

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207946Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 207946

SUPPL # O-1

HFD # 130

Trade Name Invega Trinza

Generic Name paliperidone palmitate

Applicant Name Janssen Pharmaceuticals, Inc.

Approval Date, If Known 5/18/15

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

(b) (4)

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 22264

paliperidone palmitate

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.) **NA**

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

**PSY-3012:** Randomized, double-blind, parallel group, multicenter noninferiority study of 48 weeks duration preceded by a 17-week, open-label stabilization phase with PP1M

**PSY-1005:** Randomized, single-dose, open-label, parallel group, multicenter study consisting of 4 panels, with each panel including 2 single dose treatment periods. In each panel the single dose of PP3M was followed by a 364- to 544-day observation period for PK and safety evaluations.

**PSY-3011** (Ongoing--blinded safety data submitted to support exposure for safety): Randomized, double-blind, parallel group, multicenter noninferiority study of 48 weeks duration preceded by a 17-week, open-label stabilization phase with PP1M.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO   
Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

**PSY-3012:** Randomized, double-blind, parallel group, multicenter noninferiority study of 48 weeks duration preceded by a 17-week, open-label stabilization phase with PP1M

**PSY-1005:** Randomized, single-dose, open-label, parallel group, multicenter study consisting of 4 panels, with each panel including 2 single dose treatment periods. In each panel the single dose of PP3M was followed by a 364- to 544-day observation period for PK and safety evaluations.

**PSY-3011** (Ongoing--blinded safety data submitted to support exposure for safety): Randomized, double-blind, parallel group, multicenter noninferiority study of 48 weeks duration preceded by a 17-week, open-label stabilization phase with PP1M.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
IND # 76952 YES  ! NO   
! Explain:

Investigation #2 and #3 !  
IND # 76952 YES  ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? **NA**

Investigation #1 !  
! YES  ! NO   
! Explain: ! Explain:

Investigation #2 !  
! YES  ! NO   
! Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

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Name of person completing form: Ann Sohn  
Title: Regulatory Project Manager

Date: 5/18/15

Name of Office/Division Director signing form: DPP/Mitchell Mathis  
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANN J SOHN  
05/18/2015

MITCHELL V Mathis  
05/18/2015

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 207946 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Invega Trinza Established/Proper Name: paliperidone palmitate 3 month Dosage Form: extended-release injectable suspension		Applicant: Janssen Pharmaceuticals, Inc. Agent for Applicant (if applicable): Beth Geter-Douglass
RPM: Ann Sohn		Division: Division of Psychiatry Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b>For ALL 505(b)(2) applications, two months prior to EVERY action:</b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b></li> </ul> <p><input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>5/18/15</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): type 5  
 (*confirm chemical classification at time of approval*)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) AP 5/18/15
Labeling	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul>	Acceptability Letter 3/10/15 DMEPA Review 3/3/15
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: <input checked="" type="checkbox"/> None DMEPA: <input type="checkbox"/> None 4/20/15, 5/11/15 DMPP/PLT (DRISK): <input type="checkbox"/> None 4/10/15 OPDP: <input type="checkbox"/> None 4/13/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting ( <i>indicate date of each review</i> )	12/16/14
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>4/1/15</u> If PeRC review not necessary, explain: _____</li> </ul>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 7/24/14
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 11/4/11, CMC 12/8/11
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	Pre-IND 8/20/07
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 5/18/15
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 5/15/15
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>• Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	5/11/15
<ul style="list-style-type: none"> <li>• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None Maternal 4/29/15, Pediatric 5/18/15
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested 2/25/15
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 5/7/15
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/23/15
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 5/5/15
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review 4/28/15
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/28/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/21/15, 5/8/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )	<input type="checkbox"/> None CDRH/ODE 4/14/15

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections ( <i>action must be taken prior to the re-evaluation date</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input checked="" type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/  
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ANN J SOHN  
05/18/2015

## Sohn, Ann J

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**From:** Sohn, Ann J  
**Sent:** Monday, May 11, 2015 10:46 AM  
**To:** Geter-Douglass, Beth [JRDU] (BGeterdo@its.jnj.com)  
**Subject:** NDA 207946 Information Request

Hi Beth,

Please provide information regarding the levels of two DNA-reactive (mutagenic) impurities (b) (4) and (b) (4) in the paliperidone palmitate batches No. 04J11/F013 and No. 05E26/F13D (or any other batches) used in your carcinogenicity study conducted in rats (study TOX6726 submitted to the NDA 22264) if the levels of these impurities in the carcinogenicity study batches are known. These two impurities were previously present in some paliperidone palmitate drug substance batches and we are interested in their possible qualification in the carcinogenicity study.

Please provide a response as soon as possible.

Thank you,

*Ann Sohn, Pharm.D., LCDR USPHS  
Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research, FDA  
Email: [ann.sohn@fda.hhs.gov](mailto:ann.sohn@fda.hhs.gov)*

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ANN J SOHN  
05/11/2015

## Sohn, Ann J

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**From:** Sohn, Ann J  
**Sent:** Wednesday, March 25, 2015 3:31 PM  
**To:** 'Tan, James [JRDUS]'  
**Cc:** Geter-Douglass, Beth [JRDUS]  
**Subject:** NDA 207946 Information Request

**Importance:** High

Hi Jimmy,

I have the following requests from our review team:

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.
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.
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.

Please provide your response by COB Wednesday, April 1.

Thank you,

*Ann Sohn, Pharm.D., LCDR USPHS  
Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research, FDA  
Email: [ann.sohn@fda.hhs.gov](mailto:ann.sohn@fda.hhs.gov)*

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/s/  
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ANN J SOHN  
03/25/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 207946

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Janssen Pharmaceuticals, Inc.  
1125 Trenton-Harbouton Road  
Titusville, NJ 08560

ATTENTION: Beth Geter-Douglass, PhD  
Associate Director, Global Regulatory Affairs

Dear Dr. Geter-Douglass:

Please refer to your New Drug Application (NDA) dated and received November 18, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paliperidone Palmitate, Extended-release Injectable Suspension, 273 mg/0.875 mL, 410 mg/1.315 mL, 546 mg/1.75 mL, and 819 mg/2.625 mL.

We also refer to:

- Your correspondence, dated and received December 18, 2014, requesting review of your proposed proprietary name, Invega Trinza
- Our email, dated December 29, 2014, requesting clarification of the dosage strength
- Your email response, dated January 5, 2015, and subsequent amendment, dated and received January 5, 2015, clarifying the dosage strength

We have completed our review of the proposed proprietary name, Invega Trinza and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your December 18, 2014, and January 5, 2015, submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Vasantha Ayalasomayajula, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-5035. For any other information regarding this application, contact Ann J Sohn, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2232.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Deputy Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES  
03/10/2015

**Sohn, Ann J**

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**From:** Sohn, Ann J  
**Sent:** Friday, March 06, 2015 3:23 PM  
**To:** Geter-Douglass, Beth [JRDUS] (BGeterdo@its.jnj.com)  
**Subject:** NDA 207946 Information request paliperidone

Hi Beth,

Your submission (NDA 207946) is currently under review. Reference is made to Report REP-1-JAN-PAL-PMX-1 Prepared By [REDACTED] <sup>(b) (4)</sup> To facilitate the review, we have the following information request.

Provide the reference values for paliperidone exposure after oral administration seen in Figure 12 and Figure 13 report: REP-1-JAN-PAL-PMX-1. Furthermore, provide a source for those references values.

You have not submitted justification to support management of missed dose (between 4 and 9 months post dose, more than 9 months post dose) for all PP3M dose strengths. Furthermore, you have not submitted justification to support transition from paliperidone PP3M formulation to extended release oral tablets for all PP3M dose strengths.

Submit relevant simulations or other data to justify your proposal for reinitiating paliperidone therapy and conversion to per oral treatment no later than March 20<sup>th</sup> 2015. Submit the relevant NONMEM dataset and control stream. Data files should be submitted as SAS transport files (eg, Data1.xpt) and other files be submitted as ASCII text files (eg, myfile\_ctl.txt, myfile\_out.txt).

Regards,

*Ann Sohn, Pharm.D., LCDR USPHS  
Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research, FDA  
Email: [ann.sohn@fda.hhs.gov](mailto:ann.sohn@fda.hhs.gov)*

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ANN J SOHN  
03/06/2015



NDA 207946

## INFORMATION REQUEST

Janssen Pharmaceuticals, Inc.  
Attention: Beth Geter-Douglass, PhD  
Associate Director, Global Regulatory Affairs  
1125 Trenton-Harbourton Road  
Titusville, NJ 08560

Dear Dr. Geter-Douglass:

Please refer to your New Drug Application NDA 207946 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paliperidone Palmitate extended-release injectable suspension, 273 mg, 410mg, 546mg, 819mg.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests.

### LIST COMMENTS AND INFORMATION REQUESTS

Facilities:

1. Identify the manufacturer with ultimate responsibility for the finished combination product, describe their organizational structure (i.e. organization structure chart) and explain how it controls all levels of the structure (i.e. agreements) as per 21 CFR 820.20
2. Provide a description of your design control system, including a description of development plan and its implementation as per 21 CFR 820.30. This should include a description of the design control system and how it is implemented to ensure compliance with requirement for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file.
3. Describe your supplier evaluation process and how it applies purchasing controls to the relevant suppliers as per 21 CFR 820.50. This should include your purchasing control process covering supplier evaluation, record maintenance of acceptable suppliers, and

method to assure that changes made by contractors/suppliers will not affect the final combination product through acceptance activities and supplier agreements.

4. Describe your CAPA system and CAPA initiation and resolution process as per 21 CFR 820.100.

Note that you may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

#### Biopharmaceutics:

We could not locate the dissolution method development report within the NDA; if it was included in the original submission, please provide the CTD location. In the event that this report was omitted, provide data that support the suitability and discriminating ability of the proposed dissolution method for your product. The general guidelines for the content of a dissolution method development report are as follows:

5. To support the selection of the in vitro release acceptance criteria, provide data from the pivotal clinical batches and primary (registration) stability batches. Provide the data as individual, mean, and SD in tabular format, in addition to graphical representation of in vitro release profiles. Note that it is recommended to set the acceptance criteria based on USP stage 2 testing (n=12).
6. Provide data to support the discriminating ability of the proposed in vitro release method and acceptance criteria. (b) (4)

[Redacted]

#### Process:

7. Provide a calculation to show whether (b) (4)
8. Executed batch record for the bulk validation batch EEB2V showed (b) (4)

[Redacted]

9. Provide information on [REDACTED] (b) (4)

10. Provide a yield of [REDACTED] (b) (4)

11. Provide information on [REDACTED] (b) (4)

Please respond to this Information Request by **Monday, 23 March 2015**. If you have any questions, please contact Dahlia A. Woody, Regulatory Project Manager, at (301) 796-8427.

Sincerely,

*{See appended electronic signature page}*

David Claffey, PhD  
Division of New Drug Products I  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

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/s/  
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DAHLIA A WOODY  
03/05/2015

DAVID J CLAFFEY  
03/05/2015

## Sohn, Ann J

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**From:** Sohn, Ann J  
**Sent:** Friday, February 13, 2015 9:30 AM  
**To:** Geter-Douglass, Beth [JRDUS] (BGeterdo@its.jnj.com)  
**Subject:** NDA 207946 Paliperidone 3 month Info Request

**Importance:** High

Hi Beth,

The NDA 207946 for the paliperidone palmitate 3-month formulation (F015), proposes change to the approved paliperidone palmitate 1-month formulation (F013), NDA 22264, and addition of specific gauge needles compatible to the new formulation in the kit. Please be advised that changes to the approved NDA 22264 would require compliance to 21 CFR Part 4 Final Rule. Please confirm the following,

1. Design Control changes for the new gauge needle of the new kit are included in the Design History File as per 21 CFR 820.30(j) and updated in the Design Master Record of the combination product.
2. Management with executive responsibility establishes its policy, objectives for, and commitment to quality in compliance with 21 CFR 820.20, Management Responsibility for the new Kit.
3. Corrective and preventive actions procedures to analyze, investigate, verify or validate, implement and document for the new gauge needle of the new kit are in compliance with 21 CFR 820.100, Corrective and Preventive Action.

Alternately, please provide the following:

1. A summary describing where in the design and development process the new gauge needles became the subject to Design Control as per 21 CFR 820.30 Design Controls.
2. A summary of the procedures describing how all purchased or received goods and products are evaluated and relevant controls exercised on the suppliers as per Purchasing controls, 21 CFR 820.50. The procedures also should explain how receiving product acceptance are conducted to ensure that incoming products/components and services are acceptable for the combination product's intended use.
3. A summary of how management with executive responsibility establishes its policy, objectives for, and commitment to quality in compliance with 21 CFR 820.20, Management Responsibility for the new Kit.
4. A summary of how corrective and preventive actions are identified, investigated, verified or validated, implemented, and documented in compliance with 21 CFR 820.100, Corrective and Preventive Action for the new gauge needle and the kit.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

Thank you,

*Ann Sohn, Pharm.D., LCDR USPHS  
Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I*

Center for Drug Evaluation and Research, FDA  
Email: [ann.sohn@fda.hhs.gov](mailto:ann.sohn@fda.hhs.gov)

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/s/  
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ANN J SOHN  
02/13/2015

## Sohn, Ann J

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**From:** Sohn, Ann J  
**Sent:** Thursday, February 12, 2015 2:29 PM  
**To:** Geter-Douglass, Beth [JRDUS] (BGeterdo@its.jnj.com)  
**Subject:** NDA 207946 Paliperidone 3 month

Hi Beth,

I have the following requests from our devices group for NDA 207946.

1. If applicable, please provide the 510(k) numbers for the safety needles used in the 3 month formulation.
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.

Please provide a response by the end of next week.

Thank you,

*Ann Sohn, Pharm.D., LCDR USPHS  
Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research, FDA  
Email: [ann.sohn@fda.hhs.gov](mailto:ann.sohn@fda.hhs.gov)*

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/s/  
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ANN J SOHN  
02/12/2015

## Sohn, Ann J

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**From:** Sohn, Ann J  
**Sent:** Friday, January 30, 2015 5:34 PM  
**To:** Geter-Douglass, Beth [JRDUS] (BGeterdo@its.jnj.com)  
**Subject:** NDA 207946 Info Request

**Importance:** High

Hi Beth,

I have the following requests from our review team for NDA 207946:

DMEPA:

It is our understanding that in the course of your development program for paliperidone palmitate extended-release injectable suspension (3-month injection) there were errors involving shaking of the product sufficiently to obtain proper suspension of the active ingredient prior to injection. It is also our understanding that clinical investigators involved in the preparation of this product were trained to ensure the proper technique for preparation was implemented during the pivotal clinical trial.

Please clarify if you have conducted a summative human factors study for your proposed paliperidone palmitate product. If so, you will need to submit a summary of the findings from your formative human factors work, your updated use risk analysis, and your summative study results report for our review.

We are also interested in understanding specifically what training and processes were put in place during your clinical development program to mitigate the risk of improper preparation of this product. Please submit a detailed summary of all use errors identified during your clinical development program as well as the training and other risk mitigation strategies that were implemented. Please also specify how this was used to inform your use risk analysis and commercial product interface design.

Finally, provide your rationale for why you believe all use-related risks associated with your product have been mitigated to an acceptable level and your product can be used safely and effectively if marketed.

CMC:

Provide all available data on the likelihood of failures (e.g. syringeability, etc.) should the product be shaken for a time period shorter than the labeled 15 seconds (e.g. 0, 5 or 10 seconds) and provide the data that were used to establish the 15 second shaking time. Given the syringeability failures observed during the clinical studies and the relatively long shaking time, our aim is to determine the criticality of shaking for the entire 15 seconds as it will likely not be uncommon for the health care practitioner to shake for a shorter period of time, e.g. the 10 seconds directed by the Invega Sustenna label.

Provide data to support the proposed 5 minutes in-use stability period i.e. that the syringeability, etc. reliably meets specification 5 minutes after shaking.

Given our review timelines, we request a response no later than **Friday, February 6, 2015**.

Regards,

*Ann Sohn, Pharm.D., LCDR USPHS  
Regulatory Project Manager  
Division of Psychiatry Products*

*Office of Drug Evaluation I*  
*Center for Drug Evaluation and Research, FDA*  
Email: [ann.sohn@fda.hhs.gov](mailto:ann.sohn@fda.hhs.gov)

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ANN J SOHN  
02/03/2015

**FDA Preliminary Responses**  
IND 76952 Paliperidone Palmitate 3-Month Injection  
Type B, Pre-NDA Meeting  
Janssen Research & Development, LLC  
July 24, 2014

Participants –

**FDA**

Mitchell Mathis, M.D.	Director, Division of Psychiatry Products
Mark Ritter, M.D.	Clinical Reviewer, Team Lead
Christina Burkhardt, M.D.	Clinical Reviewer
Aisar Atrakchi, Ph.D.	Pharmacology/Toxicology Supervisor
Elzbieta Chalecka-Franaszek, Ph.D.	Pharmacology/Toxicology Reviewer
Hao Zhu, Ph.D.	Clinical Pharmacology Team Lead
Kofi Kumi, Ph.D.	Clinical Pharmacology Reviewer
Kevin Krudys, Ph.D.	Pharmacometrics Team Lead
Xiaofeng Wang, Ph.D.	Pharmacometrics Reviewer
Peiling Yang, Ph.D.	Statistical Team Lead, Division of Biometrics I
Yang Wang, Ph.D.	Statistical Reviewer, Division of Biometrics I
Sapru Mohan, Ph.D.	Chemistry, Manufacturing and Controls
Ann Sohn, Pharm.D.	Regulatory Project Manager, DPP

The purpose of this meeting is to discuss the content and format of the planned NDA for paliperidone palmitate 3-month injection for the treatment of schizophrenia in adults.

**Background:**

Janssen Research and Development has requested a pre-NDA meeting to discuss the submission of a new drug application (NDA) for paliperidone palmitate 3-month injection (PP3M). The proposed indication for PP3M is for the treatment of schizophrenia in adult patients who have been treated with the paliperidone palmitate 1-month formulation (PP1M [INVEGA® SUSTENNA®]) for at least 4 months. The Sponsor has met with the FDA on 2 previous occasions in order to discuss the clinical development of the PP3M formulation: at a pre-IND meeting (8/20/2007) and at an End-of-Phase 2 (EOP2)/Pre-Phase 3 meeting (11/4/2011). Overall, the Division has been in agreement with the proposed PP3M program. The submission of the PP3M NDA is planned for November 2014.

Paliperidone (R076477) is a monoaminergic antagonist that exhibits the characteristic dopamine type 2 (D2) and serotonin (5HT2A) antagonism of the newer, or second-generation, antipsychotic drugs. The Sponsor has developed 3 formulations of paliperidone: an oral extended-release (ER) osmotic pump technology (OROS®) tablet formulation (paliperidone ER tablets, INVEGA®) and 2 long-acting injectable paliperidone palmitate formulations (PP1M [INVEGA® SUSTENNA®] and PP3M).

Paliperidone palmitate is an aqueous suspension for intramuscular injection. It has extremely low water solubility. Therefore, paliperidone palmitate dissolves slowly after injection before being hydrolyzed to paliperidone. Paliperidone then enters the systemic 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 1 month (PP1M) or 3 months (PP3M). The main difference between PP3M and PP1M is (b) (4) the increased concentration, and a larger injection volume. The proposed dose levels of PP3M are 273, 410, 546, and 819 mg, which correspond to a 3.5-fold multiple of the marketed PP1M doses of 78, 117, 156, and 234 mg, respectively.

The PP3M formulation is not currently approved in any country. Clinical development of this compound was started in 2008. A multi-panel Phase 1 pharmacokinetic (PK), safety, and tolerability study (R092670-PSY-1005) and a Phase 3, randomized, double-blind, placebo-controlled relapse prevention study (R092670-PSY-3012) in adults with schizophrenia have recently been completed. A Phase 3, randomized, double-blind, noninferiority study comparing PP3M with the PP1M product is currently ongoing (R092670-PSY-3011). Data from all 3 studies are planned to be included in the NDA (with only select blinded safety data from ongoing study R092670-PSY-3011). The pivotal relapse prevention study (R092670-PSY-3012) was terminated early based on a planned interim analysis of data demonstrating a statistically significant difference in favor of PP3M compared with placebo in delaying time to relapse ( $p=0.0002$ ).

The targeted indication for PP3M is for (b) (4) treatment in subjects with schizophrenia who have been first treated for 4 or more months with INVEGA® SUSTENNA® (PP1M). Due to the slow release characteristics of PP3M, the product is not intended to be used for initiation of treatment in acutely symptomatic patients or in patients who are immediately transitioning from oral to LAI antipsychotic therapy.

The PP3M formulation is expected to have advantages in terms of medication adherence and ease of use associated with the substantially longer dosing interval. In addition, PP3M will be supplied in prefilled syringes that do not require reconstitution or refrigeration.

### **Questions:**

#### **Chemistry, Manufacturing, and Controls**

##### **Question 1 – Cross reference to Drug Master Files**

Does the Division agree that the Sponsor may cross-reference the drug master file (DMF) 20902 and DMF 18915 for complete CMC information on the paliperidone palmitate Active Pharmaceutical Ingredient (API) in the PP3M formulation NDA?

##### **Preliminary Comments:**

*The proposal is acceptable. An assessment of whether the CMC information concerning the paliperidone palmitate active pharmaceutical ingredient in the*

*PP3M formulation provided in the DMF and/or NDA is adequate or not will be a review issue. Non-proprietary information (structure, nomenclature, etc.) should be captured within your NDA as well as acceptance criteria for material received from the DMF holder.*

### **Question 2 – Batch Record**

The sponsor plans to submit one executed batch record from one representative batch of paliperidone palmitate drug product including representative fill volume, together with an English translation of the batch record. Does the Division agree?

#### **Preliminary Comments:**

*The proposal is acceptable assuming that the executed batch is representative of the commercial process batch and be at least pilot scale or for (b) (4) units (whichever is greater). Adequacy of batch record information is a review issue and will be evaluated during the NDA review process.*

### **Nonclinical Studies**

#### **Question 3**

Based on the similarities between the paliperidone palmitate 3-month formulation (PP3M) and the approved paliperidone palmitate 1-month formulation (PP1M, INVEGA SUSTENNA), a limited toxicological program for PP3M was agreed upon at the 20 August 2007 Pre-IND meeting and at the 4 November 2011 End-of-Phase 2 (EOP2) meeting.

The NDA will consist of 2 study reports investigating the local tolerability of the PP3M formulation in the minipig and will refer to NDA 22-264 (PP1M) for other aspects of the preclinical toxicology, pharmacokinetics and pharmacology of paliperidone palmitate. Therefore, the preclinical section of the NDA is planned to be comprised of the following sections in the dossier:

- Nonclinical Overview discussing the 2 minipig studies with PP3M (Module 2.4)
- Tabulated Summaries of the 2 studies (Module 2.6.7)
- The 2 study reports (Module 4)

Does the Division agree with the proposed non-clinical content for this application?

#### **Preliminary Comments:**

*Yes, we agree with the proposed nonclinical content of the NDA.*

## **Clinical Pharmacokinetics and Bioavailability**

### **Question 4 – Cross referencing Previous Paliperidone ER Submissions for Clinical Pharmacology Data**

Does the Division agree that the Sponsor cross-references to previous paliperidone ER NDA submissions without submitting original study reports for data from absorption, metabolism, excretion, elderly, drug-drug interaction (paroxetine and trimethoprim), renal-impairment, hepatic-impairment, QT, and D2 receptor occupancy studies, to support the PP3M application?

#### **Preliminary Comments:**

*Yes. However, you should provide the NDA no. and the date of submission of the cross reference reports. During the review of the NDA, the Agency may request additional information if needed.*

### **Question 5 – Population Pharmacokinetic (PK) Analysis**

Does the Division agree with the population PK analysis approach, including the simulation plan as outlined in the attached population PK analysis plan? In particular, will the simulation approach be sufficient to support labeling language, including dosing windows, switching from PP1M, missed doses, and dosing in special populations?

#### **Preliminary Comments:**

*The population PK modeling and simulation plan seems reasonable.*

### **Question 6 – NONMEM datasets**

Is it acceptable to the Division to provide the NONMEM datasets and NONMEM table files used in the population PK analysis in .xpt format and NONMEM control streams and outputs in .txt format?

#### **Preliminary Comments:**

*Yes, the formats are acceptable.*

## **Clinical and Statistical**

### **Question 7 - Efficacy**

Subject to review of the file, does the Division agree that efficacy data from Study R092670-PSY-3012 is adequate to support filing of an NDA for PP3M for the following indication?

[TRADENAME] is indicated for the treatment of schizophrenia in adult

patients who have been treated with INVEGA SUSTENNA for at least 4 months.

**Preliminary Comments:**

*On face, the efficacy data appears adequate to support filing of an NDA for PP3M. This will be a matter for review once the full submission is available for review.*

**Question 8 – Dose Range**

The Sponsor proposes that the selection of a dose of PP3M be based on a fixed ratio (1:3.5) relative to the optimal dose of PP1M. The proposed dose levels of PP3M are 273, 410, 546, and 819 mg, which correspond to a 3.5-fold multiple of the marketed PP1M doses of 78, 117, 156, and 234 mg, respectively.<sup>a</sup> This dose range is consistent with the PP3M/PP1M dose levels evaluated in the Phase 3 PP3M studies (R092670- PSY-3012 and R092670-PSY-3011). The Sponsor has not developed a corresponding PP3M dose for the 39 mg PP1M dose level, and this PP3M dose strength is not planned to be registered or marketed, primarily due to the very low usage pattern for the 39 mg PP1M dose level in postmarketing experience. Pending the Division’s review of safety and efficacy data from the R092670-PSY-3012 study, does the Division agree with the Sponsor’s proposed recommended dose range for PP3M?

<sup>a</sup> Note that clinical doses of PP1M and PP3M are presented as milligrams (mg) of paliperidone palmitate throughout this document. The correspondence between mg of paliperidone palmitate and milligram equivalents (mg eq.) of paliperidone is provided in the following table:

<b>PP1MDose</b>		<b>Corresponding PP3MDose</b>	
(mg paliperidone palmitate)	(mg eq. paliperidone)	(mg paliperidone palmitate)	(mg eq. paliperidone)
39 mg	25 mg eq	Not applicable	Not applicable
78 mg	50 mg eq.	273 mg	175 mg eq.
117 mg	75 mg eq.	410 mg	263 mg eq.
156 mg	100 mg eq.	546 mg	350 mg eq.
234 mg	150 mg eq.	819 mg	525 mg eq.

**Preliminary Comments:**

*Yes pending review of the Population PK analysis, efficacy and safety data. The Agency may recommend modification after review of the data.*

**Question 9 - Exposure**

At the time of the planned submission of the PP3M NDA in November 2014, 379 subjects from study R092670-PSY-3012 will have received at least one dose of PP3M, of which 28 will have been exposed for at least 48 weeks. A further 325 subjects will have received a single dose of PP3M in study R092670-PSY-1005. Additionally, study R092670-PSY-3011 will be ongoing and remain blinded at the time of the NDA submission. Using a data cutoff of 31 May 2014 for R092670-PSY-3011, and assuming an equal distribution of subjects who received PP1M and PP3M based on the 1:1 randomization ratio, an estimated 508 subjects will have received at least 1 dose of PP3M, and an estimated 130 subjects will have completed at least 48 weeks of PP3M treatment. Does the Division agree that the total safety exposure (number of subjects and

duration of exposure to PP3M) at the time of filing will be sufficient for review by the Division?

**Preliminary Comments:**

*Yes, we agree.*

**Question 10 – Summary of Clinical Efficacy (Subgroup Analyses)**

The Sponsor plans to submit a Summary of Clinical Efficacy (SCE) in Module 2.7.3. The SCE will include results from a single Phase 3 study (R092670-PSY-3012). The Sponsor proposes to conduct subgroup analyses of the primary efficacy variable of study R092670-PSY-3012 to evaluate the effects of treatment for subjects grouped by age, sex, race, baseline BMI, and geographic region (including US vs. non-US). Does the Division agree with this proposal?

**Preliminary Comments:**

*Yes, we agree.*

**Question 11 – Summary of Clinical Safety (Individual Studies)**

The Sponsor plans to submit a Summary of Clinical Safety (SCS) in Module 2.7.4. The SCS will include final safety data from the completed studies R092670-PSY-3012 and R092670-PSY-1005, and limited, blinded, safety data (ie, summaries of deaths, serious adverse events, and discontinuations due to adverse events) from the ongoing study R092670-PSY-3011 up to a clinical cutoff date of 31 May 2014.

Pooling of these studies is not considered appropriate based on the differences in study designs. Therefore, the Sponsor does not plan to submit a separate Integrated Safety Summary (ISS) in Module 5. Safety results for each study will be presented individually within the SCS. Does the Division agree with this proposal?

**Preliminary Comments:**

*Yes, we agree.*

**Question 12 – Summary of Clinical Safety (Subgroup Analyses)**

For the SCS, the Sponsor proposes to conduct subgroup analyses of selected safety parameters for the 2 completed studies (R092670-PSY-3012 and R092670-PSY-1005) to evaluate the effects of treatment for subjects grouped by age, sex, race, baseline BMI, and geographic region (including US vs. non-US). Does the Division agree with this proposal?

**Preliminary Comments:**

*Yes, we agree.*

**Question 13 – Summary of Clinical Safety (Adverse Events of Special Interest)**

Adverse events of special interest will be summarized in the SCS for the 2 completed studies (R092670-PSY-3012 and R092670-PSY-1005). Does the Division agree that the proposed adverse events of special interest, specifically, EPS-related adverse events,

diabetes mellitus and hyperglycemia-related adverse events, potentially prolactin-related adverse events, suicidality, aggression and agitation, somnolence and sedation, seizures and convulsions, neuroleptic malignant syndrome, cardiac arrhythmias, orthostatic hypotension, adverse events suggestive of proarrhythmic potential, ischemia-related, potential rhabdomyolysis-related, overdose-related, weight gain-related, tachycardia-related, and injection-site related adverse events, summarized by preferred term, are appropriate adverse events of special interest for PP3M?

**Preliminary Comments:**

*Yes, we agree.*

**Question 14 – Adverse Drug Reactions**

A summary of adverse drug reactions (ADRs) from the PP3M clinical trials will be provided along with other documents as part of the NDA filing. Based upon the similar formulation characteristics and route of administration, and the identical active moiety, it is felt that ADRs identified for PP1M should also be considered as ADRs for PP3M. In addition, the Sponsor intends to identify any new ADRs on the basis of treatment-emergent adverse events reported in PP3M clinical trials. The Sponsor proposes to present the following 4 sets of information in the United States Prescribing Information (USPI) within Section 6.1, Adverse Reactions; Clinical Trials Experience:

- a) A summary table showing incidences of adverse reactions based on treatment emergent adverse events that occur at a greater incidence than placebo and at a to-be-specified cutoff (eg,  $\geq 2\%$ ) in the PP1M/PP3M arm during the Open- Label (i.e. Transition and Maintenance) and Double-Blind treatment phases of study R092670-PSY-3012
- b) A list of newly identified ADRs based on the results of the analysis of ADRs from the PP3M clinical trials (if not already captured in (a))
- c) A list of additional ADRs previously identified for PP1M during clinical trial experience with PP1M (if not already captured in (a) or (b)).
- d) A list of additional ADRs previously identified during clinical trial experience with oral paliperidone ER (if not captured in (a), (b), or (c)).

Does the Division agree with this approach?

**Preliminary Comments:**

*Yes, we agree.*

**Question 15 – 4-Month Safety Update**

Based on a planned NDA submission date of November 2014, the Sponsor plans to provide a 4-month safety update (4MSU) in March 2015. The 4MSU will include updated, cumulative safety and exposure data from the ongoing study R092670-PSY-

3011 through to a cutoff date of 11 November 2014. The Sponsor proposes to include summaries of deaths, serious adverse events, and discontinuations due to adverse events in study R092670-PSY-3011 within the 4MSU. An updated safety exposure estimate will also be provided. At the planned cutoff date for the 4MSU, it is estimated that 508 subjects will have received at least 1 dose of PP3M in study R092670-PSY- 3011, with approximately 240 subjects completing at least 48 weeks of treatment. Can the FDA confirm the adequacy of the updated safety information as well as the exposure estimate?

**Preliminary Comments:**

*Yes, your proposals for the 4MSU are acceptable. The exposure estimate appears adequate.*

**Question 16 – SAS Programs for primary efficacy**

The Sponsor plans to submit SAS programs used to analyze the primary efficacy endpoint (time to relapse) at the interim as well as final analysis only. As part of our electronic submission, the Sponsor will also provide the raw and derived datasets. Does the Division agree with this proposal?

**Preliminary Comments:**

*In addition to your proposal, please include the following in your NDA submission:*

- a) the SAS programs by which the derived variables (including relapse, time to relapse, dose levels over time as summarized in Table 13 of the briefing document) were produced from the raw variables;*
- b) a list of IND number with serial numbers and submission dates of the protocols, SAPs, amendments, and any relevant meetings;*
- c) minutes of DSMB meetings.*

*We may ask for more SAS programs during the NDA review.*

**Question 17 – Patient Profiles**

The Sponsor plans not to submit individual subject data listings, but rather to submit patient profiles for each individual subject within the NDA, in addition to SAS datasets, for study R092670-PSY-3012. Does the Division agree with this proposal?

**Preliminary Comments:**

*Yes, your proposal is acceptable.*

**Question 18 – Case Report Forms**

The Sponsor plans to provide Case Report Forms (CRF's) as part of the NDA only for those subjects who died, experienced a serious adverse event, or discontinued.

prematurely due to an adverse event in the completed studies R092670-PSY-3012 and R092670-PSY-1005. Does the Division agree with this proposal?

**Preliminary Comments:**

*Yes, your proposal is acceptable.*

**Question 19 – Narratives**

For the completed studies (R092670-PSY-3012 and R092670-PSY-1005), the Sponsor will provide narratives describing each death, other serious adverse event, and premature discontinuation due to an adverse event in the individual clinical study reports, as well as providing summary tables and listings of subjects from R092670-PSY-3012 and R092670-PSY-1005 who died during each study, experienced a serious adverse event, or discontinued prematurely due to an adverse event in the SCS. For the ongoing study (R092670-PSY-3011), the Sponsor does not plan to provide narratives because the study will still be blinded. For this study, listings of subjects who died, experienced a serious adverse event, or discontinued prematurely due to an adverse event up to the clinical cutoff date of 31 May 2014 will be provided in the SCS. For SAEs and deaths from R092670-PSY-3011, Council for International Organizations of Medical Sciences (CIOMS) I reports will also be provided. Does the Division agree with this proposal?

**Preliminary Comments:**

*Yes, your proposal is acceptable.*

**Question 20 – Literature Summary**

The Sponsor proposes to use 31 May 2014 as the cutoff date for the Literature Summary for the NDA planned for November 2014. The Sponsor plans to cross-refer to previous literature reviews submitted for the paliperidone ER and PP1M formulations up to the previous cutoff date of 28 February 2014. Any new literature and bibliography information for the complete literature search obtained since 1 March 2014 through to the cutoff date of 31 May 2014 will be included in the NDA. Does the Division agree with the planned approach and the cutoff date?

**Preliminary Comments:**

*Yes, your proposal is acceptable.*

**Question 21 – Postmarketing Safety**

The Sponsor proposes to review post-marketing data for PP1M in the schizophrenia population. The Sponsor proposes to focus the review on fatal cases, important potential risks, specific populations, relevant drug interactions and medication errors. The cutoff date for this analysis will be 31 May 2014. Does the Division agree with this approach and cutoff date?

**Preliminary Comments:**

*Yes, your proposal is acceptable.*

**Question 22 – Pediatric Waiver**

At the 4 November 2011 EOP2 meeting, the Division stated that studies with PP3M in pediatric patients aged 13 to 17 years were not required; however, a final determination would occur at submission. The Sponsor will include a full pediatric waiver request (patients 0 to 17 years) in the NDA. Does the Division agree with this approach and support the full pediatric waiver request?

**Preliminary Comments:**

*We agree with this approach. The Division would support a full pediatric waiver. However, the final determination will rest with the Pediatric Review Committee (PeRC) at the time of your NDA submission.*

**Additional Clinical Comments:**

*Please describe your plans for package labeling. Specifically, describe what precautions will be in place to prevent confusion between the PP1M product and the PP3M product.*

**General Comments:**

*This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion during the meeting scheduled for July 24, 2014 between Janssen Research & Development, L.L.C. and the Division of Psychiatry Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Ann Sohn, Regulatory Project Manager). If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to [your development plan/the purpose of the meeting/to the questions] (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact Ann Sohn, Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.*

**PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

### **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements of Prescribing Information* website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents, and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

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ANN J SOHN  
07/17/2014



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF NEW DRUG QUALITY ASSESSMENT

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<b>Sponsor Name:</b>	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
<b>Application Number:</b>	IND 76,952
<b>Product Name:</b>	paliperidone palmitate
<b>Meeting Type:</b>	Type B
<b>Meeting Category:</b>	Chemistry, Manufacturing, and Controls Meeting
<b>Meeting Date and Time:</b>	December 8, 2011; 2:00 – 3:00 p.m. EST
<b>Meeting Location:</b>	Food and Drug Administration White Oak Campus, Bldg 22 Rm. 1415, Silver Spring, MD
<b>Briefing Package Dated</b>	November 7, 2011

The following consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled December 8, 2011, 2:00 p.m. EST, at the Food and Drug Administration, White Oak Campus, Silver Spring, MD between Johnson & Johnson Pharmaceutical Research & Development, L.L.C., and the Center for Drug Evaluation and Research/Office of New Drug Quality Assessment. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Teshara G. Bouie, Regulatory Health Project Manager for Quality, (301) 796-1649). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the premeeting communications are considered sufficient to answer the questions. **Please note that if there are any major changes to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.** If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Health Project Manager for Quality to discuss the possibility of including these for discussion at the meeting.

**Question 1: JRD plans to scale up the drug product manufacturing process from batch sizes of (b) (4) and (b) (4), for clinical supplies for phase 3 to a commercial batch size of (b) (4) to (b) (4) (b) (4) to stay within a (b) (4) increase. The commercial production will utilize equipment of the same design and operating principles as that to be used for phase 3 clinical supplies and primary (registration) stability, and the scale-up will occur at the same site of manufacture (Beerse, Belgium). The NDA will include comparative release and development data (b) (4) (b) (4) from the validation batches of drug product**

produced at the commercial scale to demonstrate comparability of the process. Does the Division agree that the comparability information to be provided is adequate to support the scale-up of the manufacturing process?

*FDA Preliminary Response: This will be a review matter; however the proposed approach appears adequate.*

**Question 2:** Does the Division agree with the proposed in-vitro release method contained within this briefing document?

*FDA Preliminary Response: Your proposed in vitro release method appears reasonable.*

**Question 3:** In study PSY-1002 JRD has established a multiple level <sup>(b)</sup><sub>(4)</sub> IVIVC for paliperidone palmitate suspensions having d,50 particle size values from <sup>(b)</sup><sub>(4)</sub> confirming the biorelevance of the in vitro release method. As the particle size of paliperidone palmitate F015 falls within the particle size ranges used in study PSY-1002, and the proposed in vitro release method for F015 is the same as that approved for F013, the company plans to include this information in the NDA to support the biorelevance of the in vitro method. Does the Division agree that the information provided in this Briefing Document supports the biorelevance of the in vitro method?

*FDA Preliminary Response: Yes, we agree. Please note that in the previous review of NDA 22-264 for the 1-month injection product, the Agency concluded that your IVIVC model is not supported beyond the limit* <sup>(b)</sup><sub>(4)</sub>

*It is recommended that the IVIVC model be used for the selection of the lower and higher limits of the particle size for the proposed 3-month injection product.*

**Question 4:** Does the Division agree with the proposed drug product specification parameters contained within this briefing document, recognizing that specification limits will be reviewed upon NDA submission?

*FDA Preliminary Response: The test attributes in the drug product specification appears acceptable. Note that a second identification test should be added to the drug product specification, as the proposed test is non-specific (refer to ICH Q6A). Rationale should be provided in the NDA for not including tests for syringability and solid state properties <sup>(b)</sup><sub>(4)</sub> in the drug product specification.*

*With respect to the proposed acceptance criteria for particle size, please refer to our response for question 3.*

*Regarding the in vitro release acceptance criteria please provide in your NDA the drug release profile data from the bio-batches (clinical & PK) and stability batches supporting the selection of the acceptance criteria (i.e., specification-sampling time points and specification values. For the setting of these criteria, the following points should be considered:*

- *The in vitro drug release profiles should encompass the timeframe over which at least (b) (4) of the drug is released or where the plateau of drug released is reached if incomplete release is occurring.*
- *The establishment of at least three specification time-points covering the initial, middle, and terminal phases of the complete drug release profile data should be set. The specification ranges should be based on the overall dissolution data generated at these times.*
- *In general, for extended release products the selection of the specification ranges is based on mean target value (b) (4)% and NLT (b) (4) for the last specification time-point. However, you may also use your IVIVC model for the selection of the specification ranges. Wider ranges may be acceptable if they are supported by your IVIVC model.*
- *The in vitro drug release acceptance criteria should be set in a way to ensure consistent performance from lot to lot and these criteria should not allow the release of any lots with drug release profiles outside those that were tested clinically.*

**Question 5:** JRD proposes to perform bracketed drug product registration stability studies in accordance with the protocol provided in this briefing document. Does the Division agree with the proposed drug product registration stability protocol?

**FDA Preliminary Response:** *The proposed protocol appears acceptable. We recommend that resuspendability and injectability continue to be part of the stability appearance test.*

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*{See appended electronic signature page}*

Teshara G. Bouie  
Regulatory Health Project Manager  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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TESHARA G BOUIE  
12/05/2011

CHHAGAN G TELE  
12/05/2011  
Signed off for Ramesh Sood



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 76,952

MEETING MINUTES

Jacqueline Brown, R.Ph.  
Regulatory Affairs Professional  
Johnson&Johnson Pharmaceutical Research & Development  
920 Route 202  
Raritan, NJ 08869

Dear Ms. Brown:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for paliperidone palmitate 3-month injection (PP3M).

The purpose of this teleconference meeting was to reach agreement on the Phase 3 drug development program for this drug product.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call CDR Sonny Saini at (301) 796-0532.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** pre-Phase 3 meeting  
**Meeting Date and Time:** November 4, 2011; 1:00 – 1:15 pm  
**Meeting Location:** Teleconference  
**Application Number:** IND 76,952  
**Product Name:** paliperidone palmitate 3-month injection (PP3M)  
**Indication:** (b) (4) treatment of schizophrenia in patients stabilized on the 1-month product.  
**Sponsor/Applicant Name:** Johnson&Johnson Pharmaceutical Research & Development  
**Meeting Chair:** Thomas Laughren, M.D.  
**Meeting Recorder:** Sonny Saini, Pharm.D., MBA

### **FDA Participants:**

Thomas Laughren, M.D., Division Director, Division of Psychiatry Products  
Robert Levin, M.D., Clinical Team Leader  
Christina Burkhart, M.D., Clinical Reviewer  
Yeh-Fong Chen, Ph.D., Statistical Reviewer  
Peiling Yang, Ph.D., Statistician Team Leader  
Hao Zhu, Ph.D., OCP Team Leader  
Islam Younis, Ph.D., OCP Reviewer  
Sonny Saini, Pharm.D., MBA, Project Manager

### **J&J PRD Participants:**

Joris Berwaerts, M.D., Director, Clinical Research  
Peter Briscoe, M.D., Compound Development Team Leader  
Jacqueline Brown, R.Ph., Regulatory Affairs Professional  
Lindsay Cobbs, R.Ph., Regulatory Affairs FDA Liaison  
Danielle Coppola, M.D., Director, Clinical Research  
Srihari Gopal, M.D., Clinical Leader  
Isaac Nuamah, Ph.D., Statistical Leader  
Bart Remmerie, Chem. Eng., Clinical Pharmacology Leader  
Patrick Sterkens, Ph.D., Preclinical Leader  
James Tan, Ph.D., Global Regulatory Affairs Leader

### **Background:**

Johnson & Johnson Pharmaceutical Research & Development, LLC (J&J PRD) has requested an End-of-Phase 2/Pre-Phase 3 Meeting to reach agreement with the Division on the development program for paliperidone palmitate 3-month injection (PP3M) for the (b) (4) treatment of schizophrenia in patients stabilized on the one month product (INVEGA<sup>®</sup> SUSTENNA<sup>®</sup>).

The sponsor has developed 3 formulations of paliperidone: an oral extended-release formulation (INVEGA<sup>®</sup>), a long-acting injectable 1-month formulation (INVEGA<sup>®</sup> SUSTENNA<sup>®</sup>), and a

long-acting injectable 3-month formulation (PP3M). INVEGA<sup>®</sup> was approved in the United States for the treatment of adult schizophrenia in 2006, for the treatment of schizoaffective disorder in adults in July 2009, and for the treatment of schizophrenia in adolescents in April 2011. INVEGA<sup>®</sup> SUSTENNA<sup>®</sup> was approved in the United States for the treatment of schizophrenia in adults in July 2009.

The long-acting injectable 3-month formulation (PP3M) is in development and is not approved in any country. The product is not planned to be used as a first-line agent. It is planned to be used in patients who have already responded to treatment with INVEGA<sup>®</sup> SUSTENNA<sup>®</sup> and who have been treated for several injection cycles so that their paliperidone plasma concentrations have approached steady state. The main differences between the PP3M and PP1M (marketed Sustenna) formulations are (b) (4) the concentration of the suspension, and the injection volume.

At a pre-IND meeting on August 20, 2007, we discussed the following key points:

1. To support filing for the PP3M formulation, the Agency is requiring a single, placebo-controlled Phase 3 safety/efficacy study. If dose fluctuations of the new formulation were within the overall exposure (including peak-trough ratio) of those from approved doses of formulation, the Agency would not have required a clinical safety/efficacy study for the new formulation.
2. **The Division found the sponsor's proposal for safety exposure to be sufficient: ~400 subjects receiving at least 1 dose, 100 subjects for 6 months, and 50 subjects for 1 year.**
3. **The Division agreed with the sponsor's proposal that a single preclinical local tolerability study comparing PP1M and PP3M would be sufficient to support the clinical use of PP3M.**

Clinical development of PP3M was initiated in 2008. A multi-panel Phase 1 single-dose pharmacokinetic, safety, and tolerability study (R092670-PSY-1005) in adult subjects with schizophrenia is ongoing. Panels A and C of Study R092670-PSY-1005 have been completed. Data from Panel A led to the selection of the (b) (4) technology as the optimal manufacturing process for the formulation. In Panel B, the sponsor is evaluating the PK profiles (AUC and Cmax) for different doses and injection sites. Panel B has reached the interim milestone (15 of the targeted 25 subjects in each treatment group have completed the first 6 months of the PK observation period) and the preliminary data have been included in the **meeting package for the Division's review. A new panel, Panel D, is planned to evaluate further doses at different injection sites. Doses from 117 mg to 819 mg will be evaluated in Panels B and D.**

Particle size and injection volume/dose are the key determinants affecting the release characteristics of paliperidone palmitate. The Phase 1 program for PP1M demonstrated that (b) (4) (b) (4) In addition, a higher injected volume resulted in slower intramuscular absorption. (b) (4)

The half-life of the PP3M formulation is approximately 106 days. The  $AUC_{\infty}$  was dose proportional. The  $C_{max}$  was generally higher after deltoid injection compared to gluteal injection at comparable doses. Paliperidone plasma concentrations were in line with population PK predictions. The sponsor states that the overall safety profile of PP3M was consistent with PP1M.

The sponsor's proposed Phase 3 clinical development program for PP3M includes a relapse prevention study (R092670-PSY-3012) in adults with schizophrenia and a Phase 3 noninferiority study (Study R092670-PSY-3011) of PP3M and INVEGA® SUSTENNA® (PP1M). The sponsor proposes a 3.5-fold dose conversion factor for PP1M (78, 117, 156, and 234 mg) to PP3M (273, 410, 546, and 819 mg) in the Phase 3 studies.

**Questions:**

**Preclinical**

1) *Adequacy of Preclinical Data*

In addition to the previously completed 3-month preclinical tolerability study between the 1-month and 3-month (702 mg [450 mg eq]) formulations, J&J PRD is planning to conduct a similar additional 3-month preclinical tolerability study to assess the use of higher doses of the 3-month formulation (819 mg [525 mg eq]).

A) Assuming the results from this additional study are consistent with the completed study, does the FDA agree that these 2 studies would be sufficient to support the initiation of the proposed Phase 3 studies R092679-PSY-3011 and -PSY-3012?

**Preliminary Comments:**

*Yes, we agree.*

**Discussion at Meeting:**

*No further discussion.*

B) Does the FDA agree that these studies, along with the previously conducted nonclinical development program on the oral and 1-month injectable formulations, are sufficient to meet the requirements of the nonclinical documentation for the NDA of the PP3M product?

**Preliminary Comments:**

*Yes, we agree, as long as no new issues of concern arise from future clinical studies that may require additional nonclinical safety assessment.*

**Discussion at Meeting:**

*No further discussion.*

## Clinical Pharmacology

### 2) *Adequacy of Pharmacokinetic Data*

Clinical PK data will be obtained from PK study R092670-PSY-1005 and from semi-intensive PK sampling in the Phase 3 relapse prevention study (R092670-PSY-3012). Will these data be adequate to:

- A) Document the PK of PP3M;
- B) Support prescribing information instructions on switching from PP1M to the corresponding PP3M dose;
- C) And support filing of an NDA for the 273, 410, 546, and 819 mg (175, 263, 350, and 525 mg eq, respectively) strengths of the PP3M formulation?

#### *Preliminary Comments:*

*The proposed plan is adequate to address the above mentioned items.*

#### *Discussion at Meeting:*

*No further discussion.*

3) Based on the 6-month interim results of the Phase 1 study R092670-PSY-1005, does the FDA agree with the Company's position that the single-dose safety and PK data collected for doses up to and including the 702 mg (450 mg eq) dose in Study R092670-PSY-1005 are adequate to initiate Phase 3?

#### *Preliminary Comments:*

*You may initiate the single dose PK study for the highest dose of 819 mg (525 mg eq) in parallel with the phase 3 study. We recommend that you have at least three month safety and exposure data from the 819 mg single dose PK study before dosing the first patient with this dose in your planned phase 3 study R092670-PSY-3012.*

#### *Discussion at Meeting:*

*The sponsor stated they will have at least 3 months of safety data from the 819 mg single dose PK study before dosing the first patient with the dose in their planned phase 3 study R092670-PSY-3012. We agreed with this.*

## Clinical and Statistical

4) Does the FDA agree with the Company's proposed use of a 3.5-fold dose conversion factor for PP1M (78, 117, 156, and 234 mg) to PP3M (273, 410, 546, and 819 mg, respectively) in the Phase 3 studies?

#### *Preliminary Comments:*

*Yes, the proposed conversion factor is reasonable. It is possible that you may need to revise the conversion factor based on results of the PK study.*

**Discussion at Meeting:**  
*No further discussion.*

**5) Proposed Phase 3 Relapse Prevention Study (R092670-PSY-3012)**

A) Does the FDA agree that the overall design of the proposed placebo-controlled relapse prevention study (R092670-PSY-3012) is adequate to establish the safety and efficacy of PP3M as (b) (4) treatment of patients with schizophrenia to meet the FDA's requirements for an adequate and well-controlled study for a NDA?

**Preliminary Comments:**

*On face, the design appears adequate to support the proposed indication. This will be a matter of review. We will provide more detailed feedback once you have submitted the complete protocol.*

*Will subjects be treated with oral Invega to assess safety and tolerability before beginning treatment with Invega Sustenna?*

**Discussion at Meeting:**

*The sponsor clarified that subjects will have oral paliperidone tolerability testing for 4-6 days before beginning treatment with Invega Sustenna. This phase will be completed by Day -1.*

B) In particular, can the FDA confirm the adequacy of the following points:

- a) total number of subjects;
- b) distribution of subjects by dose;
- c) proportion of subjects from the US and other countries;
- d) duration of maintenance phase;
- e) injection site evaluations?

**Preliminary Comments:**

*The proposals for the items above are acceptable. Please make a plan to explore the potential treatment effect heterogeneity across regions.*

**Discussion at Meeting:**

*No further discussion.*

6) To support global registration of PP3M as (b) (4) treatment for schizophrenia, the Company is planning a second double-blind Phase 3 study to demonstrate noninferiority of the PP3M formulation to the approved PP1M formulation for the prevention of relapse in

patients who initially responded to treatment with PP1M. As this study will be ongoing at the time of the NDA submission, the Company plans to include limited safety information (summaries of deaths, serious adverse events, and discontinuations due to adverse events) based on a cutoff date 3 months prior to the planned NDA submission. Additional limited safety information will be included in the 4-month safety update. Does the FDA agree with this proposal for reporting information from Study R092670-PSY-3011 in the NDA and the 4-month safety update?

**Preliminary Comments:**

*Yes we agree.*

**Discussion at Meeting:**

*No further discussion.*

7) Based on Study R092670-PSY-3012, the following subject exposures are anticipated at the time of the NDA submission: 43 subjects for at least 12 months, with a total of 320 subjects receiving at least 1 dose of PP3M. Can the FDA confirm the adequacy of these exposure data for the NDA submission, review, and approval?

**Preliminary Comments:**

*The projected exposure appears reasonable. However, this will depend upon whether there are important safety signals that differ from those observed with Invega Sustenna for monthly injection.*

**Discussion at Meeting:**

*No further discussion.*

8) Does the FDA agree that studies with PP3M in pediatric patients aged 13 to 17 years are not required?

**Preliminary Comments:**

*The Division concurs that studies with PP3M in pediatric patients aged 13 to 17 years are not required, however, we cannot make a final determination until submission.*

**Discussion at Meeting:**

*No further discussion.*

9) As indicated at the pre-IND meeting, the FDA has determined and advised the Company that an adequate and well-controlled efficacy study with PP3M is required to support approval of the NDA because the PK characteristics of PP3M appear to differ substantially from the other paliperidone formulations. To satisfy this requirement, the Company will conduct Phase 3 study R092670-PSY-3012, a randomized, double-blind, placebo-controlled relapse prevention study designed to determine the efficacy and safety of PP3M in adults 18 to 65 years of age with schizophrenia. Approximately 392 subjects are planned to be enrolled in this study. The primary objective of Study R092670-PSY-3012 is to evaluate the efficacy of PP3M compared with placebo in delaying the time to first relapse of the symptoms of schizophrenia.

Because Study R092670-PSY-3012 is required by the FDA for approval of the NDA, in accordance with CFR 314.108(b)(5)(i-ii) the Company should be entitled to (b) (4) of marketing exclusivity for PP3M. Does the FDA agree that upon approval of the NDA, the PP3M formulation will be granted (b) (4) of statutory exclusivity?

**Preliminary Comments:**

*FDA does not award, comment on, or grant exclusivity prior to approval of a drug product; therefore, concurrence at this time would be premature. Exclusivity is granted post approval when new clinical studies essential for approval have been conducted.*

*Per the proposed rules as published in the Federal Register on July 10, 1989, "the Agency encourages meetings between FDA and sponsors of clinical investigations to facilitate drug development and the approval processes. However, the Agency does not agree that it is possible to determine before approval which, if any, studies will be essential based on such discussions."*

**Discussion at Meeting:**

*No further discussion.*

**Conclusions:**

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. The sponsor is responsible for notifying us of any significant differences in understanding their group has regarding the meeting outcomes.

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

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THOMAS P LAUGHREN  
11/04/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

PIND 76,952

Johnson and Johnson Pharmaceutical Research, L.L.C.  
Attention: Rodney Malchow, JD  
1125 Trenton-Harbourton Road  
P.O. Box 200  
Titusville, NJ 08560-0200

Dear Mr. Malchow:

Please refer to your Pre-Investigational New Drug Application (PIND) file for paliperidone palmitate injection.

We also refer to the meeting between representatives of your firm and the FDA on August 20, 2007. The purpose of the meeting was to discuss the preclinical and clinical program for a new 3-month formulation.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kimberly Updegraff, Regulatory Project Manager, at (301) 796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF MEETING

pIND 76,952; Paliperidone Palmitate 3-Month Injection  
Johnson & Johnson PR&D  
Pre-IND / Type B  
August 20, 2007

Participants –

### FDA

Thomas Laughren, MD	Division of Psychiatry Products Director
Mitchell Mathis, MD	Deputy Director
Karen Brugge, MD	Medical Reviewer
Barry Rosloff, PhD	Pharmacology/Toxicology Supervisor
Elzbieta Chalecka-Franasek, PhD	Pharmacology/Toxicology Reviewer
Ron Kavanagh, BSP, PharmD, PhD	Clinical Pharmacology Reviewer
Raman Baweja, PhD	Clinical Pharmacology Team Leader
Chhagan Tele, PhD	Chemistry Reviewer
Kimberly Updegraff, RPh, MS	Regulatory Project Manager

### Sponsor

Peter Briscoe, MD	CDT Leader
David Hough, MD	Clinical Leader
Adriaan Cleton, PhD	Clinical Pharmacology
Pilar Lim, PhD	Statistical Leader
Jaya Natarajan, PhD	Phase 1 Stat Manager
Jaskaran Singh, MD	Project Physician
Eric Yuen, MD	Therapeutic Area Head, CNS Clinical
Joseph Palumbo, MD	Psy Franchise Medical Leader
Dawn Kracht	Regulatory CMC Leader
James Tan, PhD	Global Regulatory Leader
Scott Reines, MD	CNS Clinical Head
WeiPing Li	Regulatory Head for J&JPRD (China) (Observer)
Kathleen Basmadjian, PhD	Regulatory Psychiatry Franchise Leader
Rodney Malchow, JD	Regulatory Leader

### Background:

Paliperidone is currently approved for the short-term and (b) (4) treatment of schizophrenia in an extended release formulation which was developed under IND

65,850.

(b) (4)

Paliperidone palmitate injection, a long-acting depot formulation of paliperidone (for q 1 month injections), is being developed for both the acute and maintenance treatment of schizophrenia, under IND 67,356.

(b) (4)

An NDA for the acute and maintenance treatment of schizophrenia with q 1 month paliperidone palmitate is planned for 4Q2007. This NDA would be based predominantly on 2 relatively short-term, placebo-controlled studies (R092670-PSY-3003; R092670-PSY-3004) and 1 maintenance trial (R092670-PSY-3001). Studies 3003 and 3004 were 13-week, placebo-controlled, fixed dose studies (50, 100, and 150 mg eq for study 3003 and 25, 50, and 100 mg eq for study 3004). Study 3001 was a maintenance study involving schizophrenia patients who had been stabilized during a 33-week open label phase on paliperidone ER and the responders were randomized to flexible-dosing with paliperidone palmitate (25, 50, 75, or 100 mg eq), or placebo. The primary endpoint was time to relapse. Data will also be provided for study R092670-SCH-201, an 11-week study comparing 2 fixed doses of paliperidone palmitate (50 and 100 mg eq) vs placebo in acute schizophrenic patients. There are several ongoing studies as well. At the time of filing, the sponsor expects to have at least 300 patients exposed for at least 6 months and at least 100 patients exposed for at least 1 year.

IND 76,952 is for an every 3-month formulation of paliperidone palmitate. It has the same active ingredient and excipients as the once-monthly formulation.

(b) (4)

Also, the maximum volume to be injected would increase.

(b) (4)

OCP has made some predictions about the comparative pk properties of the q 3 mo formulation, and has estimated that the C<sub>max</sub> will be roughly twice that seen with the OROS paliperidone formulation, and the C<sub>min</sub> roughly 30% less than OROS. Thus, they predict that, depending on dose (the range of doses will be 75 to 450 mg q 3 months), this formulation may be associated with excessive exposures at the high end and possibly subtherapeutic exposures at the low end.

The purpose of the meeting is to discuss the preclinical and clinical program for this new formulation. A pk study for this formulation is planned for later this year (R092670-PSY-1005). The purpose of this study is to assess the safety, pk, and dose proportionality of the 3-month formulation, and to study switching from the 1-month to 3-month formulation.

(b) (4)

## **Questions:**

### **1.1.1. CMC**

**Question 1:** Does the Division agree that the Sponsor cross-reference IND 67,356 for complete CMC information for the paliperidone palmitate Active Pharmaceutical Ingredient (API) information for the paliperidone palmitate 3-month formulation IND, as the information remains unchanged.

**Preliminary Comments:** *Your plan to cross-reference IND 67,356 for drug substance information is acceptable; however, information will need to be submitted showing how the drug substance particle size is controlled and tested. In addition, the CoAs of the drug substance lots to be utilized should also be submitted as part of the IND.*

**Discussion at Meeting:** *The sponsor clarified that the particle size limits will be part of the drug product specifications and not part of the API specifications.*

### **1.1.2. Preclinical Development Plan**

**Question 2:** The Sponsor has conducted an extensive preclinical development program involving paliperidone ER (IND 65,850, NDA 21-999 approved 19 December 2006, and NDA 22-043 approved 27 April 2007) and paliperidone palmitate (IND 67,356). Additionally, the Sponsor is executing a comparative 3-month preclinical tolerability study between the 1-month and the 3-month formulations. Does the Division agree that the preclinical development programs on the oral and intramuscular formulation, together with the tolerability study are sufficient:

A) To support the initiation of the planned Phase 1 clinical study?

**Preliminary Comments:** *Yes.*

**Discussion at Meeting:** *There was no further discussion of this question.*

B) To meet the requirements of the preclinical documentation for the NDA filing of the paliperidone palmitate 3-month formulation?

**Preliminary Comments:** *Yes, assuming no new issues arise in the future which need further study.*

**Discussion at Meeting:** *There was no further discussion of this question.*

### 1.1.3. Clinical Pharmacology/Clinical

**Question 3:** Does the Division agree with the Sponsor's proposal to provide in the paliperidone palmitate 3-month formulation IND, a summary of the efficacy and safety from the ongoing paliperidone palmitate 1-month formulation program in module 2.7 and cross-refer to IND 67,356 for all supporting documentation?

***Preliminary Comments:*** *It should be acceptable to provide a summary of the efficacy and safety from the ongoing paliperidone palmitate 1-month formulation program in module 2.7. However, we ask that you clarify what is meant by supporting documentation. Due to a lack of experience with INDs submitted in the eCTD format, the reviewability of cross referenced material is unknown. Until we have more experience with this format we believe that it would be prudent for information critical to the review not to be cross-referenced. Consequently, we ask that you please provide critical information in the 3 month formulation IND.*

***Discussion at Meeting:*** *The sponsor agreed to submit full reports of key studies to the IND and cross reference certain other data. After some discussion, the sponsor agreed to provide incidence tables (by organ system/AE term) of serious AEs (SAEs) and adverse dropouts (ADO) for trials in the 1 month IM IND (e.g. summary tables they plan to include in Module 2.7.4 for a future NDA for the 1 month product). They will also summarize any results that may suggest a new safety signal. The sponsor was asked to provide narratives for these subjects (post-meeting note: it would be helpful to hyperlink each case summary to the corresponding narrative).*

**Question 4:** Does the Division agree that the data [REDACTED] (b) (4) would be adequate to document the full pharmacokinetics of the 3-month paliperidone palmitate formulation for the NDA?

***Preliminary Comments:*** *No.* [REDACTED] (b) (4)

***Discussion at Meeting:*** [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]  
[REDACTED]. OCP is now in agreement with

*the plan. All agreed that we will not have a better sense of the extent of fluctuation between peak and trough concentrations until the planned phase 1 study is completed.*

**Question 5:** Given the extensive preclinical and clinical development work on paliperidone ER and paliperidone palmitate, is it acceptable to use the dose range of 75 mg eq. to 450 mg eq. of the 3-month paliperidone formulation as described in the proposed Phase 1 protocol provided in Appendix 3?

**Preliminary Comments:** *Yes.*

**Discussion at Meeting:** *There was no further discussion of this question.*

**Question 6:**

A. Does the Division concur that [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED] would be sufficient to support approval (assuming positive results and review) of an NDA for the 3-month paliperidone palmitate drug product for the treatment of schizophrenia indication?

**Preliminary Comments:** *No.* [REDACTED] (b) (4)  
[REDACTED]

*An adequate and well-controlled efficacy study would be needed, because the pk characteristics for the 3 month formulation appear to differ substantially from the other available formulations.*

**Discussion at Meeting:** *The sponsor is now proposing a placebo-controlled randomized withdrawal study involving patients who have been treated and responded adequately to the 1-month formulation and have been stable responders for a period of 13 to 25 weeks prior to randomization. These patients would be randomized to either the 3-month formulation or to placebo and observed for relapse. The sponsor indicated that supplementation with the ER formulation would be needed only during the initial switching (i.e., after first dose of the 3-month formulation). We indicated that, in principle, a design such as that proposed would be acceptable.*

[REDACTED] (b) (4)

B. [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED] does the Division agree that a [REDACTED] (b) (4) will provide sufficient data to support safety and efficacy requirements for approval of the 3-month formulation?

**Preliminary Comments:** No. [REDACTED] (b) (4)  
[REDACTED]

**Discussion at Meeting:** *We indicated that, in principle, the revised program would likely produce sufficient safety data to support an application. However, this will depend in part on the actual safety experience and pharmacokinetic properties of this formulation observed in the planned studies.*

#### 1.1.4. Safety

**Question 7:** Given the available safety data from the approved INVEGA (NDA 21-999 and NDA 22-043) and RISPERDAL/ RISPERDAL CONSTA (NDA 20-272, 20-588 and 21-346) programs, does the Division agree that [REDACTED] (b) (4) [REDACTED] will provide sufficient safety data to support approval of an NDA for use of the 3-month drug product, contingent on the approval of the 1-month drug product NDA?

**Preliminary Comments:** No. See answer to question 6.

**Discussion at Meeting:** See answer to question 6.

#### 1.1.5 Regulatory

**Question 8:** Does the Division agree that the proposed IND can follow the e-CTD specifications, listing items using the CTD modular headers as provided in the draft table of contents presented in Appendix 5?

**Preliminary Comments:** *Generally, the structure for the eCTD should suffice. However, individual disciplines may request modifications. For example, OCP feels that the number of header levels may not provide sufficient granularity to allow appropriate navigation of an application. At a minimum the number of header levels should include study titles and should begin with the study number. In addition, certain subtitles under the eCTD are misleading and more appropriate divisions and subtitle headers are needed.*

**Discussion at Meeting:** *The sponsor acknowledged these concerns and will attempt to address them.*

**Conclusions:**

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Johnson & Johnson PR&D is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

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Kimberly Updegraff, M.S., R.Ph.  
Regulatory Project Manager

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this page is the manifestation of the electronic signature.**  
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/s/

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Thomas Laughren  
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