

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**NDA 21-999/S-004**

***Trade Name:*** Invega Extended Release

***Generic Name:*** paliperidone

***Sponsor:*** Johnson & Johnson Pharmaceutical R. & D., LLC

***Approval Date:*** December 22, 2009

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**NDA 21-999/S-004**

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**CENTER FOR DRUG EVALUATION AND  
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***APPLICATION NUMBER:***  
**NDA 21-999/S-004**

**APPROVAL LETTER**



NDA 21-999/S-004

**APPROVAL LETTER**

Ortho-McNeil-Jassen Pharmaceuticals, Inc.  
Attention: James (Jimmy) Tan, Ph.D.  
Director, Global Regulatory Affairs  
920 Route 202 South  
P.O. Box 300  
Raritan, NJ 08869

Dear Dr. Tan:

Please refer to your supplemental new drug application dated November 7, 2007, received November 8, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for INVEGA™ (paliperidone) Extended-Release Tablets.

We acknowledge receipt of your submissions dated May 30, 2008, June 30, 2008, September 16, 2009, and November 25, 2009.

Your submission of September 16, 2009 constituted a complete response to our June 30, 2009 action letter.

This “Prior Approval” supplemental new drug application provides for revision of the dissolution acceptance criteria for the 1.5 mg, 3.0 mg, 6.0 mg, 9.0 mg, and 12.0 mg tablets as follows:

Sampling Time	% Dissolved of labeling claim
2h	(b) (4)
8h	
14h	
18 h	
24h	

We completed our review of this supplemental new drug application, as amended. This supplement is approved.

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Teshara G. Bouie, Regulatory Health Project Manager, at (301) 796-1649.

Sincerely,

*{See appended electronic signature page}*

Eric P. Duffy, Ph.D.

Director

Division of Post-Marketing Evaluation

Office of New Drug Quality Assessment

Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21999	SUPPL-4	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	INVEGA

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/s/

ERIC P DUFFY  
12/22/2009

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**NDA 21-999/S-004**

**OTHER ACTION LETTERS**



NDA 21-999/S-004

**COMPLETE RESPONSE**

Ortho-McNeil-Jassen Pharmaceuticals, Inc.  
Attention: James (Jimmy) Tan, Ph.D.  
Director, Global Regulatory Team Leader  
920 Route 202 South  
P.O. Box 300  
Raritan, NJ 08869

Dear Dr. Tan:

Please refer to your supplemental new drug application (sNDA) dated November 7, 2007, received November 8, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for INVEGA™ (paliperidone) Extended-Release Tablets, 3 mg, 6 mg, 9 mg, and 12 mg.

We acknowledge receipt of your amendment dated May 30, 2008 and June 30, 2008.

The June 30, 2008 amendment constituted a complete response to our March 7, 2008 action letter.

This supplemental new drug application provides for (b) (4) the dissolution specification based upon an *In Vitro-In Vivo* Correlation (IVIVC) study.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

Your proposal for (b) (4) release specifications for the paliperidone ER tablet based upon the submitted IVIVC study as proposed is unacceptable, however we recommend adopting revised dissolution acceptance criteria as follows: at 14 hours, (b) (4) and at 18 hours, (b) (4)

Before the IVIVC can be accepted validation data showing the predictability of correlation as outlined in the IVIVC guidance should be presented. While the approach used by the sponsor might be acceptable from a statistical point of view (b) (4)

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission



must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/cder/guidance/2125fnl.htm>).

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Teshara Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

*{See appended electronic signature page}*

Eric P. Duffy, Ph.D.  
Director  
Division of Post-Marketing Evaluation  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

-----  
Eric Duffy  
6/30/2009 02:28:17 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-999/S-004

Johnson & Johnson Pharmaceutical R & D, L.L.C.  
c/o Janssen, L.P.  
Attention: Lori Birkenberger, Ph.D., Director, Regulatory Affairs  
920 Route 202 South, P.O. Box 300  
Raritan, NJ 08869

Dear Dr. Birkenberger:

Please refer to your supplemental new drug application dated November 7, 2007, received November 8, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for INVEGA™ (paliperidone) Extended-Release Tablets, 3 mg, 6 mg, 9 mg, and 12 mg.

This "Prior Approval" supplemental new drug application provides for (b) (4) the in vitro release specifications of INVEGA Tablets and study R076477-SCH-1018.

We completed our review of this supplemental application, and it is approvable. Before this supplement may be approved, however, you must address the following deficiencies:

The following clarifications and additional analyses are needed for full assessment of the study results.

- A) Inspection of individual plasma concentration-time data following administration of the three paliperidone ER formulations (designated as Fast, Target and Slow prototypes) show that there is significant overlap in individual data. For example, paliperidone mean  $\pm$  SD Cmax values for Fast, Target, and Slow release formulations are (b) (4) respectively.
- 1) Please calculate and provide a statistical comparison of partial AUC values for these formulations: (b) (4) as carried out for the submitted PK parameters.
  - 2) Please pool all pharmacokinetic parameters (Cmax, AUC values and tmax) from the (b) (4) formulations and the above partial AUC values and provide a cluster analysis. It would be desirable, to explore the data in quartiles, in addition, to the clusters that will be dictated by the data. To the extent possible, please provide confidence interval comparisons using the cluster that represents the central tendency as reference.  
Please provide a list of these values, per cluster and for each value, please also indicate the formulation and the period when it was received.

B) Please provide the following clarification and reanalyses for further assessment of the IVIVC model.

(b) (4)



Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

*{See appended electronic signature page}*

James D. Vidra, Ph.D.  
Branch Chief  
Branch VII, Division of Post-Marketing Evaluation  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

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Jim Vidra

3/7/2008 04:13:49 PM

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***APPLICATION NUMBER:***  
**NDA 21-999/S-004**

**SUMMARY REVIEW**



## Memorandum

Date: 6/30/2009

To: NDA 21-999/S-004, Invega (paliperidone) Extended-Release Tablets

Subject: Signatory Decision

From: Eric P Duffy, PhD, Director, DPE, ONDQA

---

This memorandum serves to summarize the decision made leading to the complete response action 6/30/2009.

This supplement provided for (b) (4) the dissolution specification based upon an In Vitro-In Vivo Correlation (IV/IVC) study. Note that the study design had been agreed to following meetings with the Office of Clinical Pharmacology. The second cycle CMC review was performed by Dr Donald Klein (see reviews dated 4/6/2009 and 6/29/2009) and the Biopharmaceutics review was performed by Dr Arzu Selen (see review dated 4/1/2009). The CMC review conclusion was to defer to the conclusion of the Biopharmaceutics review, which in turn was that the IV/IVC had not been established which was based largely upon the conclusion that (b) (4) and therefore the supplement was not approvable.

No progress was seen to be accomplished in the interactions between J&J and the Agency to resolve the issues identified in the Biopharmaceutics reviews, therefore an alternative approach to resolution was sought. After discussions with Dr Marroum regarding this issue, it was agreed that change in the dissolution specification could not be made based upon the submitted IV/IVC study. However, in accordance with recommendations in the *Guidance for Industry, Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations*, for dissolution specification change in the absence of an established IV/IVC, the acceptance criteria, could be changed by the guidance recommended amount. In addition, the recommended approach for acceptable conduct of an IV/IVC study would be communicated in the action letter. It should be noted that Dr Selen disagrees with this decision and the recommendation.

The following was communicated in the Complete Response letter:

Your proposal for (b) (4) release specifications for the paliperidone ER tablet based upon the submitted IVIVC study as proposed is unacceptable, however we recommend adopting revised dissolution acceptance criteria as follows: at 14 hours, (b) (4) and at 18 hours, (b) (4)

Before the IVIVC can be accepted validation data showing the predictability of correlation as outlined in the IVIVC guidance should be presented. While the approach used by the sponsor might be acceptable from a statistical point of view, (b) (4)

[REDACTED]



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21999	SUPPL-4	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	INVEGA

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/s/

ERIC P DUFFY  
12/22/2009

**CENTER FOR DRUG EVALUATION AND  
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***APPLICATION NUMBER:***  
**NDA 21-999/S-004**

**CHEMISTRY REVIEW(S)**

**NDA 21-999, S-004**

**DIVISION OF POST-MARKETING EVALUATION  
Review of Chemistry, Manufacturing, and Controls**

**NDA#: 21-999**

**DATE REVIEWED: 12/11/2009**

**REVIEW #: 3**

**REVIEWER: Donald N. Klein, Ph.D.**

<b><u>SUBMISSION TYPE</u></b>	<b><u>DOCUMENT DATE</u></b>	<b><u>CDER DATE</u></b>	<b><u>ASSIGNED DATE</u></b>
<b>PA (EDR)</b>	11/7/07	11/8/07	12/7/07
CMC Review # 1 (Team review with Dr. Selen and Dr. Mahayni)	3/7/08	3/7/08	n/a
<b>AE Letter</b>	3/7/08	3/7/08	n/a
(BZ) Amendment	5/28/08	5/28/08	6/12/08
(AC) Response	6/30/08	6/30/08	6/30/08
ONDQA Biopharmaceutics Review	4/1/09	4/1/09	4/1/09
CMC Review # 2 (Team review with Dr. Selen)	4/6/09	4/6/09	n/a
<b>Complete Response Letter</b>	6/30/09	6/30/09	n/a
Meeting Request Letter	8/13/09	8/13/09	n/a
Agency (Dr. Duffy) denies Meeting request	9/4/09	9/4/09	n/a
(b) (4)			
(BC) Amendment	11/25/09	11/25/09	11/25/09
ONDQA Biopharmaceutics Review	11/30/09	11/30/09	11/30/09

**NAME & ADDRESS OF APPLICANT:**

Johnson & Johnson Pharmaceutical R & D, L.L.C.  
920 Route 202, South  
P.O. Box 300  
Raritan, NJ 08869

**On behalf of:**

Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
1125 Trenton-Harbourton Road  
P.O. Box 200  
Titusville, NJ 08560

**DRUG PRODUCT NAME:**

Proprietary: Invega<sup>®</sup>.  
Established (2004): Paliperidone.  
Code: JNJ16232411; R076477.

**PHARMACOL. CATEGORY/INDICATION:** Schizophrenia and schizoaffective disorder.

**DOSAGE FORM:** Extended Release Tablets.

**STRENGTHS:** 1.5 mg (F078), 3.0 mg (F039), 6.0 mg (F040), 9.0 mg (F041), and 12.0 mg (F045).

**ROUTE OF ADMINISTRATION:** Oral.

**Rx/OTC:** Rx.

**SPECIAL PRODUCTS:** \_\_\_ Yes xx No.

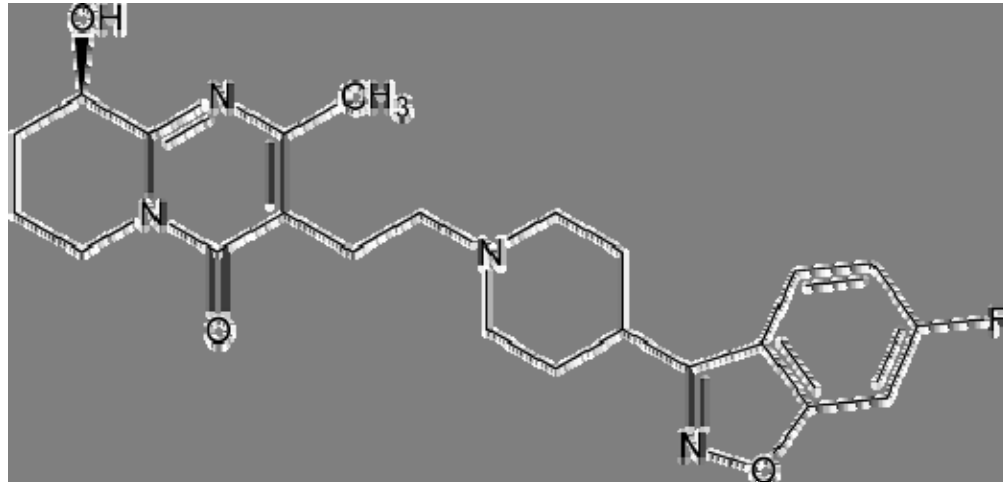
**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Chemical Name: (b) (4)

Molecular Formula: C<sub>23</sub>H<sub>27</sub>FNH<sub>4</sub>O<sub>3</sub>.

MW: (b) (4)

CAS: 144598-75-4.

**Chemical Structure:**

**SUPPLEMENT PROVIDES FOR:** Revision of the dissolution acceptance criteria for the 1.5 mg, 3.0 mg, 6.0 mg, 9.0 mg, and 12.0 mg tablets as follows:

14 hours: (b) (4)

18 hours: (b) (4)

**RELATED SUPPLEMENTS:**

1. N21-999, S-005 (PA (OND managed), **Approved 8/26/08**; Review chemist: Dr. Klein):  
1.5 mg dosage strength.

(b) (4)

**CONCLUSION:** Recommend Approval.

3 Pages Immediately Following Withheld - b(4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21999	SUPPL-4	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	INVEGA

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/s/

DONALD N KLEIN

12/11/2009

PA; 3rd review cycle; DUE 1/16/2010; Approval recommended.

JAMES D VIDRA

12/11/2009

**NDA 21-999, SCS-004**

**DIVISION OF POST-MARKETING EVALUATION  
Review of Chemistry, Manufacturing, and Controls**

**NDA#:** 21-999

**DATE REVIEWED:** 4/2/09

**OND:** HFD-130

**REVIEW #:** 2

**REVIEWER:** Donald N. Klein, Ph.D.

<b><u>SUBMISSION TYPE</u></b>	<b><u>DOCUMENT DATE</u></b>	<b><u>CDER DATE</u></b>	<b><u>ASSIGNED DATE</u></b>
PA (EDR)	11/7/07	11/8/07	12/7/07
CMC Review # 1	3/7/08	3/7/08	n/a
AE Letter	3/7/08	3/7/08	n/a
(BZ) Amendment	5/28/08	5/28/08	6/12/08
(AC) Response	6/30/08	6/30/08	6/30/08

**NAME & ADDRESS OF APPLICANT:**

Janssen, L.P.  
Johnson & Johnson Pharmaceutical R & D, L.L.C.  
920 Route 202 South  
P.O. Box 300  
Raritan, NJ 08869

**DRUG PRODUCT NAME:**

Proprietary: Invega®  
Established (2004): Paliperidone.

**PHARMACOL. CATEGORY/INDICATION:** Schizophrenia.

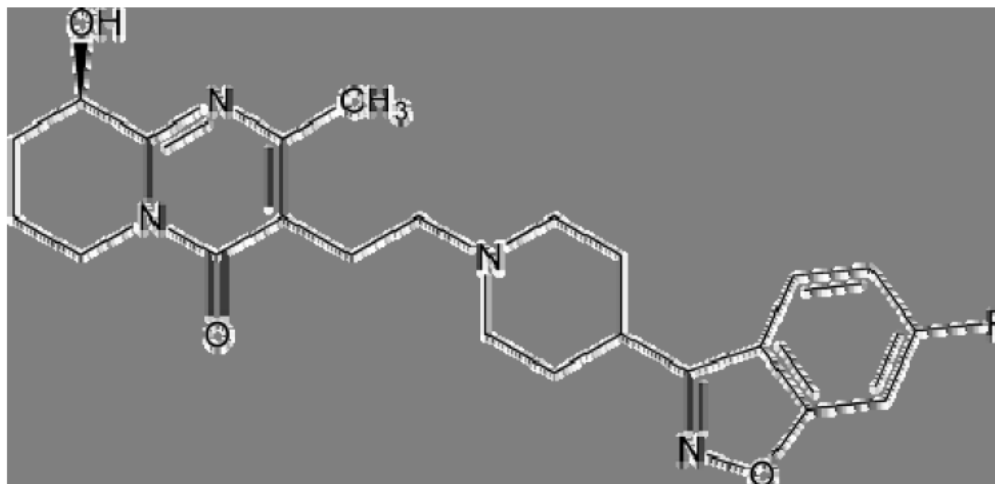
**DOSAGE FORM:** Extended Release Tablets.

**STRENGTHS:** 3.0 mg, 6.0 mg, 9.0 mg, 12.0 mg (b) (4)

**ROUTE OF ADMINISTRATION:** Oral.

**Rx/OTC:** Rx.

**SPECIAL PRODUCTS:** \_\_\_ Yes xx No.

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:****Chemical Name:** (b) (4)**Molecular Formula:**  $C_{23}H_{27}FNH_4O_3$ .**MW:** (b) (4)**CAS:** 144598-75-4.**Chemical Structure:****SUPPLEMENT PROVIDES FOR:** (b) (4) the *in vitro* release Specifications of the drug product.**CONCLUSION:** **Recommend Not Approvable;** Considering Dr. Selen's recommendation, Dr. Klein suggests SCS-004 be issued a not approvable letter.

4 Pages Immediately Following Withheld - b(4)



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/s/

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Donald Klein

4/2/2009 01:48:12 PM

CHEMIST

Dr. Selen completed her review on 4/1/09. Dr. Selen's  
evaluation is critical for the evaluation of the  
proposed change. Based on her review, this S-004  
should receive a NA Letter.

2nd review cycle (PA); I recommend a NA Letter be issued.

Jim Vidra

4/6/2009 09:45:31 AM

CHEMIST

**NDA 21-999, SCS-004**

**DIVISION OF POST-MARKETING EVALUATION  
Review of Chemistry, Manufacturing, and Controls**

**NDA#: 21-999**

**DATE REVIEWED: 3/7/08**

**REVIEW #: 1**

**REVIEWER:** Donald N. Klein, Ph.D.

<b><u>SUBMISSION TYPE</u></b>	<b><u>DOCUMENT DATE</u></b>	<b><u>CDER DATE</u></b>	<b><u>ASSIGNED DATE</u></b>
PA (EDR)	11/7/07	11/8/07	12/7/07

**NAME & ADDRESS OF APPLICANT:**

Janssen, L.P.  
Johnson & Johnson Pharmaceutical R & D, L.L.C.  
920 Route 202 South  
P.O. Box 300  
Raritan, NJ 08869

**DRUG PRODUCT NAME:**

Proprietary: Invega<sup>®</sup>  
Established (2004): Paliperidone.

**PHARMACOL. CATEGORY/INDICATION:** Schizophrenia.

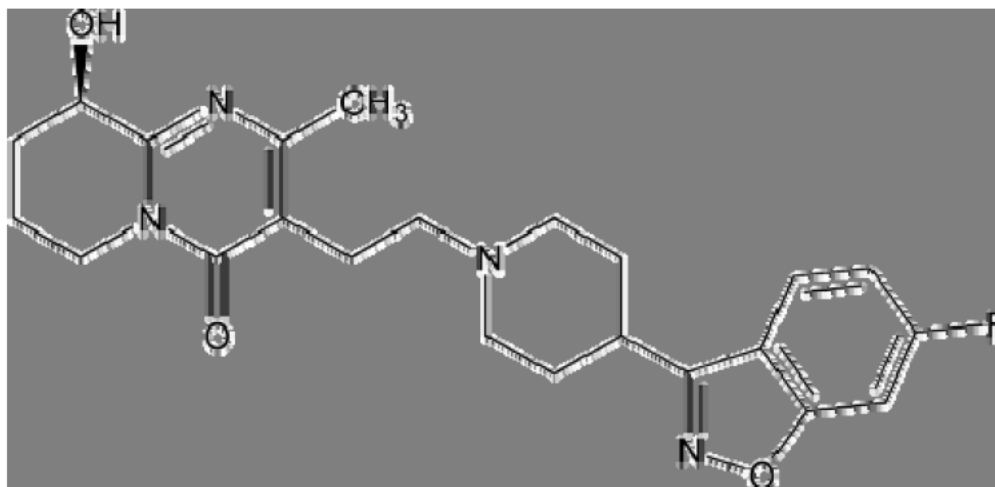
**DOSAGE FORM:** Extended Release Tablets.

**STRENGTHS:** 3.0 mg, 6.0 mg, 9.0 mg, 12.0 mg, (b) (4)

**ROUTE OF ADMINISTRATION:** Oral.

**Rx/OTC:** Rx.

**SPECIAL PRODUCTS:** \_\_\_ Yes xx No.

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:****Chemical Name:** (b) (4)**Molecular Formula:** C<sub>23</sub>H<sub>27</sub>FNH<sub>4</sub>O<sub>3</sub>.**MW:** (b) (4)**CAS:** 144598-75-4.**Chemical Structure:****SUPPLEMENT PROVIDES FOR:** (b) (4) the *in vitro* release Specifications of the drug product.**RELATED SUPPLEMENT:** N21-999, SCM-005 (PA (OND managed), DUE on 3/20/08): Proposed the 1.5 mg dosage strength. Also, the applicant proposed the (b) (4) of the Release Rate as proposed in this SCS-004:

0 – 14 h (b) (4) of label claim

0 – 18 h (b) (4) of label claim

**CONCLUSION:** Recommend Approvable.

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/s/

-----  
Donald Klein  
3/7/2008 03:28:31 PM  
CHEMIST  
Team review with Dr. Selen.  
PA: DUE 3/8/08.

Jim Vidra  
3/7/2008 03:46:27 PM  
CHEMIST

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**NDA 21-999/S-004**

**CLINICAL PHARMACOLOGY AND**  
**BIOPHARMACEUTICS REVIEW(S)**

## ONDQA BIOPHARMACEUTICS REVIEW

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<b>NDA#:</b>	<b>21-999/S-004</b>
<b>Submission Date:</b>	9/16/09
<b>Brand Name:</b>	Invega
<b>Generic Name:</b>	Paliperidone
<b>Formulation:</b>	Extended Release Tablets
<b>Strength:</b>	1.5, 3, 6, 9, 12mg
<b>Sponsor:</b>	J&J
<b>Reviewer:</b>	John Duan, Ph.D.
<b>Submission Type:</b>	(b) (4) the In Vitro Release specifications

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### BACKGROUND

Prior Approval Supplement (S-004) proposed (b) (4) the dissolution specifications based upon an In Vitro-In Vivo Correlation (IVIVC) study and seeking agreement on IVIVC submitted on 8 November 2007. FDA issued an approvable letter for S-004 on March 7, 2008 and the sponsor submitted a Complete Response to the approvable letter on June 30, 2008. FDA subsequently issued a Complete Response letter dated June 30, 2009, including revised dissolution acceptance criteria. In response, the sponsor submitted a Meeting Request with new proposed dissolution acceptance criteria on August 13, 2009. FDA denied the meeting request and concurred with the sponsor's proposed dissolution acceptance criteria.

Included in this submission is Complete Response to FDA's Complete Response Letter of June 30, 2009. Also provided are the release and stability specifications for INVEGA® ER Tablets. The sponsor is accepting the revised specifications and foregoing seeking approval of the IVIVC at this time. The application of the specifications to the 1.5 mg tablet strength approved while S-004 was under review is requested.

### ACCEPTANCE CRITERIA OF DISSOLUTION SPECIFICATIONS

In the Agency's Complete Response letter dated June 30, 2009, the Agency recommended adopting revised dissolution acceptance criteria as follows:

14 hours: (b) (4)  
18 hours: (b) (4)

On August 13, 2009, the Sponsor requested a meeting to discuss these recommended specifications for which the 0 – 18 hour specification was not aligned well with clinical or commercial batches. The Sponsor proposed adopting revised dissolution acceptance criteria as follows:

14 hours: (b) (4)  
18 hours: (b) (4)

In a letter dated September 4, 2009, the Agency accepted the Sponsor's proposed dissolution acceptance criteria.

#### **WITHDRAWAL OF IVIVC MODEL AND AMENDMENT OF S-004**

The sponsor requests to remove the IVIVC model from NDA 21-999/S-004.

The sponsor amends NDA 21-999 S-004 to include the 1.5 mg paliperidone ER INVEGA® Tablets. The 1.5 mg tablet was approved while S-004 was under review.

The revised dissolution acceptance criteria for the 3 mg, 6 mg, 9 mg and 12 mg tablets are proposed to be applied to the 1.5 mg tablets. The Invega 1.5 mg tablets are (b) (4) qualitatively the same to other strengths; all strengths have the same release mechanism and all strengths are dose proportional. All strengths have similar in vitro dissolution profiles. To confirm the similarity of dissolution profiles among different strengths, the reviewer obtained the dissolution data for 1.5 mg strength from the current submission and the dissolution data for other strengths from the batch analysis submitted in previous supplement dated April 30, 2008 as shown in the following table.

Tablet Strength	Batch	2 h	8 h	14 h	18 h	24 h	Source
1.5	608069	(b) (4)					Current
1.5	608070						Current
1.5	607179						Current
3	7JD0039-X						April 30, 2008
3	7JD0040-X						April 30, 2008
3	7JD0041-X						April 30, 2008
6	7HD0004-X						April 30, 2008
9	7LD0047-X						April 30, 2008
9	7LD0048-X						April 30, 2008
9	7LD0049-X						April 30, 2008
12	602596						April 30, 2008
12	7AG1026-X						April 30, 2008

All these batches have similar dissolution profiles evidenced by f2 calculation as shown in the following table.

Comparison	f2	Comparison	f2
608069 to 608070	78.9	7JD0039-X to 7LD0047-X	67.0
608069 to 607179	88.1	7JD0039-X to 7LD0048-X	78.0
608069 to 7JD0039-X	75.7	7JD0039-X to 7LD0049-X	87.4
608069 to 7JD0040-X	73.0	7JD0039-X to 602596	74.6
608069 to 7JD0041-X	89.6	7JD0039-X to 7AG1026-X	87.5
608069 to 7HD0004-X	74.8	7JD0040-X to 7JD0041-X	80.5
608069 to 7LD0047-X	64.1	7JD0040-X to 7HD0004-X	65.3
608069 to 7LD0048-X	73.8	7JD0040-X to 7LD0047-X	69.5
608069 to 7LD0049-X	84.9	7JD0040-X to 7LD0048-X	73.2
608069 to 602596	80.6	7JD0040-X to 7LD0049-X	67.6

608069 to 7AG1026-X	79.9	7JD0040-X to 602596	81.0
608070 to 607179	88.1	7JD0040-X to 7AG1026-X	69.3
608070 to 7JD0039-X	76.6	7JD0041-X to 7HD0004-X	71.2
608070 to 7JD0040-X	76.4	7JD0041-X to 7LD0047-X	65.9
608070 to 7JD0041-X	78.9	7JD0041-X to 7LD0048-X	74.6
608070 to 7HD0004-X	79.5	7JD0041-X to 7LD0049-X	78.6
608070 to 7LD0047-X	75.0	7JD0041-X to 602596	85.5
608070 to 7LD0048-X	87.4	7JD0041-X to 7AG1026-X	76.2
608070 to 7LD0049-X	76.9	7HD0004-X to 7LD0047-X	69.6
608070 to 602596	87.0	7HD0004-X to 7LD0048-X	81.3
608070 to 7AG1026-X	83.6	7HD0004-X to 7LD0049-X	83.9
607179 to 7JD0039-X	74.0	7HD0004-X to 602596	76.2
607179 to 7JD0040-X	79.2	7HD0004-X to 7AG1026-X	88.1
607179 to 7JD0041-X	88.1	7LD0047-X to 7LD0048-X	81.7
607179 to 7HD0004-X	74.8	7LD0047-X to 7LD0049-X	65.4
607179 to 7LD0047-X	68.4	7LD0047-X to 602596	74.3
607179 to 7LD0048-X	78.6	7LD0047-X to 7AG1026-X	70.0
607179 to 7LD0049-X	78.6	7LD0048-X to 7LD0049-X	76.6
607179 to 602596	85.3	7LD0048-X to 602596	86.4
607179 to 7AG1026-X	81.5	7LD0048-X to 7AG1026-X	84.1
7JD0039-X to 7JD0040-X	64.3	7LD0049-X to 602596	78.7
7JD0039-X to 7JD0041-X	71.2	7LD0049-X to 7AG1026-X	86.4
7JD0039-X to 7HD0004-X	96.3	602596 to 7AG1026-X	80.2

## REVISED SPECIFICATIONS

Revised specifications for all strengths (1.5 mg, 3 mg, 6 mg, 9 mg and 12 mg) are provided. The release rate testing of paliperidone ER tablets, as summarized below, is performed with a USP Release Rate Apparatus Type VII in 50 mL of modified artificial gastrointestinal fluid (NaCl 0.2% w/w in 0.0825 N HCl, pH 1.0 ± 0.5) that has been equilibrated in a constant temperature water bath controlled to 37 ± 0.5 °C. Paliperidone ER 1.5-mg tablets are each placed in a sample holder and immersed in the acidified water medium, with agitation via a reciprocating arm. At the end of specified test intervals, aliquots of test solutions are analyzed by HPLC with UV detection at 275 nm.

**Apparatus:** USP Release Rate Apparatus Type VII

**Medium:** Modified artificial gastrointestinal fluid (NaCl 0.2% w/w in 0.0825 N HCl, pH 1.0 ± 0.5) that has been equilibrated in a constant temperature water bath

**Volume:** 50 mL

**Temperature:** 37 ± 0.5 °C.

The revised dissolution acceptance criteria are summarized in the following table (with the values at 18 hours rounded).

Sampling Time	% Dissolved of labeling claim
2h	(b) (4)
8h	



14h	(b) (4)
18 h	
24h	

## COMMENTS

1. As indicated in the letter issued September 4, 2009, the proposed dissolution acceptance criteria for 3, 6, 9, and 12 mg strengths are acceptable. Please note the values for 18 h should be rounded (this was conveyed to the sponsor and agreement was reached).
2. The acceptance criteria can also applied to 1.5 mg strength of Paliperidone ER tablets.

## RECOMMENDATION

The proposed dissolution acceptance criteria are adequate with the values for 18 h rounded as shown below. An approval is recommended.

**Apparatus:** USP Release Rate Apparatus Type VII

**Medium:** Modified artificial gastrointestinal fluid (NaCl 0.2% w/w in 0.0825 N HCl, pH  $1.0 \pm 0.5$ ) that has been equilibrated in a constant temperature water bath

**Volume:** 50 mL

**Temperature:**  $37 \pm 0.5$  °C.

Sampling Time	% Dissolved of labeling claim
2h	(b) (4)
8h	
14h	
18 h	
24h	

\_\_\_\_\_  
John Duan, Ph.D.  
**Reviewer**  
**ONDQA Biopharmaceutics**

\_\_\_\_\_  
Date

\_\_\_\_\_  
Patrick Marroum, Ph.D.  
**ONDQA Biopharmaceutics**

\_\_\_\_\_  
Date

cc: NDA 21999  
Patrick Marroum, Angelica Dorantes, John Duan

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21999	SUPPL-4	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	INVEGA

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/s/

JOHN Z DUAN  
11/30/2009

PATRICK J MARROUM  
11/30/2009

## BIOPHARMACEUTICS REVIEW

NDA Number, submission date	NDA 21-999 S004, November 7, 2007, interim response to AE letter: 5/28/2008, and complete response: 6/30/2008
Sponsor	Johnson & Johnson Pharm. Research and Development L.L.C. in 2007. NDA rights transferred to Ortho-McNeil-Janssen Pharmaceuticals on 12/31/2007
Drug name (Generic name), formulation, and strengths	INVEGA (paliperidone) Extended Release Tablets, 3 mg, 6 mg, 9 mg and 12 mg
Clinical Division	Psychiatry Products
Primary CMC Reviewer	Donald Klein, Ph.D.
Biopharmaceutics Reviewer	Arzu Selen, Ph.D.

### EXECUTIVE SUMMARY AND RECOMMENDATION

Paliperidone is the 9-hydroxy metabolite (9-hydroxy) of risperidone and belongs to atypical antipsychotic class of psychotropic drugs. Paliperidone is a racemate of (+)- and (-)- paliperidone. It is a centrally active dopamine D2 antagonist with serotonergic 5-HT<sub>2A</sub> antagonistic activity. INVEGA<sup>TM</sup> (paliperidone) Extended Release Tablets for acute and maintenance treatment of schizophrenia were approved by the FDA in December 2006 and in April 2007, respectively. Invega ER tablets are manufactured according to ALZA OROS® osmotic drug release technology.

In November 2007, the Sponsor submitted a Prior Approval Supplement to NDA 21-999 to support (b) (4) the *in vitro* release specifications of the ER Tablets (specifically, the 0-14 hr and 0-18 hr samples). A pharmacokinetic study (Study R076477-SCH-1018) "Pharmacokinetic Evaluation of the Relative Bioavailability of Three Paliperidone Extended Release (ER) Formulations with Different *in vitro* Release Profiles and Comparison to Paliperidone Immediate Release (IR) in Healthy Male Subjects" was submitted to support a Level A *in vitro-in vivo* Correlation (IVIVC) for Invega ER tablets. Several review findings resulted in an approvable letter sent to the Sponsor in March 2008 and subsequently, a teleconference took place with the Sponsor to provide clarification on the requested data analyses. The interim analysis results were submitted to FDA on the 28<sup>th</sup> of May, followed by complete response on June 30<sup>th</sup>, 2008 (included in Appendix A).

This review is an assessment of the bioavailability study performed with 12 mg ER tablets with different *in vitro* release profiles, the *in vitro-in vivo* correlation (IVIVC) modeling efforts submitted by the Sponsor claiming development of a Level A IVIVC model for paliperidone ER tablets and the Sponsor's June 30<sup>h</sup> dated response to the biopharmaceutics questions raised in the March 2008 AE letter. The primary Quality/CMC reviewer for the related paliperidone submissions listed above is Donald Klein, Ph.D.

As background leading to this second attempt for developing an IVIVC, in the original NDA, the Sponsor had attempted to develop a Level A IVIVC model which was reviewed by Dr. Ronald Kavanagh (please see Dr. Kavanagh's Clinical Pharmacology and Biopharmaceutics review dated 9/12/2006). The proposed IVIVC submitted in the original NDA was unacceptable (b) (4)

Furthermore, in contrast to the approach in this supplement, (b) (4)

Prior to conduct of the study in this supplement, the Sponsor met with the Agency on February 22, 2007, to discuss the design of the relative bioavailability that the Sponsor was considering for (b) (4) the paliperidone release specification and for establishing a Level A IVIVC model for Invega ER tablets. The meeting minutes are included in Appendix B of this review. In summary, application of IVIVC for specification setting and the design of a bioavailability study that would support this approach were discussed.

In this submission, the Sponsor is proposing the following changes to the paliperidone cumulative release at 0-14 and 0-18 hr.

Time for Cumulative Release Assessment (hr)	Current Acceptance Criteria	Proposed Acceptance Criteria
(b) (4)		

The two main areas of focus of this review are:

- 1) Assessment of relative bioavailability of the products, reliability of parameters such as C<sub>max</sub> and AUC for this product as bioequivalence parameters, its relevance for release specification setting and the possible impact of proposed specification change (i.e. whether the revised specification change yield products with similar exposure and in vivo performance as the approved product studied in the pivotal clinical trials).
- 2) Validity of the proposed Level A IVIVC for paliperidone ER tablets.

Supporting representative figures and pharmacokinetic parameter tables are attached to this review (Appendix C).

### 1) Assessment of Relative Bioavailability/Bioequivalence:

Due to high variability in pharmacokinetic parameters, Study R076477-SCH-1018 was conducted in 80 healthy volunteers. The study treatments were 10 mL of 0.1 mg/mL paliperidone IR solution dose and 12 mg paliperidone ER tablets with the three different release profiles as described above ("Target", "Slow" and "Fast"). Of the three formulations studied, the "Target" formulation was similar in release profile to that studied in clinical studies and the "slow" and "fast" formulations had cumulative 0-14 hr release of (b) (4) respectively.

The descriptive summary of the paliperidone pharmacokinetic parameters are presented in the following table.

Table 4: Main Pharmacokinetic Parameters (Mean  $\pm$  SD) of Paliperidone  
(Study R076477-SCH-1018: Pharmacokinetic Analysis Set)

Treatment	C <sub>max</sub> (ng/mL)	AUC <sub>last</sub> (ng.h/mL)	AUC <sub>∞</sub> (ng.h/mL)	T <sub>max</sub> <sup>a</sup> (h)	t <sub>1/2</sub> (h)
1 mg IR solution (N=80)	(b) (4)				
12 mg target release formulation (n=74)					
12 mg slow release formulation (n=73)					
12 mg fast release formulation (n=73)					

<sup>a</sup>T<sub>max</sub>: median (range)

Cross Reference: [Module 5.3.1.2\R076477-SCH-1018\Attachment 2.1](#)

Inspection of individual plasma concentration-time data from the three ER tablets showed similar characteristics such as occurrence of multiple peaks, and rather erratic concentrations at earlier times (24 to 30 hrs after dosing). Despite the high variability (approximately, (b) (4) CV in C<sub>max</sub> and AUC values), mean C<sub>max</sub> and AUC values show proportional differences suggesting differences in the extent of absorption. As listed above, paliperidone mean (SD) for C<sub>max</sub> for the Target, Slow and Fast Formulations were (b) (4) ng/mL, respectively. Similar, proportional differences are noted in the AUC values. Since the difference in these products was stated to be the difference in release rates and not in the extent of absorption, it prompted further assessment of the paliperidone PK parameters from this dosage form and resulted in the questions raised in Section A of the AE letter.

Given the target for a t<sub>max</sub> of 20 or 24 hrs for paliperidone ER tablets, it is to be expected that the slower release would lower the amount of drug available at the site(s) of absorption along the GI tract and this effect would be more apparent with the "Slow" release formulation. And another consideration is that the current approach is based on comparison of pharmacokinetic parameters (C<sub>max</sub>, AUC(0-last detectable concentration) and AUC(0-infinity)), and these parameters reflect total dose absorbed and are not suitable to characterize the timing and magnitude of differences in the extent of paliperidone absorption from these ER tablets. This consideration led to requesting partial AUC calculations.

Cumulative partial AUC values are compared to the (b) (4) value in the following figure.



This figure shows that the earlier cumulative partial AUC values such as



As presented above, partial AUC assessments allow better comparison of the products and their relative bioavailability, particularly, in this case more than comparison of (b) (4) CI for Cmax and AUC values.

Statistical comparison of paliperidone Cmax and AUC values from the “Slow” and “Fast” release products relative to “Target” release product are presented in the following table. The (b) (4) CI around the ratio of Cmax and AUC values of the “Slow” and “Fast” release products relative to the “Target” release product, range from (b) (4) (b) (4) respectively, indicating possibility of an approximate (b) (4) range in the paliperidone availability.

Table 10: Summary of Analysis of Variance by Treatment for Pharmacokinetic Parameters of Paliperidone ER formulations (Study R076477-SCH-1018: Pharmacokinetic Analysis Set)<sup>a,b</sup>

Parameter	(b) (4)
$C_{max}$ (ng/mL)	
$AUC_{last}$ (ng.h/mL)	
$AUC_{\infty}$ (ng.h/mL)	

<sup>a</sup> Ratio: ratio of least-squares geometric means

<sup>b</sup> Analysis on logarithmic scale, but results were transformed to the original scale

In a typical bioequivalence assessment, in addition to confidence intervals meeting the acceptance criteria, the distribution of the data are expected to be centered around the reference mean. In this case, the mean ratios for the test treatments ("Slow" and "Fast" release) relative to the reference ("Target" release is (b) (4) consistently, indicating lower or higher bioavailability than the "Target" release product.

These results further confirm that consistently, not just rate but there is a difference in extent of paliperidone delivered and absorbed with the "Slow" and "Fast" release products and that  $C_{max}$  in this case is more of a measure of extent of paliperidone absorption rather than a typical indicator of both rate and extent of absorption. The Sponsor's analyses also shows that log-transformed  $C_{max}$  is highly correlated with log-transformed (b) (4) values.

The 90% CI calculated for the cumulative partial AUC values are presented in the following table which provide better characterization of paliperidone absorption from the ER tablets.

Table 2: Ratio of geometric means and 90% confidence intervals, expressed as percentages

PK	Ratio	Lower Limit	Upper Limit	Ratio	Lower Limit	Upper Limit
----	-------	-------------	-------------	-------	-------------	-------------

(b) (4)						
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### Summary:

- Paliperidone bioavailability from the "Slow" and "Fast" release products relative to "Target" release product show that claiming bioequivalence based on acceptance criteria range is not applicable in this case for this product. The submitted information, as discussed, prevent from concluding that these products are bioequivalent.
- There is no IVIVC established and if indeed, an *in vitro* and *in vivo* correlation existed, the release specification associated with the "Slow" and "Fast" release products would lead to ER products that are different than the approved product.

## 2) Assessment of in vitro and in vivo relationships

The release of paliperidone from the ER tablets is controlled by the (b) (4) in the tablet as it moves down the GI tract, and the paliperidone suspension is released in (b) (4) in the GI tract at the sites that may or may not be favorable for its absorption. A complicating component of this product is the delayed t<sub>max</sub> which occurs approximately after (b) (4) hrs postdosing. As a result, paliperidone bioavailability is (b) (4) from the "Slow", "Target" and "fast" release products relative to the IR solution dose.

The Sponsor to date has submitted two different approaches for developing an IVIVC Level A relationship for paliperidone ER tablets and in each case has not been able to establish such a relationship. The main areas of difficulty for the two attempts to develop IVIVC for the ER tablets, center around the (b) (4)

(b) (4)



**Summary:**

- There is no IVIVC established for paliperidone ER tablets. In the review, as described by the trend analyses, in vitro release testing method is not predictive of in vivo performance of the ER tablets.

***The following, although not considered pertinent for this supplement, may be communicated to the Sponsor to avoid future confusion.***

In the Sponsor's response dated June 30, 2008, on Page 10, the following statement is made. "The dose proportionality of paliperidone ER has been assessed over the dose range of 1.5 to 15 mg in Studies R076477-P01-1010 (3, 6, 9, 12 and 15 mg) (NDA 21-999\0000\Mod5.3.1.1) and R076477-SCH-1015 (1.5 and 3 mg) (NDA 21-999\S-005\Mod5.3.1.1). In Study R076477-P01-1010, all doses were bioequivalent to the 15 mg dose as well as to the next higher dose (i.e. 3 vs. 6, 6 vs. 9, 9 vs. 12 and 12 vs 15 mg). The 1.5 and 3 mg doses were also shown to be bioequivalent in Study R076477-SCH-1015."

This reviewer agrees that dose-proportionality of paliperidone is evaluated and established over the stated dose range. Since "bioequivalence" assessment requires comparison at the same molar dose, the statement that different doses are bioequivalent is incorrect.

## **RECOMMENDATION**

The Sponsor's proposal for (b) (4) release specifications for the paliperidone ER tablets is unacceptable.

Based on the submitted data and its analyses, proposed (b) (4) of the release specification for the paliperidone ER tablets should not be supported. Even with absence of a point to point correlation between in vitro and in vivo data, the submitted data and analyses confirm that the product with the proposed (b) (4) release specification will result in paliperidone ER tablets that are significantly different than the approved product.

Submitted data show that typical bioequivalence parameters C<sub>max</sub> and AUC, in this case are not representing rate and extent of paliperidone absorption from the Invega tablets. In the future relative bioavailability assessments for this dosage form, it is recommended that the Sponsor also evaluate cumulative partial AUC values.

The submitted in vitro in vivo correlation approach does not provide a predictive model that can be utilized to estimate in vivo exposure based on vitro data. (b) (4)

(b) (4)  
A robust predictive Level A IVIVC model that can provide a reliable, point to point correlation between in vitro and in vivo data has not been established for the current paliperidone ER product.

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**Arzu Selen, Ph.D.**  
**Associate Director, Biopharmaceutics**  
**Office of New Drug Quality Assessment**

## REVIEW

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## BACKGROUND

Paliperidone has a molecular weight of 426.49 Daltons and is a basic compound with a pKa1 of 8.2 (piperidine moiety) and a pKa2 of 2.6 (pyrimidine moiety). As a result, a substantial portion of the molecule is ionized at physiological pH. Paliperidone is relatively insoluble in water (0.003 g/ 100 mL water at pH 7.4). The solubility decreases at higher pH (0.001 g/ 100 mL at pH 12.9) and significantly increases at lower pH (3 g/ 100 mL at pH 5.3). The partition coefficient octanol/water (log P) is 2.39.

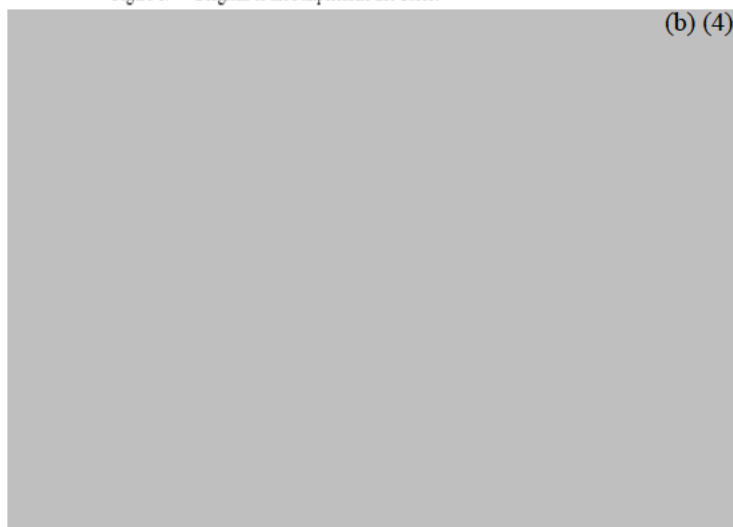
In the original NDA (page 261 of R076477-P01-1007), it is stated that paliperidone absolute bioavailability in human subjects is unknown, however, estimated to be at least 80% based on urinary recovery following administration of a single dose of a 1-mg oral solution of 14C-paliperidone.

Invega ER Tablets were developed utilizing ALZA's OROS® pushpull™ osmotic drug release technology and the functional structure of the ER tablet is depicted in the following figure (Figure 1).

Figure 1

2.3.P Drug Product – Paliperidone Extended Release Tablets

Figure 1: Diagram of the Paliperidone ER Tablet



During development it was shown that drug release from the tablet is (b) (4)

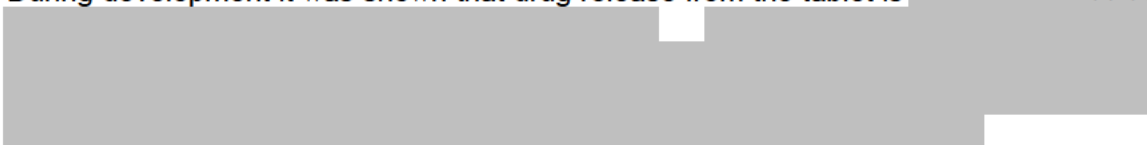


Table 1: (b) (4) Release Profile Lots: Membrane Weight per Tablet Versus 14-hr Cumulative Amount of Drug Released

Release rate profile	Lot number	Average membrane weight (mg)	14-hr cumulative Amount of Drug Released (%LC)
Slow	701038	(b) (4)	(b) (4)
Target	701037		
Fast	701036		

Cross-reference: [Module 3.2.P.2.2.3.1.4](#)

## METHODS

### In vitro release testing and the ER tablets Studied

The USP Apparatus VII (reciprocating disk) is used for release testing of paliperidone from the paliperidone ER tablets. Paliperidone release is measured at every 2 hr interval over a 24 hr period. The release media is 50 mL of artificial gastric fluid (AGF: 0.2% w/w NaCl in 0.0825 N HCl, pH 1.0 ± 0.5) kept at a constant temperature of 37°C. The media is agitated by the reciprocating arm (30 cycles per minute, cpm). Drug concentration released in each individual tube is measured by high performance liquid chromatography (HPLC) with ultra-violet (UV) detection set for absorption at 275 nm. The amount released at each interval is added to obtain cumulative amount of drug released (as in Table 2 and the figure).

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BIOPHARMACEUTICS

## BIOPHARMACEUTICS REVIEW

NDA Number, submission date	NDA 21-999 S004, November 7, 2007
Sponsor	Johnson & Johnson Pharm. Research and Development L.L.C.
Drug name (Generic name), formulation, and strengths	INVEGA (paliperidone) Extended Release Tablets, 3 mg, 6 mg, 9 mg and 12 mg
Clinical Division	Psychiatry Products
Primary CMC Reviewer	Donald Klein, Ph.D.
Biopharmaceutics Reviewer	Arzu Selen, Ph.D.

### EXECUTIVE SUMMARY AND RECOMMENDATION

INVEGA<sup>TM</sup> (paliperidone) Extended Release Tablets for the treatment of schizophrenia was approved by the FDA on 19 December 2006. Subsequently, Invega tablets were approved for maintenance treatment of schizophrenia on 27 April 2007 (NDA 22-043). Paliperidone's therapeutic activity in schizophrenia is thought to be mediated through a combination of central dopamine Type 2 (D2) and serotonin Type 2 (5-HT2A) receptor antagonism. Paliperidone, the major active metabolite of risperidone, 9-OH risperidone, is used in the treatment of schizophrenia.

This Prior Approval Supplement to NDA 21-999 is submitted to support (b) (4) the in vitro release specifications of the ER Tablets (specifically, the 0-14 hr and 0-18 hr samples). The Sponsor has submitted a pharmacokinetic study, study R076477-SCH-1018: "Pharmacokinetic Evaluation of the Relative Bioavailability of Three Paliperidone Extended Release (ER) Formulations with Different In Vitro Release Profiles and Comparison to Paliperidone Immediate Release (IR) in Healthy Male Subjects". This supplement was also intended to support a Level A In Vitro-In Vivo Correlation for Invega ER tablets.

Invega ER Tablets were developed utilizing ALZA's OROS® pushpull<sup>TM</sup> osmotic drug release technology. It is stated that the controlled ascending release rate of paliperidone from the formulation enables initiation of treatment with an effective dose without the need for initial dose titration. Paliperidone ER is currently approved in doses of 3, 6, 9, and 12 mg for once-daily oral administration. The recommended dose is 6 mg once daily administered in the morning. Allowable dose adjustment within the range of 3 mg to 12 mg per day is based on clinical response and tolerability.

This review is specific for the biopharmaceutics aspects of this submission, please see Dr. Donald Klein's review for the complete CMC review.

The Sponsor had previously attempted to develop a Level A IVIVC model. As detailed in Dr. Ronald Kavanagh's clinical pharmacology and biopharmaceutics review (dated 9/12/2006), the proposed IVIVC submitted in the original NDA was found unacceptable and was not used for setting release specification. On February 22, 2007, a meeting

took place between the Agency and the Sponsor to discuss a relative bioavailability study which the Sponsor was considering to design and conduct for (b) (4) the release specification and for establishing a Level A IVIVC model for Invega ER tablets. The minutes of the February 2007 meeting are pertinent for the conducted relative BA study.

Key points supporting the recommendation section of this review are in Attachment 1.

## RECOMMENDATION

The following comments should be provided to the Sponsor.

As the Sponsor previously discussed with the FDA (February 2007), a relative bioavailability study was designed and conducted to support (b) (4) of the specification for cumulative drug released by 14 and 18 hrs ( 0-14 hr and 0-18 hr samples) and to develop an IVIVC model.

The following clarifications and additional analyses are needed for full assessment of the study results.

A) Inspection of individual plasma concentration-time data following administration of the three palliperidone ER formulations (designated as Fast, Target and Slow prototypes) show that there is significant overlap in individual data. For example, palliperidone mean  $\pm$  SD Cmax values for Fast, Target, and Slow release formulations are (b) (4) respectively.

1) Please calculate and provide a statistical comparison of partial AUC values for these formulations: (b) (4) as carried out for the submitted PK parameters.

2) Please pool all pharmacokinetic parameters (Cmax, AUC values and tmax) from the three formulations and the above partial AUC values and provide a cluster analysis. It would be desirable, to explore the data in quartiles, in addition, to the clusters that will be dictated by the data. To the extent possible, please provide confidence interval comparisons using the cluster that represents the central tendency as reference. Please provide a list of these values, per cluster and for each value, please also indicate the formulation and the period when it was received.

B) Please provide the following clarification and reanalyses for further assessment of the IVIVC model.

(b) (4)

---

**Arzu Selen, Ph.D.**  
**Associate Director, Biopharmaceutics**  
**Office of New Drug Quality Assessment**



## ATTACHMENT 1

**Note:** A detailed biopharmaceutics review is not written, however, the following figures and tables from the submission are compiled for future reference.

### FORMULATIONS STUDIED

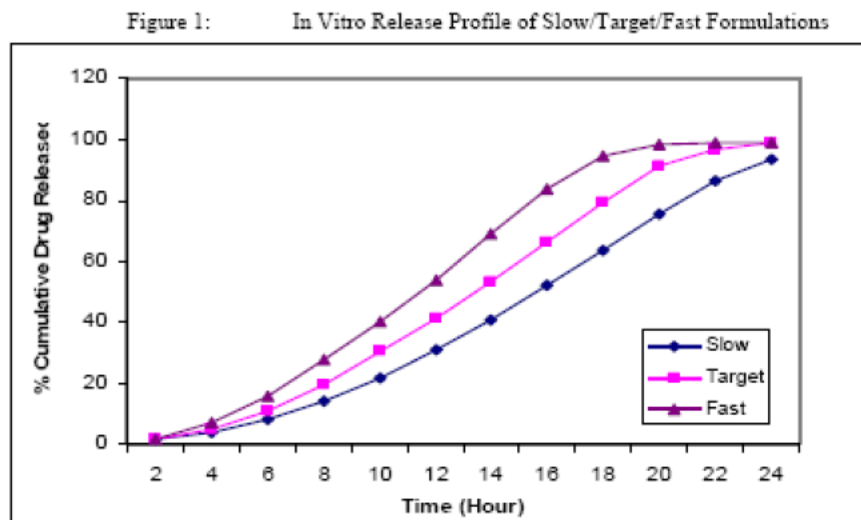
The following formulations were studied. Their 14-hr cumulative drug release rates are listed in Table 1.

Table 1: Slow/Target/Fast Release Profile Lots: Membrane Weight per Tablet Versus 14-hr Cumulative Amount of Drug Released			
Release rate profile	Lot number	Average membrane weight (mg)	14-hr cumulative Amount of Drug Released (%LC)
Slow	701038		(b) (4)
Target	701037		
Fast	701036		

Cross-reference: [Module 3.2.P.2.2.3.1.4](#)

The drug release testing of paliperidone ER tablets was performed using a USP Type VII (which is also shown to produce superimposable dissolution profiles with USP II in the submission).

Analysis of paliperidone concentrations in the samples was performed according to an HPLC/UV method and the mean cumulative release data are shown in the following figure, Figure 1.



Cross-reference: [Module 3.2.P.2.2.3/Figure 7](#)

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## IN VITRO DISSOLUTION/RELEASE SPECIFICATION

The following table (Table 4) summarizes the current regulatory method. The proposed changes were for the 0-14 hr and 0-18 hr samples. The Sponsor proposed (b) (4) % for the 0-14 hr sample and (b) (4) for the 0-18 hr sample.

**Table 4**

**Table 1** Final Regulatory Dissolution Method and Specifications for Paliperidone Extended Release Tablets 3 mg, 6 mg, 9 mg, and 12 mg

Parameter	Dissolution Method and Specifications	
Apparatus type:	USP Type VII Reciprocating Disk	
Media:	NaCl 2 gm/L (0.2% w/w) in 0.0825 N HCl pH 1.0 ± 0.5	
Volume:	50 ml	
Temperature:	37 ± 0.5 °C	
Frequency:	Agitation by Reciprocating Arm 30 cycles per minute (cpm)	
Amplitude:	2 – 3 cm	
Sampling Times:	2, 8, 14, 18, and 24 hours	
Specifications (% of Label Claim)	2 hours	(b) (4)
	8 hours	
	14 hours	
	18 hours	
	24 hours	
Acceptance Criteria:	Conforms to USP XXVIII <724> acceptance Table 1 for extended-release articles	

## RELATIVE BIOAVAILABILITY STUDY

**“Pharmacokinetic Evaluation of the Relative Bioavailability of Three Paliperidone Extended Release (ER) Formulations With Different In Vitro Release Profiles and Comparison to Paliperidone Immediate Release (IR) in Healthy Male Subjects”.  
STUDY R076477-SCH-1018**

The primary objective of this study was to evaluate the pharmacokinetics and relative bioavailability of paliperidone ER formulations with slow, target, and fast *in vitro* release rates after administration of a single 12 mg dose. The slow and fast releasing ER tablets had *in vitro* release rates outside the current commercial specifications.

**Composition of the IR formulation used in this study:**

Table 5

The quantitative composition of this IR solution is provided in [Table 1](#).

(b) (4)



**Study Design:** The *in vivo* performance of three ER formulations (12 mg), along with the reference paliperidone oral solution (1 mg), was evaluated in a four-treatment, four-period crossover study in healthy male subjects.

In Period 1, all subjects received a 1 mg dose of paliperidone immediate release (IR) solution, administered as a single oral dose under fasted conditions (Treatment A). In Periods 2 to 4, all subjects received a single 12 mg dose of the target, slow and fast paliperidone ER formulations (Treatment B, Treatment C, or Treatment D, respectively) in random order under fasted conditions. A washout period of 10 to 21 days separated each study drug administration.

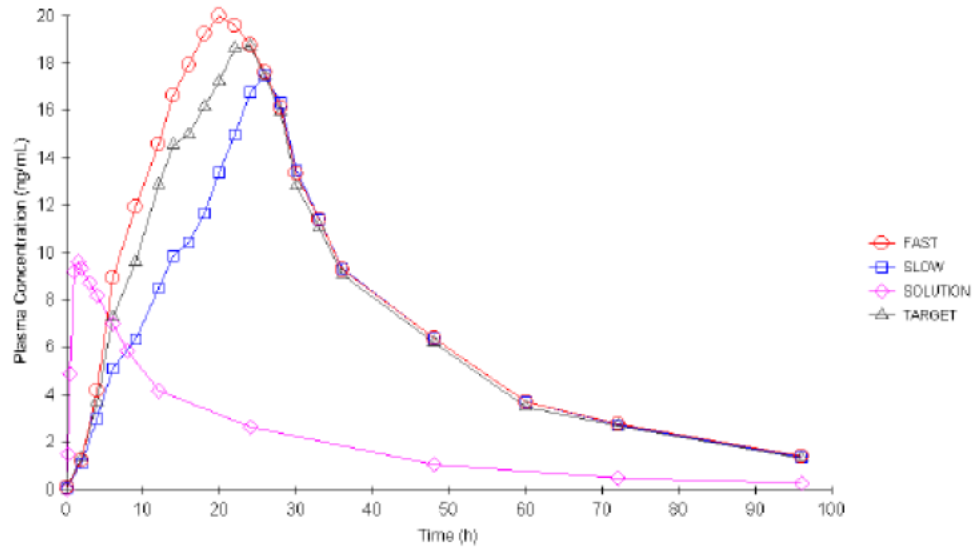
Serial blood samples were taken predose, and during the 96 hours following study drug administration for the determination of the plasma concentration of paliperidone. Plasma samples were analyzed for paliperidone using liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) techniques.

Pharmacokinetic parameters were available from 80 subjects after administration of paliperidone IR solution, 74 subjects after administration of the target release ER tablet, and 73 subjects after administration of the slow and fast release ER tablet. Pharmacokinetic parameters were calculated for each subject during each period using non-compartmental analysis.

The following figures (Figures 3-6) represent the mean and the individual concentration-time profiles obtained following administration of paliperidone formulations.

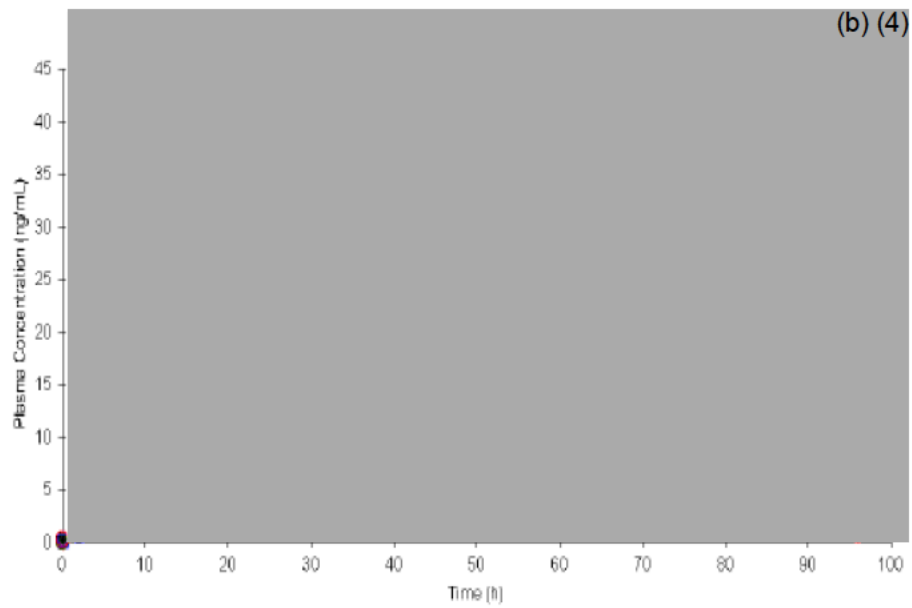
**Figure 3**

**Figure 10: Index Average Plasma Concentration-Time Profiles for the ER Formulations**



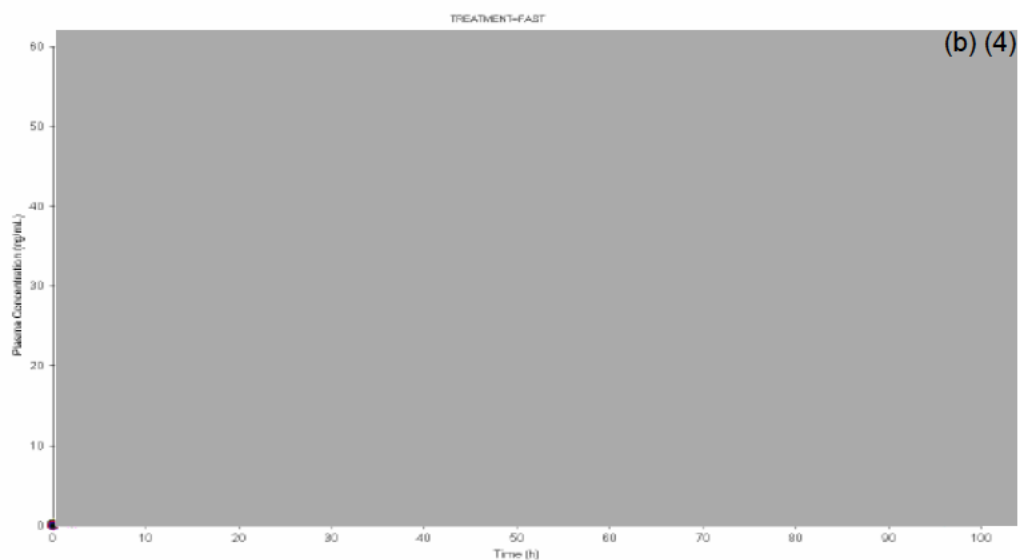
**Figure 4**

**Figure 2: Index Individual Plasma Concentration-Time Profiles for the Target Formulation**



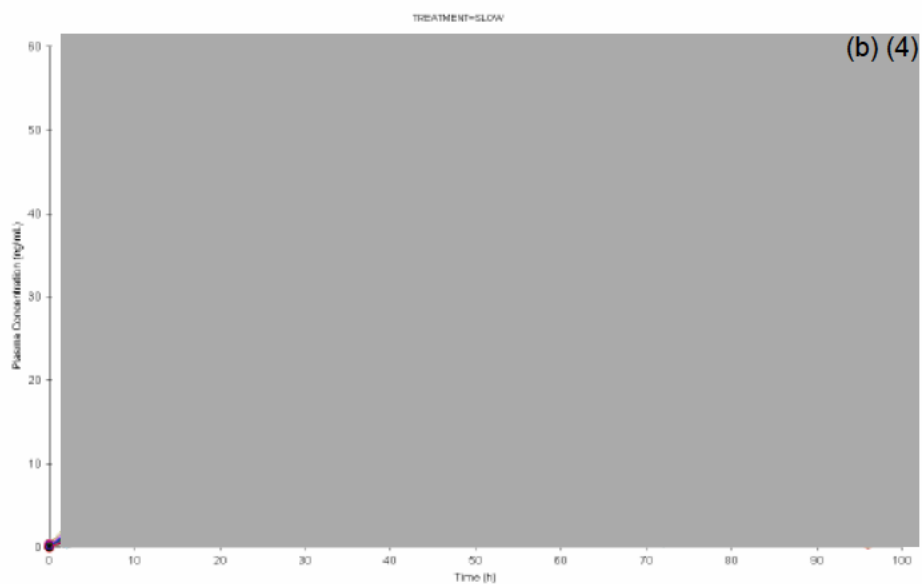
### **Figure 5**

**Figure 3: Index Individual Plasma Concentration-Time Profiles for the Fast Formulation**



### **Figure 6**

**Figure 4: Index Individual Plasma Concentration-Time Profiles for the Slow Formulation**



The mean pharmacokinetic parameters are summarized in Table 6 and the results of their statistical comparison are in Table 7.

**Table 6**

Table 4: Main Pharmacokinetic Parameters (Mean  $\pm$  SD) of Paliperidone  
(Study R076477-SCH-1018: Pharmacokinetic Analysis Set)

Treatment	$C_{max}$ (ng/mL)	$AUC_{last}$ (ng.h/mL)	$AUC_{\infty}$ (ng.h/mL)	$T_{max}^*$ (h)	$t_{1/2}$ (h)
1 mg IR solution (N=80)					(b) (4)
12 mg target release formulation (n=74)					
12 mg slow release formulation (n=73)					
12 mg fast release formulation (n=73)					

\* $T_{max}$ : median (range)

Cross Reference: [Module 5.3.1.2\R076477-SCH-1018\Attachment 2.1](#)

**Table 7**

Table 5: Summary of Analysis of Variance by Treatment for Pharmacokinetic Parameters of  
Paliperidone ER Formulations  
(Study R076477-SCH-1018: Pharmacokinetic Analysis Set)

Parameter	Slow/Target Release		Fast/Target Release	
	Ratio (%)	90% Confidence Interval (%)	Ratio (%)	90% Confidence Interval (%)
$C_{max}$	(b) (4)			
$AUC_{last}$				
$AUC_{\infty}$				

Analysis on log-scale but results were transformed to the original scale; ratio: ratio of least-squares geometric means.

Cross-Reference: [Module 5.3.1.2\R076477-SCH-1018\ Attachment 2.2](#)

## LEVEL A IVIVC MODEL DEVELOPMENT EFFORTS

The Sponsor provided the following description of their approach (which forms the basis of many of the questions raised in the recommendations).

(b) (4)

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/s/

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Arzu Selen  
3/7/2008 05:49:53 PM  
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-999/S-004**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



## MEMORANDUM OF TELECON

DATE: November 23, 2009

APPLICATION NUMBER: NDA 21-999/S-004, Invega (paliperidone) Extended-Release Tablets

BETWEEN:

Name: Peter Quigley  
Phone: 510-248-2320  
Representing: J&J Pharmaceutical Research & Development, L.L.C.

AND

Name: Teshara G. Bouie  
ONDQA/DPE

SUBJECT: Modified Dissolution Specifications

S-004 provides for (b) (4) the dissolution specification based upon an *In Vitro-In Vivo* Correlation (IVIVC) study. The applicant was notified that the proposed dissolution specification at 18 hours, (b) (4) should be modified to (b) (4). The applicant accepted the modification to the dissolution specifications.

---

Teshara G. Bouie  
Regulatory Health Project Manager

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21999	SUPPL-4	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	INVEGA

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/s/

TESHARA G BOUIE  
11/23/2009



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 21-999/S-004

**MEETING DENIED**

Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceuticals R & D, L.L.C.  
Attention: James (Jimmy) Tan, Ph.D., Director, Regulatory Affairs  
920 Route 202 South  
P.O. Box 300  
Raritan, NJ 08869

Dear Dr. Tan:

Please refer to your supplemental New Drug Application (sNDA) dated November 7, 2009, received November 8, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Invega (paliperidone) Extended Release Tablets, 3 mg, 6 mg, 9 mg, and 12 mg.

We also refer to your August 13, 2009, correspondence requesting a meeting to discuss the Agency's comments in the June 30, 2009 Complete Response Letter. We have considered your request and concluded that the meeting is unnecessary. Below are our responses to the questions included in your meeting request.

- **Please clarify the Division's decision making process for the choice of these specifications?**

Recommendations were made based upon the *Guidance for Industry, Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations*, for dissolution specification change in the absence of an established IV/IVC.

- **Does the Division accept adopting revised dissolution acceptance criteria s follows: at 14 hours, (b) (4) and at 18 hours, (b) (4) %?**

We concur.

If you have any questions, call Teshara G. Bouie, Regulatory Project Manager at (301) 796-1649.

Sincerely,

*(See appended electronic signature page)*

Eric P. Duffy, Ph.D.  
Director

Division of Post-Marketing Evaluation  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21999	GI-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	INVEGA

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/s/

ERIC P DUFFY  
09/04/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<h2 style="margin: 0;">REQUEST FOR CONSULTATION</h2>		
TO (Office/Division): <b>Patrick Marroum</b>			FROM (Name, Office/Division, and Phone Number of Requestor): <b>Teshara G. Bouie, ONDQA/Division of Post-Marketing Assessment, 301-796-1649</b>	
DATE <b>July 16, 2009</b>	IND NO.	NDA NO. <b>21-999</b>	TYPE OF DOCUMENT <b>SCM-004</b>	DATE OF DOCUMENT <b>November 7, 2007; May 28, 2008; June 30, 2008</b>
NAME OF DRUG <b>Invega</b>	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
NAME OF FIRM: <b>Ortho McNeil Janssen</b>				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <input type="checkbox"/> NEW PROTOCOL  <input type="checkbox"/> PROGRESS REPORT  <input type="checkbox"/> NEW CORRESPONDENCE  <input type="checkbox"/> DRUG ADVERTISING  <input type="checkbox"/> ADVERSE REACTION REPORT  <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION  <input type="checkbox"/> MEETING PLANNED BY         </div> <div style="width: 33%;"> <input type="checkbox"/> PRE-NDA MEETING  <input type="checkbox"/> END-OF-PHASE 2a MEETING  <input type="checkbox"/> END-OF-PHASE 2 MEETING  <input type="checkbox"/> RESUBMISSION  <input type="checkbox"/> SAFETY / EFFICACY  <input type="checkbox"/> PAPER NDA  <input type="checkbox"/> CONTROL SUPPLEMENT         </div> <div style="width: 33%;"> <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER  <input type="checkbox"/> FINAL PRINTED LABELING  <input type="checkbox"/> LABELING REVISION  <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE  <input type="checkbox"/> FORMULATIVE REVIEW  <input type="checkbox"/> OTHER (SPECIFY BELOW):         </div> </div>				
<b>II. BIOMETRICS</b>				
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <input type="checkbox"/> PRIORITY P NDA REVIEW  <input type="checkbox"/> END-OF-PHASE 2 MEETING  <input type="checkbox"/> CONTROLLED STUDIES  <input type="checkbox"/> PROTOCOL REVIEW  <input type="checkbox"/> OTHER (SPECIFY BELOW):         </div> <div style="width: 50%;"> <input type="checkbox"/> CHEMISTRY REVIEW  <input type="checkbox"/> PHARMACOLOGY  <input type="checkbox"/> BIOPHARMACEUTICS  <input type="checkbox"/> OTHER (SPECIFY BELOW):         </div> </div>				
<b>III. BIOPHARMACEUTICS</b>				
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <input type="checkbox"/> DISSOLUTION  <input type="checkbox"/> BIOAVAILABILITY STUDIES  <input type="checkbox"/> PHASE 4 STUDIES         </div> <div style="width: 50%;"> <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS  <input type="checkbox"/> IN-VIVO WAIVER REQUEST         </div> </div>				
<b>IV. DRUG SAFETY</b>				
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL  <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES  <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)  <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         </div> <div style="width: 50%;"> <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY  <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE  <input type="checkbox"/> POISON RISK ANALYSIS         </div> </div>				
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <input type="checkbox"/> CLINICAL         </div> <div style="width: 50%;"> <input type="checkbox"/> NONCLINICAL         </div> </div>				
<p><b>COMMENTS / SPECIAL INSTRUCTIONS:</b> This supplement provides for (b) (4) the dissolution specification based upon an In Vitro-In Vivo Correlation (IVIVC) study. Please review.</p> <p>This supplement is located in the EDR.</p>				
SIGNATURE OF REQUESTOR <b>Teshara G. Bouie</b>			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
PRINTED NAME AND SIGNATURE OF RECEIVER			PRINTED NAME AND SIGNATURE OF DELIVERER	

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/s/

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Teshara Bouie  
7/16/2009 05:13:25 PM

## Bouie, Teshara

---

**From:** Bouie, Teshara  
**Sent:** Monday, April 07, 2008 12:04 PM  
**To:** 'Birkenberger, Lori [PRDUS]'  
**Subject:** NDA 21-999 S-004 - Reviewer Comments

Hi Lori,

Regarding the supplement above, we have the following comments:

1. In-vivo bioequivalence alone is not adequate to (b) (4) dissolution specification; the dissolution test should be predictive of in-vivo performance (i.e. an established IVIVC is needed to support the link between the dissolution method and the in-vivo performance of the drug product).
2. Prior to calculation of confidence intervals and application of statistical criteria, it is important to understand the magnitude of site-specific (time-dependent) absorption on the three proto-types. Pooled analysis for Cmax, tmax, and AUC values (including partial AUC values) is intended for better characterization of the products. The raw data list should include one parameter value, prototype and subject number and one cluster group. While variability and its effect on cluster analyses is a concern, it is also important to know if differences exist between clusters, with respect to variability as well.

Please contact me if you have any questions or concerns.

Thanks,

***LCDR Teshara G. Bouie, MSA, OTR/L***  
***United States Public Health Service***  
***Regulatory Health Project Manager***  
***FDA/CDER/OPS/ONDQA***  
***Division Of Post-Marketing Evaluation***  
***Phone (301)796-1649***  
***Fax (301)796-9749***



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/s/

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Teshara Bouie  
4/7/2008 12:08:22 PM  
PROJECT MANAGER FOR QUALITY