlined in Table 1.

In addition, a backstop will be assembled to the syringe. Two sizes of backstop will be used to accommodate the different syringe sizes. The small backstop will be clipped on the 1-mL Long syringe, while the large backstop will be clipped on the 2.25-mL and the 2.8-mL syringe as outlined in Table 1.

Table 1: Three Syringe Sizes and their Corresponding Plunger Stopper, Plunger Rod, and Backstop

Package	Syringe Size	Plunger Stopper	Plunger Rod Size	Backstop Size
1	1-mL Long	1-mL Long	1-mL Long	Small
2	2.25-mL syringe	1-3-mL	2.25-mL	Large
3	2.8-mL syringe	1-3-mL	3-mL	Large

Note that apart from the dimensions, the 3 different syringes and plunger rods and the 2 different plunger stoppers and backstops are identical.

Primary Packaging Components

Package Type	Description	Manufacturer	DMF[a]
1. Syringe	Transparent plastic (COC) syringe with integrated luer lock	(b) (4)	
a. (b) (4) b. Masterbatch	(b) (4)	(b) (4)	
2. Tip cap	Dark gray rubber tip cap		(b) (4)
a. Material	Bromobutyl rubber (b) (4) dark gray		
3. Plunger stopper[c]	Coated bromobutyl rubber plunger stopper		
a. Material	Bromobutyl rubber (b) (4) gray coated (b) (4)		
b. (b) (4)	(b) (4)		

[a] Letters of Authorization to cross refer to the respective DMFs are available in Module 1.

Secondary Packaging

The drug product commercial presentation will contain an assembled prefilled syringe (with plunger rod attached), a backstop and 2 types of commercially available needles: a 22 G thin walled, 1½ in. safety needle and a 22 G thin walled, 1 in. safety needle to provide the possibility for gluteal and deltoid injection.

The applicant states the 510(k) number for (b) (4) Safety Needles manufactured by (b) (4) and used in paliperidone palmitate 3-month formulation is (b) (4).

The following specific needs were taken into consideration during selection of the needles:

- Appropriate needle length (1-1½ in.) to allow for deltoid or gluteal injection.
- Appropriate outer needle diameter to minimize the pain without risk of needle breakage.
- Needle cannula with a minimum inner diameter of 0.44 mm (22 G thin walled

needle), according to ISO 9626 Amd 1: 2001 to assure adequate syringeability and injectability.
As active concentration (b) (4) are higher for the 3-month formulation compared to the 1-month formulation, safety needles with a wider internal diameter (a 22 G thin walled needle) were selected. The outer diameter remains identical to the largest needle in the approved paliperidone palmitate 1-month formulation (F013). This results in an injection force and penetration force (same outer needle diameter) that are close to those of the approved paliperidone palmitate 1-month formulation (F013).
The container closure system of the proposed 3-month formulation (F015) is based on the current 1-month extended release formulation (F013). Both formulations have a container closure system identical in design and operating principle. In order to accommodate the highest dose volume and the higher active concentration for the 3-month formulation (F015), the appropriate syringe length and the appropriate internal diameter of the needle cannula were selected.

A side-by-side comparison of the 1-month formulation (F013) container closure system and the 3-month formulation (F015) container closure system is presented in Table 1 (primary packaging components) and Table 2 (secondary packaging components

Comparison of Primary Components of the Container Closure System Used in the Approved Paliperidone Palmitate 1-Month Formulation (F013) (NDA 22264) and Paliperidone Palmitate 3-Month Formulation (F015).

Component Type	Component description		Justification/Rationale
	1month formulation (F013)	3-month formulation (F015)	
Syringe	Transparent plastic (COC) syringe with integrated luer lock. 3 Syringe Sizes for commercial use Syringe Sizes: 0.5-mL 1-mL Long 2.25-mL	Transparent plastic (COC) syringe with integrated luer lock. 3 Syringe Sizes for commercial use Syringe Sizes: 1-mL Long 2.25-mL 2.8-mL	The syringes used are identical in composition, design, and operating principle for both formulations. The same materials of construction and supplier are used for both products. The smallest syringe size (0.5-mL syringe) is not used for the 3-month formulation as the minimum dose volume is 0.875 mL. The same 1-mL Long and 2.25-mL syringes are used for both formulations. The largest syringe size (2.8-mL syringe) is used only for the 3-month formulation to deliver the maximum dose volume of 2.625 mL. The 2.8-mL syringe has the same diameter as the 2.25-mL syringe, and only differs in length.

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Tip Cap	Dark gray Bromobutyl rubber tip cap	Dark gray Bromobutyl rubber tip cap	The tip cap is identical for both formulations.
Plunger Stopper	Coated bromobutyl rubber plunger stopper. 2 Plunger Stopper Sizes for commercial use Plunger Stopper Sizes: 1-mL Long 1-3-mL	Coated bromobutyl rubber plunger stopper. 2 Plunger Stopper Sizes for commercial use Plunger Stopper Sizes: 1-mL Long 1-3-mL	The plunger stoppers used are identical for both formulations. The 1-mL Long plunger stopper is used with the 0.5-mL and 1-mL Long syringes. The 1-3-mL plunger stopper is used with the 2.25-mL and 2.8-mL syringes.
Plunger Rod	White (b) (4) plunger rods	White (b) (4) plunger rods 3 Plunger Rods Sizes for commercial use	

Table 2: Comparison of Secondary Components of the Container Closure System Used in the Approved Paliperidone Palmitate 1-Month Formulation (F013) (NDA 22264) and Paliperidone Palmitate 3-Month Formulation (F015).

Component	Component		Justification/Rationale
	1-month formulation (F013)	3-month formulation (F015)	
Plunger Rod	White (b) (4) plunger rods 2 Plunger Rods Sizes for commercial use Plunger Rod sizes: 1-mL Long 2.25-mL	White (b) (4) plunger rods 3 Plunger Rods Sizes for commercial use Plunger Rod sizes: 1-mL Long 2.25-mL 3-mL	The plunger rods used are identical in composition, design, and operating principle for both formulations. The same materials of construction and supplier are used for both products. The 3-mL plunger rod is used only for the 3-month formulation in combination with the 2.8-mL syringe.

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Backstop	Backstop Small Large CBE-30 submitted 3rd October 2014 to include backstop as a packaging component.	Backstop Small Large	The backstops are identical for both formulations. The small backstop is used with the 0.5-mL and 1-mL Long syringes. The large backstop is used with the 2.25-mL
Safety needle	22G, regular walled 1 ½ in. safety needle, grey hub 23G, regular walled 1 in. safety needle, blue hub	22 G thin walled, 1½ in. safety needle, cream hub 22 G thin walled, 1 in. safety needle, pink hub	The safety needles are (b) (4) safety needles and are of the same composition, design, operating principle, and length for both formulations. To dose the more concentrated 3-month formulation, a 22G thin walled needle is used. The selection of 22G thin walled needles for the 3-month formulation results in a similar injection force compared to the regular walled needles used in the 1-month formulation. Specific hub colors are used to differentiate the needles.

Tests have been performed in order to demonstrate comparabiiity between 22 G thin walled (b) (4) safety needles used during ciinical phase 3 testing of the paliperidone palmitate 3-month formulation (F015) and the 22 G thin walled (b) (4) safety needles to be used in the commercial kit.

The critical dimensional parameters to establish comparability of the needles are:

- the internal diameter of the cannula, a parameter that can influence the injectability force and thus the flow or speed of administration of the product;
- the free length, a parameter that influences the deposition site of the product;
- the outer diameter of the cannula, a parameter that can influence the pain sensation during administration of the product.

Functionality During Administration

The functional suitability of the kitted associated components (pre-package, presterilized intramuscular needles) has been assessed in testing with the pre-filled syringe based on recognized ISO standards.

The connection between the needle and the syringes has been qualified through:

- Measurement of detachment torque after attaching the needle to the syringe luer fitting with a torque of 0.12 Nm as per ISO 594. In tests of 20 sets, the measured detachment torque were greater than (b) (4) Nm for all samples, demonstrating conformance to this standard.
- Measurement of the axial separation force between needle and syringe in sets of

6

10 samples to confirm that the connection can withstand a force exceeding 35 N as per ISO 594-2.

Further testing also confirmed that the tip cap of the syringe luer can be removed with an average torque of (b) (4) Nm and maximum (b) (4) Nm which is well below (b) (4) Nm which provides both adequate storage security of the seal and easy removal by the user according to the supplier's (b) (4) information. The needle safety shield that is applied by the user following the injection can be activated with forces below (b) (4) N, which confirms that the shield can be activated with one finger as described in the IFU.

The plunger stopper cannot be pulled out from rear of the syringe with forces of at least (b) (4) N, confirming the suitability of the backstop feature as protection against a user inadvertently pulling back on the plunger handle at a force greater than the stopper breakloose force.
Transportation simulation testing has demonstrated that the plunger rod and backstop will not separate from the syringe during shipment.
Plunger/stopper break loose and travel forces with the suspension and with the new thin walled needle are reported in section 1.2, and demonstrate that the expected hand forces used for this product are similar to the approved 1-month paliperidone palmitate formulation (F013) with typical values between (b) (4) N and raise no new usability questions.

3. **Documents Reviewed:**
ICC1400765 consult request
NDA 207946-container closure system
FDA 510(k) Database (b) (4) (Listed as (b) (4) Safety Needle not (b) (4))

4. **CDRH Review and Comments:**
This review was limited to the proposed prefilled syringe and safety needles.

The Applicant states that the syringes used in the 3 month formulation are identical to the approved 1 month formulation except for a larger syringe size to accommodate for the larger drug volume.

Due to the active concentration (b) (4) are higher for the 3-month formulation compared to the 1-month formulation, safety needles with a wider internal diameter (a 22 G thin walled needle) were selected.

The Applicant has completed acceptable performance testing on the needle and syringe connectivity in accordance to ISO 594-1 & 2. The Applicant has also referenced and complied with ISO 7864 and 9626 for hypodermic needle specifications and requirements.

The Applicant has provided adequate sterilization data, test reports and validation test reports on the plastic syringe used in the container closure system. I was unable to

determine if testing was completed to confirm sterility of the syringe fluid path upon exiting the primary syringe closure.

The Applicant stated that the manufacturer of the syringes (b) (4) has confirmed that all syringes meet:

☐ Syringe Body (COC):
☐ USP <88> Biological Test for Plastics, Class VI
☐ USP <661> Physicochemical Tests - Plastics
(b) (4)
☐ Tip Cap (rubber):
☐ Ph. Eur. 3.2.9 Rubber Closures for Containers for Aqueous Parenteral Preparations, for Powders and for Freeze-Dried Powders
☐ USP <87>: Biological Reactivity
☐ USP <381>: Elastomeric Closures for Injections, Physicochemical Test Procedures

A copy of the Letter of Authorization allowing the FDA access to the Type III DMF (b) (4) held by (b) (4) pertaining to the plastic syringes is provided in Module 1.

The Applicant was asked by CDRH to provide a list of any adverse events with the 1 month formulation container closure system and to describe the corrective actions taken.

The applicant provided a detailed chart listing the adverse events and the following actions associated with the design related adverse events which have led to improvement in the design of the container closure system for paliperidone palmitate 3-month, have been implemented:

- (b) (4) parameters for the needles used for 1-month paliperidone palmitate product were adjusted to improve the durability of luer fitting of the needle when attached to the syringe; luer brittleness had been potentially associated with luer-to-needle leakage and cracked needle hubs. This corrective action has been applied to the 3-month paliperidone palmitate product.
- The injection molded syringe barrel was improved for dimensional tolerances (roundness) of its luer fitting. This also addresses connection leakage and needle hub cracking, and this change has been incorporated into the 3-month paliperidone palmitate product.
- The IFU for the paliperidone palmitate 1-month includes revised figures that depict the backstop, as submitted in the above CBE-30. The IFU layout and content for the 3-month product have been validated in the paliperidone palmitate 3-month Human Factors Study, and should further reduce use errors. All feasible corrective actions have been made to both the paliperidone palmitate 3-month and the paliperidone palmitate 1-month container closure systems to address known and confirmed adverse events. The corrective actions implemented for the paliperidone palmitate 1-month product and corrective measures applied during development program of paliperidone palmitate 3-month product, the bench test data submitted for paliperidone palmitate 3-month product, and clinical study data

for the paliperidone palmitate 3-month product, together support its safe and effective use.

CDRH Biocompatibility review was completed by Dr. Honggang Wang. Dr. Wang had some deficiencies but they have been deemed not necessary for the Applicant to address. Dr. Wang was not clear as to his scope of the biocompatibility review. The leachable deficiencies he identified will be addressed by CDER and the needle biocompatibility questions will be addressed in the 510(k) submission. There are no outstanding biocompatibility deficiencies from CDRH/ODE.

5. **Communication with the Applicant:**

- The Applicant was contact by email on January 21, 2015 via Ann Sohn and asked 1 question from CDRH:

1. Please send us a side by side comparison of the current device 1 month formulation container closure system and the proposed device 3 month container closure system. Please specify any changes that have been made to the proposed container closure system and a rationale for those changes.
The Applicant's response was adequate.

- The Applicant was contacted by email on February 12, 2015 via Ann Sohn and asked 2 question from CDRH:

1. If applicable, please provide the 510(k) numbers for the safety needles used in the 3-month formulation.
The Applicant stated that the 510(k) number was (b) (4) Safety needle.
In the FDA 510(k) database it does not state this. The Sponsor will be asked to clarify.
2. You have stated that the container closure system of the proposed 3-month formulation is based upon the current 1-month extended release formulation. If applicable, please provide any adverse event reports and corrective actions for the current 1-month formulation container closure system.
The Applicant's response was adequate.

6. Recommendation:
Please provide the following recommendations to the Applicant.

You have not provided adequate information regarding the performance of the device constituent parts of the pre-filled syringe combination products. The Agency expects that you will provide all necessary information to support the safety and functionality of the constituent parts. Please provide the requested additional information:

1. You state that the safety needle in the container closer system is the (b) (4) Safety Needle cleared under 510(k) (b) (4). In the FDA 510(k) database the needle cleared under (b) (4) is listed as (b) (4) Safety Needle. Please clarify and resolve this discrepancy. In addition, please provide a Letter of Authorization from the company stating that you have authorization to use and access (b) (4) device information.

Applicant's Response:
The (b) (4) Safety Needle listed under 510(k) (b) (4) are the same needles as the (b) (4) Safety Needle, which is the trade name of the (b) (4) Safety Needle manufactured by (b) (4) (Attachment 1). (b) (4) was acquired by (b) (4), previously known as (b) (4), and as such, (b) (4) brands became part of (b) (4). The history of the company and overview of (b) (4) safety products is provided in Attachment 2.

The Letter of Authorization issued by (b) (4) for reference to 510 (k) (b) (4) is provided in Attachment 3.

CDRH's Discussion: The Applicant's response is adequate.

2. In sections 3.2.P.7 and 3.2.P.2.4 you have provided a brief overview of the performance testing completed on the needle and syringe connectivity. In addition, you state the syringe materials, composition, design, and operating principle for both the 1 month and 3 month formulations are identical. You have not provided performance bench testing data and reports for the 1 month or 3 month syringes used in the container closure system. Please provide all performance elements and performance bench test reports for the container closure system.

Applicant's Response:
As per Janssen response to the FDA information request dated 22 January 2015, it was noted that the container closure system of the proposed 3-month formulation (F015) is based on the currently marketed 1-month INVEGA SUSTENNA extended release formulation (NDA 22-264, formulation F013). The packaging components of both formulations are made of identical materials that have a long history of safe use based on the marketing experience of INVEGA SUSTENNA, approved by the FDA on 31 July 2009.
In this response Janssen is providing bench test reports for paliperidone palmitate 3-month formulation (F015) to supplement the test data and results previously reported in NDA 207-946 section 3.2.P.2.4, which included needle to syringe detachment torque force, axial separation force, tip cap removal torque, needle safety shield activation forces, plunger rod withdrawal protection force, needle internal/external diameter and free length and characterization data on injectability force (piston travel forces) in the representative paliperidone palmitate 3-month formulation (F015). Needle internal/external diameter and free length and characterization data on injectability force (piston travel forces), are summarized in report DS-VAL-82061 (Attachment 4).
Based on design verification activities, the full set of performance elements for the container closure system which are verified by bench testing are:
- Torque to unseal the tip cap: not more than (b) (4) Nm.
- Torque required to detach the needles from the syringe: not less than (b) (4) Nm.

□ Needle safety shield activation force: not more than [redacted]N.
□ Leakage between syringe and needle: no leaks (determined by displacement) with an applied syringe plunger force of [redacted]N for [redacted]s ([redacted]N for 1 mL Long syringe).
□ Needle hub crack: not more than [redacted]n [redacted]ested crack (Custom worst case test to discriminate potential weaknesses).
□ Syringe-needle separation force testing: no separation at [redacted]N for [redacted]s.
□ Injectability force: will not exceed [redacted]N for the 2.25 mL and 2.8 mL syringe and [redacted]N for 1 mL Long syringe.
The Design Verification Test Reports DS-TEC-59003 (Part I) and DS-TEC-59943 (Part II) for paliperidone palmitate 3-month formulation (F015) are provided in Attachment 5 and Attachment 6, respectively.
The Design Verification Test Report DS-TEC-59003 (Part I) describes the following parameters tested for paliperidone palmitate 3-month formulation (F015) kit:

□ Verification of torque to unseal the tip cap. i.e., removal of the tip cap from the syringes.
□ Verification of the torque required to detach the needles from the syringe force.
□ Verification of the needle safety shield activation.
The Design Verification Test Report DS-TEC-59943 (Part II) describes the following parameters tested for paliperidone palmitate 3-month formulation (F015) kit:
□ Verification of absence of leakage between syringe and needle.
□ Verification of needle hub crack under extreme conditions.
□ Verification of syringe-needle separation force.
The data on injectability force is provided in report DS-TEC-58005 and included in Attachment 7.

All tested devices passed the predetermined acceptance criteria.

CDRH's Discussion: The Applicant's response is adequate.

3. Within your description of verification activities, you do not appear to list testing which demonstrates that the device constituent part of the combination product will meet essential performance elements after pre-conditioning to aging. The Agency expects that you will include information verifying the device components will perform as expected after aging.

Applicant's Response:
The [redacted] needles and [redacted] syringe barrels are being assessed for the effects of aging using functional stability indicating parameter tests associated with dimensional changes and brittleness that could impact interconnection security and essential performance elements.
Samples of the needles and syringes are under examination for the following essential performance elements after aging:

- Torque to unseal the tip cap.
- Torque required to detach the needles from the syringe.
- Leakage between syringe and needle.
- Needle hub crack.
- Leakage of tip cap on syringe barrel.
- Syringe–needle separation force.
- Injectability force testing.

Accelerated aging storage conditions at elevated temperatures are being employed to simulate long term storage conditions.
The data on the tests performed is expected to be available the week of April 13th. Note that the data on injectability force is provided in report DS-TEC-58005, in Attachment 7, and includes sample product lots aged between 22 and 27 months.

April 17, 2015 Response with test reports:
A summary of the results for the testing of the Paliperidone Palmitate 3-month device components is provided below. The data demonstrate that the device components meet the criteria of essential performance elements and confirm the components will perform as expected after aging.
The device components of Paliperidone Palmitate 3-month formulation (F015) were either stored for at least 24 months at room temperature or have been aged at 50 degrees C, simulating at least 2 years of shelf life. The following test results are outlined in this response:

- Torque to unseal the tip cap
- Torque required to detach the needles from the syringe
- Leakage between syringe and the needle
- Needle hub crack
- Leakage of tip cap on syringe barrel
- Syringe needle separation force
- Injection force

The device components listed in Table 1 and Table 2 have been used to perform the tests as required by protocol DS-TEC-58643. The component samples were taken from the representative commercial batches, placed on stability at 50 degrees C on July 29, 2014 and pulled out of the stability chamber on February 25, 2015. The component samples were stored for a total of 211 days at 50 degrees C which corresponds to 27 months at 30 degrees C (Calculated according to ASTM F1980-07 with ambient temperature 30 degrees C, (b) (4)).

The tests of the aged components demonstrate that the effects of aging likely to be encountered over the shelf life of the product will have no significant effect on product performance or safety, and, where applicable, will continue to meet recognized (e.g., ISO) acceptance criteria for connection security and leakage.

CDRH's Discussion: The Applicant has provided the requested test reports and the response is adequate.

Recommendation: The Applicant has adequately responded to all requests for additional information. I have no additional recommendations or deficiencies for the Applicant.

Please contact Kathleen FitzGerald at (301) 796 – 6292, if you have any questions.

Digital Signature Concurrence Table		
Reviewer Sign-Off	Kathleen E. Fitzgerald -S	Digitally signed by Kathleen E. Fitzgerald -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0010093027, cn=Kathleen E. Fitzgerald -S Date: 2015.04.17 12:00:49 -04'00'
Team-Leader Sign-Off	FDA	Digitally signed by Keith G. Marin -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Keith G. Marin -A, 0.9.2342.19200300.100.1.1=0011250397 Date: 2015.04.17 13:43:02 -04'00'
Branch Chief Sign-Off		Digitally signed by Richard C. Chapman -S Date: 2015.04.17 21:40:11 -04'00'
Division Sign-Off		

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: **April 13, 2015**

To: Ann Sohn, PharmD
Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: Susannah K. O'Donnell, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 207946**
INVEGA TRINZA™ (paliperidone palmitate) extended-release injectable suspension

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OPDP has reviewed the draft product labeling (PI) and patient package insert (PPI) for INVEGA TRINZA™ (paliperidone palmitate) extended-release injectable suspension (Invega Trinza) as requested in the consult from DPP dated December 16, 2014.

OPDP's comments on the draft PI for Invega Trinza are based on the version provided by Ann Sohn via email on April 3, 2015. Combined OPDP and Division of Medical Policy Programs (DMPP) comments on the proposed PPI were provided to DPP on April 10, 2015.

If you have any questions, please feel free to contact me by phone at 301-796-3245 or by email at Susannah.ODonnell@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments on these materials. Thank you!

85 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

SUSANNAH O'DONNELL
04/13/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	April 9, 2015
To:	Mitchell Mathis, MD Director **Division of Psychiatry Products (DPP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Melissa Hulett, MSBA, MSN, FNP-BC, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Twanda Scales, RN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Susannah O'Donnell, MPH Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	INVEGA TRINZA (paliperidone palmitate)
Dosage Form and Route:	extended-release injectable suspension, for intramuscular use
Application Type/Number:	NDA 207946
Applicant:	Janssen Research & Development, LLC (Janssen)

1 INTRODUCTION

On November 18, 2014, Janssen Pharmaceutical Inc., submitted for the Agency's review an Original New Drug Application (NDA-207946) for INVEGA TRINZA (paliperidone palmitate) extended-release, injectable suspension. INVEGA TRINZA (paliperidone palmitate) extended-release, injectable suspension is indicated for the treatment of schizophrenia in patients who have been adequately treated with the 1-month paliperidone palmitate extended-release injectable suspension INVEGA SUSTENNA for a least four months.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry Products (DPP) on March 9, 2015, and December 16, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for INVEGA TRINZA (paliperidone palmitate) extended-release, injectable suspension.

2 MATERIAL REVIEWED

- Draft INVEGA TRINZA (paliperidone palmitate) extended-release, injectable suspension PPI received on November 18, 2014, and received by DMPP on April 4, 2015.
- Draft INVEGA TRINZA (paliperidone palmitate) extended-release, injectable suspension PPI received on November 18, 2014, and received by OPDP on April 3, 2014.
- Draft INVEGA TRINZA (paliperidone palmitate) extended-release, injectable suspension Prescribing Information (PI) received on November 18, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on April 4, 2015.
- Draft INVEGA TRINZA (paliperidone palmitate) extended-release, injectable suspension Prescribing Information (PI) received on November 18, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on April 3, 2014.
- INVEGA SUSTENNA (paliperidone palmitate) extended-release, injectable suspension comparator labeling dated November 12, 2014.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

5 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

TWANDA D SCALES
04/09/2015

SUSANNAH O'DONNELL
04/10/2015

MELISSA I HULETT
04/10/2015

LASHAWN M GRIFFITHS
04/10/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 02/24/2015

TO: Ann Sohn, Regulatory Project Manager
Christina Burkhart, M.D., Clinical Reviewer
Lucas Kempf, M.D., Team Leader
Division of Psychiatry Products (DPP)

FROM: Jenn W. Sellers, M.D., Ph.D., F.A.A.P.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 207946

APPLICANT: Janssen Pharmaceuticals, Inc.

DRUG: Paliperidone Palmitate Extended-Release 3-Month Injection (b) (4)

NME: Yes

REVIEW: Priority Review

INDICATION: Schizophrenia

CONSULTATION REQUEST DATE: 12/19/2014

INSPECTION SUMMARY GOAL DATE: 03/25/2015

PDUFA DATES: 05/18/2015

I. BACKGROUND

This original NDA 207946 included a randomized withdrawal study (Protocol R092670-PSY-3012) of paliperidone palmitate extended-release 3-month injection (PP3M) for the treatment of schizophrenia in adult patients who have been adequately treated with paliperidone palmitate 1-month injection (PP1M) for at least four months.

Paliperidone palmitate is an atypical antipsychotic that was initially approved in the United States (U.S.) in 2006 for the treatment of schizophrenia. It is the palmitate ester of paliperidone. Paliperidone is an antagonist of dopamine type 2 (D_2) and serotonin (5-hydroxytrptamine [5- HT]) type 2A ($5HT_{2A}$).

The sponsor submitted the following study in support of the application: Protocol R092670-PSY-3012 entitled, "*A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3-Month Formulation for the Treatment of Subjects with Schizophrenia*."

Protocol R092670-PSY-3012 was a double-blind, placebo-controlled, randomized withdrawal study in schizophrenia patients aged 18 to 70 years to evaluate the efficacy and safety of PP3M in the prevention of relapse of schizophrenia. The study consisted of the following phases: a Screening Phase (up to 3 weeks); an Open-label Phase (a 17-week flexible-dose Transition Phase and a 12-week fixed-dose Maintenance Phase); and a randomized, double-blind, fixed dose, placebo-controlled relapse prevention Phase. Eligible subjects started the Open-label Transition Phase with the treatment of flexible dose PP1M (50, 75, 100, or 150 mg equivalents) for 17 weeks. Those subjects who completed the Transition Phase and met the prospectively defined criteria entered the Open-label Maintenance Phase with the treatment of a single injection of PP3M at the start of the 12-week Maintenance Phase (Day 120/Week 17).

Eligible subjects were randomly assigned, in a 1:1 ratio, to receive either a fixed dose of PP3M or placebo at the start of the Double-blind Phase (Day 204/Week 29). Subjects assigned to PP3M received the same dose of study agent that was administered on Day 120 of the Maintenance Phase. The dose was to remain fixed throughout the Double-blind Phase.

Subjects remained in the Double-blind Phase until they experienced a relapse event (based on prospectively defined criteria), they met one or more of the study discontinuation/withdrawal criteria, or the study was terminated by the sponsor based on positive results of the interim analysis or because 70 relapse events had occurred when interim analysis was not positive. The study primary efficacy measurement was the time from randomization to first relapse in the Double-blind Phase. The date of relapse was the date of the first assessment for symptoms of relapse.

The sponsor's efficacy analyses showed that PP3M was superior to placebo in delaying relapse of symptoms of schizophrenia in subjects who had achieved satisfactory symptom control during the Open-label Phase.

The Division of Psychiatry Products (DPP) requested inspections of the following clinical investigator sites based primarily on large subject enrollment.

II. RESULTS (by Site):

Name of Clinical Investigator Location	Protocol Study Site Number of Subjects Enrolled (n)	Inspection Date	Classification*
Jason Bermak, M.D., Ph.D. SF-CARE Inc. 1330 Lincoln Avenue, Suite 308 San Rafael, CA 94901	R092670-PSY-3012 Site 001933 N = 14	01/20/2015 to 01/22/2015	NAI
John Sonnenberg, Ph.D. Uptown Research Institute, LLC. 1021 West Lawrence Avenue Chicago, IL, 60640	R092670-PSY-3012 Site 001970 N = 15	02/05/2015 to 02/11/2015	Preliminary: NAI
Ronald Brenner, M.D. Neurobehavioral Research, Inc. 74 Carman Avenue Cedarhurst, NY, 11516	R092670-PSY-3012 Site 001971 N = 20	02/10/2015 to 02/12/2015	Preliminary: NAI

*Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Deviation(s) from regulations. Data acceptable
OAI = Significant deviations from regulations. Data unreliable
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. **Jason Bermak, M.D., Ph.D.**
   1330 Lincoln Avenue, Suite 308, San Rafael, CA 94901

   a. **What was inspected**: At this site, 21 subjects were screened, 14 subjects were enrolled, 8 were randomized, and 6 subjects completed the study. A complete review of all 14 enrolled subjects' records was conducted. Partial 3 screen failure subject records were also reviewed.

   b. **General observations/commentary:** No discrepancies were found between the source data and the data submitted by the sponsor. No significant regulatory violations were noted, and no Form FDA 483 (List of Inspectional Observations) was issued.

   c. **Assessment of data integrity**: The study appears to have been conducted adequately, and data generated by this site appear acceptable in support of the respective indication.

2. **John Sonnenberg, Ph.D.**
   1021 West Lawrence Avenue, Chicago, IL, 60640

   a. **What was inspected**: At this site, 17 subjects were screened, 2 subjects were considered screen failures, 15 were enrolled, and 13 subjects completed the study. An audit of all 15 enrolled subjects' records was conducted. In addition, the regulatory binder including the site training logs, monitoring visit logs, test article logs, delegation

of authority logs, sponsor correspondence and IRB correspondence, and temperature and calibration logs was reviewed.

b. **General observations/commentary:** No significant regulatory violations were noted, and no Form FDA 483 was issued. The source data including Baseline data, lab results, and AEs were compared to the data submitted by the sponsor and no major discrepancies were found.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. **Ronald Brenner, M.D.**
74 Carman Avenue, Cedarhurst, NY, 11516

a. **What was inspected:** At this site, 22 subjects were screened, 20 were enrolled, and 10 completed the study (3 subjects relapsed and 7 were terminated by the Sponsor). A 100% review of all screened subjects was conducted in the following areas: informed consent form, primary endpoint, protocol procedures, and AEs. Seventy-five percent (75%) of randomized subjects' records for the study were reviewed for additional protocol adherence. A random review was conducted for the following documents: protocol deviations, randomization, concomitant medications, study inclusion/exclusion, lab results, and blinding procedures. A review of 33% of subjects was conducted on test article accountability.

b. **General observations/commentary:** No significant regulatory violations were noted and no Form FDA 483 was issued. There were no major deviations noted during review of records. The primary efficacy endpoint data were verifiable and there was no evidence of under-reporting of AEs.

c. **Assessment of data integrity:** The study appears to have been conducted adequately and data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigator sites were inspected in support of this NDA and no significant regulatory violations were noted at these sites.

Based on results of these inspections, it appears that the data submitted by the Applicant in support of the requested indication are acceptable and the studies appear to have been conducted adequately.

Note: Final classification for Drs. Sonnenberg and Brenner are pending and will be determined when the final EIR and associated exhibits are received and/or reviewed. An addendum to this clinical inspection summary will be forwarded to DPP should there be a change in the final classification.

{See appended electronic signature page}

Jenn W. Sellers, M.D., Ph.D., F.A.A.P.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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/s/

JENN W SELLERS
02/25/2015

SUSAN D THOMPSON
02/25/2015

KASSA AYALEW
02/25/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

<table>
<tr><th colspan="3">Application Information</th></tr>
<tr><td>NDA # 207946
BLA#</td><td>NDA Supplement #: S-
BLA Supplement #: S-</td><td>Efficacy Supplement Category:
☐ New Indication (SE1)
☐ New Dosing Regimen (SE2)
☐ New Route Of Administration (SE3)
☐ Comparative Efficacy Claim (SE4)
☐ New Patient Population (SE5)
☐ Rx To OTC Switch (SE6)
☐ Accelerated Approval Confirmatory Study (SE7)
☐ Animal Rule Confirmatory Study (SE7)
☐ Labeling Change With Clinical Data (SE8)
☐ Manufacturing Change With Clinical Data (SE9)
☐ Pediatric</td></tr>
<tr><td colspan="3">Proprietary Name:
Established/Proper Name: paliperidone palmitate
Dosage Form: extended-release injectable suspension
Strengths: 273 mg, 410 mg, 546 mg, 819 mg</td></tr>
<tr><td colspan="3">Applicant: Janssen Pharmaceuticals, Inc.
Agent for Applicant (if applicable): Beth Geter-Douglas</td></tr>
<tr><td colspan="3">Date of Application: 11/18/14
Date of Receipt: 11/18/14
Date clock started after UN:</td></tr>
<tr><td colspan="2">PDUFA Goal Date: 5/18/15</td><td>Action Goal Date (if different):</td></tr>
<tr><td colspan="2">Filing Date: 1/17/15</td><td>Date of Filing Meeting: 12/15/14</td></tr>
<tr><td colspan="3">Chemical Classification (original NDAs only) :
☐ Type 1- New Molecular Entity (NME); NME and New Combination
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
☐ Type 3- New Dosage Form; New Dosage Form and New Combination
☐ Type 4- New Combination
☒ Type 5- New Formulation or New Manufacturer
☐ Type 7- Drug Already Marketed without Approved NDA
☐ Type 8- Partial Rx to OTC Switch</td></tr>
<tr><td colspan="3">Proposed indication(s)/Proposed change(s): schizophrenia/new 3 month formulation</td></tr>
<tr><td colspan="2">Type of Original NDA:
AND (if applicable)
Type of NDA Supplement:

If 505(b)(2): Draft the “505(b)(2) Assessment” review found at:
http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</td><td>☒ 505(b)(1)
☐ 505(b)(2)
☐ 505(b)(1)
☐ 505(b)(2)</td></tr>
</table>

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☒ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☒ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 76952	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking***	☒	☐		

system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☐ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted	☐	☒		

questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: (b) (4) ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	

NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		

Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and*	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☐		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☒	☐	Applicant states it will be submitted separately
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	CDRH
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

End-of Phase 2 meeting(s)? **Date(s):** 11-4-11, 12-8-11 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 7-24-14 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 12-15-14

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Ann Sohn	Y
	CPMS/TL:	Keith Kiedrow	N
Cross-Discipline Team Leader (CDTL)	Lucas Kempf		Y
Division Director/Deputy	Mitch Mathis/Tiffany Farchione		Y/N
Office Director/Deputy			
Clinical	Reviewer:	Christina Burkhart	Y
	TL:		
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Kofi Kumi	Y
	TL:	Hao Zhu	Y
Biostatistics	Reviewer:	Yang Wang	Y
	TL:	Peiling Yang	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Elzbieta Chalecka-Franaszek	N
	TL:	Aisar Atrakchi	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for protein/peptide products only)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	David Claffey	N
	TL:		
Biopharmaceutics	Reviewer	Salaheldin Hamed	N
	TL:	Angelica Dorantes	N
Quality Microbiology	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Loretta Holmes	Y
	TL:	Irene Chan	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO

• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (protein/peptide products only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> • Was the Microbiology Team consulted for validation of sterilization? **Comments**:	☐ Not Applicable ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Mitch Mathis

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V):

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60
☒	If priority review:

	• notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN J SOHN
12/16/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 207946

Application Type: New NDA

Name of Drug/Dosage Form: (paliperidone palmitate) extended-release injectable suspension

Applicant: Janssen Pharmaceuticals, Inc.

Receipt Date: November 18, 2014

Goal Date: May 18, 2015

1. Regulatory History and Applicant's Main Proposals

Application proposes new 3-month extended release product.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by February 20, 2015. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *Waiver has not been granted*

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required

Selected Requirements of Prescribing Information

• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 36. In the BW, all text should be **bolded**.

Comment:

YES 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN J SOHN
12/16/2014