Janssen Research & Development, LLC

May 9, 2013

BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061, HFA-305
Rockville, Maryland 20852

Re: Draft Guidance on Paliperidone Palmitate for Intramuscular Injection, Docket No: FDA-2007-D-0369

Dear Sir or Madam:

On behalf of Janssen Research and Development, L.L.C. ("JRD"), I herewith enclose a Citizen Petition and accompanying addendum of exhibits requesting the Food and Drug Administration ("FDA") to adopt specific bioequivalence requirements in its review of proposed generic and follow-on versions of INVEGA® SUSTENNA®. In addition to the comments that JRD previously submitted on this draft guidance on February 28, 2012, I respectfully request that FDA consider this information and adopt the bioequivalence parameters requested in this citizen petition in any final guidance on bioequivalence for intramuscular paliperidone palmitate products. The filing of this citizen petition and accompanying materials in this docket does not relieve FDA of its obligation to respond separately to this citizen petition or to take the actions requested in that petition with respect to applications seeking approval of follow-on versions of INVEGA SUSTENNA.

Thank you in advance.

Sincerely,

Donald L. Heald

Donald L. Heald, M.S., Ph.D.
Clinical Pharmacology Therapeutic Area Head for Neurosciences

2013-3458

FDA-2007-D-0369

CP

Janssen Research & Development, LLC
1125 Trenton-Harbourton Road
Titusville, NJ 08560
609.730.2000 telephone

1953 13 MAY -9 P1 :58

Janssen
PHARMACEUTICAL COMPANIES
OF Johnson & Johnson

May 9, 2013

BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061, HFA-305
Rockville, Maryland 20852

Dear Sir or Madam:

On behalf of Janssen Research and Development, L.L.C., I herewith enclose a Citizen Petition and accompanying addendum of exhibits requesting the Food and Drug Administration ("FDA") to adopt and apply specific bioequivalence requirements in its review of proposed generic and follow-on versions of INVEGA® SUSTENNA®. I respectfully request FDA to direct any correspondence relating to this petition to me at the above address and facsimile number and to counsel identified below:

Joy J. Liu
Ropes & Gray, LLP
One Metro Center, Suite 900
700 12th Street, N.W.
Washington, D.C. 20005
(202) 508-4691
(202) 383-8324 (facsimile)

Thank you in advance.

Sincerely,

Donald L. Heald

Donald L. Heald, M.S., Ph.D.
Clinical Pharmacology Therapeutic Area Head for Neurosciences

CITIZEN PETITION CONCERNING BIOEQUIVALENCE OF PROPOSED GENERIC VERSIONS OF INVEGA® SUSTENNA®

TABLE OF CONTENTS

Page

I. ACTIONS REQUESTED 1

II. STATEMENT OF GROUNDS 3

A. Background 3

1. Schizophrenia: A Debilitating Disease 3

2. INVEGA® SUSTENNA®: An LAI to Treat Schizophrenia 4

3. The Statutory Scheme Governing Review of Generic Drugs 6

B. Clinical Issues Associated with Improper Release of Paliperidone 8

1. Inadequate Treatment May Lead to Relapses 8

2. Excessive Treatment May Have Adverse Clinical Impacts 9

C. Particle Size and Distribution Controls the Release Rate 12

D. Traditional Bioequivalence Parameters May Not Capture Clinically Meaningful Differences in Proposed Generic Products 14

E. FDA Should Require Partial AUCs to Evaluate the Bioequivalence of Proposed Generic Versions of INVEGA® SUSTENNA® 23

III. ENVIRONMENTAL IMPACT 28

IV. ECONOMIC IMPACT 28

V. CERTIFICATION 29

CITIZEN PETITION

I. ACTIONS REQUESTED

On behalf of Janssen Pharmaceuticals, Inc. ("JPI"), Janssen Research & Development, L.L.C. ("JRD")[1] herewith submits this Citizen Petition pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act"), codified at 21 U.S.C. § 355, and regulations published by the Food and Drug Administration ("FDA" or "the agency") governing the filing of citizen petitions. 21 C.F.R. § 10.30. As set forth herein, JRD respectfully requests FDA to require specific bioequivalence parameters to govern the review and approval of any proposed generic or follow-on product where the reference listed drug ("RLD") is INVEGA® SUSTENNA® (paliperidone palmitate).[2]

In August 2011, FDA issued draft guidance outlining recommendations to evaluate the bioequivalence of injectable paliperidone palmitate products where INVEGA® SUSTENNA® would be the RLD for such a study (hereinafter "Draft Guidance").[3] In response to that Draft Guidance, JRD submitted comments on February 29, 2012, calling for removal of the term "steady state" from the design section (single-dose, parallel, steady state, *in vivo*) in the Draft Guidance, the use of additional parameters to evaluate bioequivalence, and demonstration of bioequivalence at least at the highest and lowest strengths.[4] FDA has previously indicated that it is not required to publish draft or final product-specific bioequivalence recommendations before it

---

[1] JRD is the authorized regulatory agent for JPI. JPI is the holder of the New Drug Application for INVEGA® SUSTENNA® (paliperidone palmitate).

[2] For the purposes of this citizen petition, the term "generic drug product" refers to a product that is reviewed and/or approved under Section 505(j) of the FDCA. 21 U.S.C. § 355(j). The term "follow-on product" refers to a product that is reviewed and/or approved under Section 505(b)(2) of the FDCA. 21 U.S.C. § 355(b)(2). Although this petition focuses principally on the bioequivalence standards that should govern FDA review of proposed generic versions of INVEGA® SUSTENNA®, JRD requests FDA to apply such standards to any bioequivalence assessment conducted in connection with a Section 505(b)(2) application for a follow-on version of INVEGA® SUSTENNA®. As of the date of this petition, JRD is not aware of any application for a proposed generic drug product or a proposed follow-on product that falls within the scope of this petition and is pending before FDA under Section 505(j) or 505(b)(2) of the FDCA. Neither JPI nor JRD has received a paragraph IV certification from any applicant seeking approval of a generic or follow-on version of INVEGA® SUSTENNA®. As a result, JRD believes that this citizen petition is not subject to the requirements of Section 505(q) of the FDCA. 21 U.S.C. § 355(q). *See* FDA, *Guidance for Industry, Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act* (June 2011), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079353.pdf.

[3] *See* FDA, *Draft Guidance on Paliperidone Palmitate* (Aug. 2011), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM270384.pdf.

[4] Rodney Malchow, *Comments on Draft Guidance on Paliperidone Palmitate for Intramuscular Injection*, 1–2, Docket FDA-2007-D-0369-0015 (Feb. 28, 2012) (Exh. 1).

approves a generic or follow-on version of an RLD.[5] To date, FDA has not issued final guidance or otherwise responded to the comments of JRD calling for revision of the Draft Guidance.

As set forth in those comments and more fully described herein, JRD has demonstrated that potentially significant safety and efficacy issues may arise if FDA accepts bioequivalence determinations for proposed generic products based solely on the traditional metrics of maximum concentration ("C_{max}"), area under the concentration-time curve from time zero to time t ("AUC_{0-t}"), and area under the concentration-time curve, from time zero to infinity ("$AUC_{0-\infty}$"). Indeed, reliance solely on these metrics may not detect potentially significant and clinically meaningful differences stemming from different pharmacokinetic profiles ("PK profiles") of INVEGA® SUSTENNA® and proposed test products. That would be especially problematic if INVEGA® SUSTENNA® and generic products with different release properties are switched, resulting in patients undergoing periods with inadequate paliperidone release that could result in decreased efficacy and clinically significant relapses.

Specifically, INVEGA® SUSTENNA® is characterized by a biphasic release profile: an initial zero-order release phase during the first two weeks, and subsequently a first-order release phase. As FDA has recognized, the release profile is controlled by the particle size and distribution of paliperidone palmitate. JRD simulated two different switching scenarios—a delayed release scenario and an altered release scenario—to investigate whether products with different release properties but the same C_{max} and AUC after single dosing could, upon switching, have a different trough concentration ("C_{trough}"), C_{max}, and the area under the concentration-time curve during a dosing interval ("AUC_{tau}") during the next dosing cycles. Both simulations demonstrated that such switching can result in significant changes in the systemic drug concentrations for a significant time after switching.

JRD believes that generic and follow-on products with different PK profiles will unnecessarily place patients at risk for adverse events from improper release of paliperidone palmitate. Accordingly, and in light of these potentially significant safety and efficacy issues, JRD herewith respectfully requests FDA to refrain from approving any generic or follow-on product where INVEGA® SUSTENNA® is the RLD unless applicants evaluate bioequivalence by measuring the partial area under the concentration-time curve, from zero to 72 hours ("$pAUC_{0-72h}$"), and partial area under the concentration-time curve, from zero to 28 days ("$pAUC_{0-28d}$"), in addition to the traditional bioequivalence metrics of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.[6] As described in detail below, only

---

[5] FDA, *Guidance for Industry: Bioequivalence Recommendations for Specific Products* 3 (June 2010), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072872.pdf. In this guidance, FDA did indicate that when the same bioequivalence issue is under consideration in different contexts, the agency will take into account the status of related matters in determining how to best address scientific issues. *Id.* FDA went on to declare that it may coordinate the consideration of a pending citizen petition with the development and publication of a product-specific bioequivalence recommendation. *Id.* at 3-4. JRD believes that FDA should do so in the instant case.

[6] FDA has previously indicated that, for follow-on products reviewed under Section 505(b)(2) of the FDCA, the agency will require applicants to conduct bioequivalence studies in support of approval of such

through use of these additional parameters will FDA be able to ensure that proposed generic and follow-on versions of INVEGA® SUSTENNA® do not raise significant safety and efficacy issues for patients.

II. STATEMENT OF GROUNDS

A. Background

1. Schizophrenia: A Debilitating Disease

Schizophrenia is a chronic, debilitating psychiatric disorder in which patients suffer from disorganized and bizarre thoughts, delusions, and hallucinations.[7] The disease affects approximately 2.4 million American adults annually, which represents 1.1% of the adult population in a given year.[8] Schizophrenia can be viewed as a disorder that develops in three phases: premorbid, prodromal, and psychotic.[9]

Specifically, the premorbid phase encompasses a period of normative function, although the individual may experience events that contribute to the development of the subsequent illness. During the prodromal phase, the person experiences substantial functional impairment and nonspecific symptoms such as sleep disturbance, anxiety, irritability, depressed mood, poor concentration, fatigue, and behavioral deficits such as deterioration in role functioning and social withdrawal. Positive symptoms such as perceptual abnormalities, ideas of reference, and suspiciousness develop late in the prodromal phase and herald the imminent onset of psychosis.

The psychotic phase progresses through an acute phase, a recovery or stabilization phase, and a stable phase. The acute phase refers to the presence of florid psychotic features such as delusions, hallucinations, formal thought disorder, and disorganized thinking. Negative symptoms often become more severe, and patients are usually not able to care for themselves appropriately. The stabilization (recovery) phase refers to a period of 6 to18 months after acute treatment. During the stable phase, negative and

---

applications. *See* FDA, *Draft Guidance for Industry: Applications Covered by Section 505(b)(2)* 8 (Oct. 1999), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf. More recently, however, FDA stated that 505(b)(2) applications typically are not required to demonstrate bioequivalence to a listed drug. *See Citizen Petition Response Regarding ADDERALL XR®*, 1 n.3, Docket No. FDA-2005-P-0120 (June 22, 2012), *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2005-P-0120-0030. In the event that FDA requires a 505(b)(2) applicant to conduct a bioequivalence assessment evaluating the proposed follow-on product to INVEGA® SUSTENNA®, JRD believes that assessment should be governed by the standards and parameters requested herein.

[7] Am. Psychiatric Ass'n, *Diagnostic and Statistical Manual of Mental Disorders* 297–344 (4th ed., text rev., 2000).

[8] *The Numbers Count: Mental Disorders in America*, National Institute of Mental Health, http://www.nimh.nih.gov/health/publications/the-numbers-count-mental-disorders-in-america/index.shtml (last visited Apr. 26, 2013) (Exh. 2).

[9] Am. Psychiatric Ass'n, *Practice Guideline for the Treatment of Patients with Schizophrenia* 63 (2d ed. Feb 2004) (Exh. 3).

residual positive symptoms that may be present are relatively consistent in magnitude and usually less severe than in the acute phase. Some patients may be asymptomatic whereas others experience non-psychotic symptoms such as tension, anxiety, depression, or insomnia.

One of the major impediments to improvement and remission of schizophrenia is patient discontinuation of treatment, particularly pharmacotherapy. Indeed, discontinuation of medication has been shown to be among the strongest risk factors for relapse.[10] With relapse, there is an exacerbation of symptoms and deterioration of function, which leads to increased use of mental health resources, decreased quality of life, and may require involuntary commitment.[11] The cumulative first relapse rate in schizophrenia is about 80% by five years, and the risk of relapse is increased almost five-fold by discontinuation of antipsychotic drug therapy.[12] Each successive relapse results in an increase in the severity of patients' symptoms and further deterioration.

2. INVEGA® SUSTENNA®: An LAI to Treat Schizophrenia

To help address the problem of non-adherence in the schizophrenia patient population, JPI obtained approval by FDA on July 31, 2009, of a New Drug Application ("NDA") authorizing marketing of INVEGA® SUSTENNA® for the acute and maintenance treatment of schizophrenia in adults. INVEGA® SUSTENNA® is a professionally administered long-acting injectable ("LAI") product which provides continuous therapeutic concentrations of antipsychotic medication over an extended period of time.[13]

The active ingredient in INVEGA® SUSTENNA® is paliperidone palmitate. The product is available as a sterile aqueous extended-release suspension for intramuscular injection in dose strengths ranging from 39–234 mg paliperidone palmitate.[14] Although

---

[10] Delbert Robinson et al., *Predictors of Relapse Following Response from a First Episode of Schizophrenia or Schizoaffective Disorder*, 56 Arch. Gen. Psychiatry 241, 244–45 (Mar. 1999) (Exh. 4).

[11] Stephen Almond et al., *Relapse in Schizophrenia: Costs, Clinical Outcomes and Quality of Life*, 184 Brit. J. Psychiatry 346, 347-50 (2004) (Exh. 5).

[12] Robinson, *supra* note 10, at 241–2.

[13] Current practice guidelines recommend offering an LAI antipsychotic to patients in whom non-adherence has been demonstrated and linked to repeated relapse. John M. Kane & Carlos Garcia-Ribera, *Clinical Guideline Recommendations for Antipsychotic Long-Acting Injections*, 195 Brit. J. Psychiatry S63, S64 (2009) (Exh. 6). With such medications, physicians and other mental health care professionals gain an earlier knowledge and awareness of non-adherence through missed injections. *Id.* This contrasts with patients being treated with oral antipsychotic medications, where non-adherence, although extremely common, often goes undetected for much longer periods of time due to the physician's reliance on the patient's report. Johnson & Johnson Pharmaceutical Research & Development, *Response to FDA June 28, 2002 Action Letter Concerning NDA 21-346, Section 2: Literature Review on the Need for an LAI Injectable Formulation of a Second-Generation Antipsychotic for the Treatment of Schizophrenia*, 4 (2003) (Exh. 7).

[14] "INVEGA® SUSTENNA® is available . . . in dose strengths of 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg paliperidone palmitate. The drug product hydrolyzes to the active moiety, paliperidone, resulting in dose strengths of 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg of paliperidone, respectively." Janssen Pharms., Inc., *INVEGA® SUSTENNA® Prescribing Information* § 11 (2012), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022264s005lbl.pdf.

the mechanism of action of paliperidone is not known, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of central dopamine Type 2 ("D2") and serotonin Type 2 receptor antagonism.

INVEGA® SUSTENNA® is designed to deliver paliperidone over a monthly period. The label for the product provides that dosing is initiated with a 234 mg injection on treatment day 1 and a 156 mg injection one week later, both administered in the deltoid muscle. Thereafter, the recommended monthly maintenance dose is 117 mg (in either the deltoid or gluteal muscle), although some patients may benefit from lower or higher maintenance doses within the additional available strengths.

The initiation regimen for INVEGA® SUSTENNA® was "designed to rapidly attain steady-state paliperidone concentrations when initiating therapy without the use of oral supplementation."[15] Indeed, paliperidone exposure is comparable to the exposure observed after 6 mg paliperidone extended release ("ER") between 24 and 48 hours after injection of the first intramuscular dose of 234 mg paliperidone palmitate in the deltoid muscle.[16] When compared to 3 mg paliperidone ER (lowest effective dose), 234 mg paliperidone palmitate achieved comparable plasma exposure as early as 4 hours after the first intramuscular dosing. These data reflect the systemic exposure upon administration of LAI paliperidone palmitate to patients not being pre-treated with an oral formulation. With regard to onset of efficacy, INVEGA® SUSTENNA® at the recommended initiation dose of 234 mg is adequate to achieve efficacy as soon as three days after the 234 mg initiation dose.[17, 18]

---

[15] *Id.* at § 12.3.

[16] Malchow, *supra* note 4, at 5.

[17] In a Phase 3 study, mean Positive and Negative Syndrome Scale ("PANSS") total score improved (decreased) significantly ($p<0.01$) from day 1–4 (i.e., 72 hours after dosing) in both paliperidone palmitate given at the recommended initiation dose of 234 mg on day 1 and oral risperidone (1–6 mg) groups in acutely exacerbated schizophrenia. *Id.* at 9. The clinical improvement was associated with the pharmacokinetic findings: the median plasma concentration-time profiles of active moiety (i.e., paliperidone for the paliperidone palmitate group and risperidone plus paliperidone for the oral risperidone group) were similar as of three days after the first injection of paliperidone palmitate and over the first 36 days of treatment. *Id.* at 10–11. Initiation of treatment with 234 mg on day 1 followed by a 156-mg dose on day 8, consistent with the current label recommendations, resulted in mean paliperidone plasma concentrations that exceeded a previously established antipsychotic efficacy threshold of 7.5 ng/mL from the first sampling point after dosing (day 4, i.e., 72 hours after dosing) and thereafter. *Id.* at 9–11.

[18] The efficacy of antipsychotics in improving symptoms of schizophrenia has traditionally been measured using a 30-item instrument known as PANSS. Stanley R. Kay et al., *The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia*, 13 Schizophr. Bull. 261, 261 (1987) (Exh. 8). The PANSS was published in 1987 and is widely used to assess changes in symptoms for subjects with schizophrenia. The scale is comprised of 30 items focusing on three clusters of symptoms commonly observed in schizophrenia: positive symptoms, negative symptoms and general psychopathology. Each of the 30 items within the PANSS is rated on a scale of one (minimal symptoms) to seven (maximal symptoms). The total score for the PANSS therefore ranges between 30–210. Since symptoms of schizophrenia fluctuate considerably over time, the PANSS was designed to be sensitive to change. The PANSS has been translated into dozens of languages and the validity and reliability of the scale has been widely accepted. Stanley R. Kay & Lewis A. Opler, *The Positive-Negative Dimension in Schizophrenia: Its Validity and Significance*, 5 Psychiatric Devs. 79 (1987) (Exh. 9); Morris Bell, Robert Milstein, Joseph Beam-Goulet, Paul Lysaker, and Domenic Cicchetti, *The Positive and Negative Syndrome Scale and the Brief Psychiatric*

As stated in the labeling for INVEGA® SUSTENNA®, paliperidone palmitate has extremely low water solubility and, as a result, dissolves slowly after intramuscular injection before being hydrolysed to paliperidone and absorbed in systemic circulation. Following a single intramuscular dose, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median time to maximum plasma concentration ("T_{max}") of 13 days. The release of the drug starts as early as the first day and lasts for as long as 126 days. The labeling further states that "the two initial deltoid intramuscular injections . . . help attain therapeutic concentrations rapidly" and "the release profile and dosing regimen of INVEGA® SUSTENNA® results in sustained therapeutic concentrations."

3. The Statutory Scheme Governing Review of Generic Drugs

Under Section 505(j) of the FDCA, an applicant may file an abbreviated new drug application ("ANDA") for approval of a generic drug product.[19] In an ANDA, and with certain limited exceptions described below, the applicant need not and, indeed, cannot conduct clinical studies in support of its application. Rather, the applicant references FDA's findings of safety and effectiveness for a previously approved RLD. To rely on those findings, the applicant must demonstrate (among other things) that its proposed product is the same as the RLD with respect to active ingredient, dosage form, route of administration, strength, labeling, and conditions of use. 21 U.S.C. § 355(j)(2)(A)(i)-(iii), (v).

In addition to demonstrating that its product is the same as the RLD, an ANDA applicant must also show that its proposed product is bioequivalent to the RLD. 21 U.S.C. § 355(j)(2)(A)(iv). Specifically, an ANDA applicant must demonstrate, and FDA must find, that "the rate and extent of absorption of the [test] drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single-dose or multiple doses."[20] In its regulations implementing these statutory provisions, FDA directs all ANDA applicants to "conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and

---

Rating Scale. Reliability, Comparability, and Predictive Validity, 180 J. Nerv. Ment. Dis. 723 (1992) (Exh. 10); Victor Peralta & Manuel J. Cuesta, *Psychometric Properties of the Positive and Negative Syndrome Scale (PANSS) in Schizophrenia*, 53 Psychiatry Res. 31 (1994) (Exh. 11).

[19] In connection with its consideration of any application seeking approval of a new drug product under these provisions, FDA is bound by the fundamental purpose underlying the FDCA—to ensure that all drug products marketed in the United States are safe and effective. Indeed, that "essential purpose pervades the FDCA." *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000).

[20] 21 U.S.C. § 355(j)(8)(B)(i). The FDA has further indicated that two drug products will be considered bioequivalent if they "display comparable bioavailability when studied under similar experimental conditions." FDA, *Approved Drug Products with Therapeutic Equivalence Evaluations* viii (33d ed. 2013), *available at* http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071436.pdf. Bioavailability is, in turn, defined as "the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of the drug action." 21 U.S.C. § 355(j)(8)(A)(i).

reproducible approach available" among certain methodologies set forth in the regulations.[21]

To establish the bioequivalence of systemically absorbed drugs, FDA generally recommends that applicants conduct single-dose, crossover or parallel-group PK studies, measuring the concentrations of the generic and reference drugs in the blood or plasma as a function of time.[22] These data are plotted on a curve where time is represented on the x-axis and concentration is represented on the y-axis. Applicants then rely upon certain parameters to compare the drug concentration vs. time "curve" or PK profile. For most products, these parameters typically include C_{max} and $AUC_{0-\infty}$. C_{max} is relied upon to reflect the rate of the drug's absorption into systemic circulation, while $AUC_{0-\infty}$ is used to measure the extent of a drug's absorption.[23]

If the proposed generic product does not satisfy these requirements, then there is no way to assure that FDA's findings of safety and efficacy for the RLD are applicable to the generic drug product. [24] Thus, strict compliance with the foregoing requirements is critical because, upon approval of an ANDA (except those that were subject to a suitability petition), FDA designates the generic product as "therapeutically equivalent" to the RLD and assigns an "A" rating to that product in its publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"). As FDA declared therein, "products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product." Physicians and pharmacists consider the "A" rating to mean that a generic drug is fully substitutable for the RLD.[25]

---

[21] 21 C.F.R. § 320.24(a).

[22] 21 C.F.R. § 320.24(b)(1)(i).

[23] *See* 21 C.F.R. § 320.26(c)

[24] The entry of generic and follow-on products into the marketplace is "subsumed by the overriding necessity of ensuring public access to safe commercial drugs." *Schering Corp. v. FDA*, 51 F.3d 390, 396 (3d Cir. 1995). That is the case even where it is the innovator drug manufacturer that identifies inconsistencies with the requirements of the FDCA. In fact, innovator drug manufacturers such as JRD frequently "possess the scientific data to recognize when FDA may stray from the legislatively mandated testing requirements that impact the safety and effectiveness of the generic drug." *Id.* at 396; s*ee Mova Pharm. Corp. v. Shalala*, 955 F. Supp. 128, 131 (D.D.C. 1997) ("Faithful application of the Hatch-Waxman provisions ensuring the safety and efficacy of follow-on drugs far outweighs the marginal interest in the availability of follow-on drug products.").

[25] By operation of certain state laws and numerous health insurance programs, FDA's designation of an "A" rating often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient. As of the date of this petition, at least 16 state statutes require mandatory substitution: (FL) Fla. Stat. § 465.025, (HI) Haw. Rev. Stat. § 328-92, (KY) Ky. Rev. Stat. Ann. § 217.822, (ME) Me. Rev. Stat. Ann. tit. 32, § 13781, (MA) Mass. Gen. Laws ch. 112, § 12D, (MN) Minn. Stat. § 151.21, (NV) Nev. Rev. Stat. § 639.2583, (NJ) N.J. Rev. Stat. § 24:6E-7, (NY) N.Y. Educ. Law § 6816-a, (PA) 35 P.S. § 960.3, (RI) R.I. Gen. Laws § 5-19.1-19, (TN) Tenn. Code Ann. § 53-10-205(a), (VT) Vt. Stat. Ann. tit. 18, § 4605, (WA) Wash. Rev. Code § 69.41.130, (WV) W. Va. Code § 30-5-12b, (WI) Wis. Stat. § 450.13(1) (Exhs. 12–27).

B. Clinical Issues Associated with Improper Release of Paliperidone

In connection with its consideration of any ANDA where INVEGA® SUSTENNA® is the RLD, FDA will need to ensure that the release profile for the proposed generic product is closely equivalent to that of INVEGA® SUSTENNA®. That is critical since even subtle differences in the plasma time-concentration profiles may have adverse impacts for patients. Those impacts may arise both from inadequate treatment of schizophrenia, as well as excessive release of paliperidone.

1. Inadequate Treatment May Lead to Relapses

Even short periods of treatment interruption of patients with schizophrenia can lead to an increase in the number of patients who relapse into an acute episode. This has been shown in an exploratory analysis of data from a randomized, double-blind, withdrawal-of-treatment study designed to evaluate the efficacy of flexibly dosed ER OROS® paliperidone. Following one week of treatment in the double-blind phase, recurrence occurred in 1 of 104 subjects (1.0%) who received ER OROS® paliperidone, and in 4 of 101 subjects (4.0%) who received placebo. Following two weeks of treatment in the double-blind phase, recurrence occurred in 8 of 104 subjects (7.7%) who received ER OROS® paliperidone, and in 16 of 101 subjects (15.8%) who received placebo. The data from the placebo group are analogous to a drug exposure gap of one or two weeks.[26]

This situation is somewhat analogous to that of patients being treated with oral antipsychotics, but with poor or partial adherence to treatment. It has been demonstrated that even "partial compliance" can be associated with a significantly increased risk of relapse and hospitalization. For example, in a study of California Medicaid patients with schizophrenia, the presence of any gap in medication (defined as the longest period during which no medication appeared to be available over a one-year period) was associated with increased risk of hospitalization. Even gaps as small as 1–10 days were associated with increased risk of hospitalization (odds ratio = 1.98); the risk of hospitalization increased further with increasing medication coverage gap.[27] These findings strongly suggest that even small and temporary reductions in exposure may pose significant risks of clinical relapse and the consequent need for hospitalization.

Indeed, relapse in schizophrenia is common and often extremely serious, with significant consequences for the patient and his/her support network. Recurrence may manifest both positive and negative symptoms of the disorder. Positive symptoms may include, but are not limited to, hallucinations, delusions, disorganization of thought and behavior, and aggressive or even violent outbursts. Negative symptoms are generally characterized by increasing social withdrawal, flattening of affect, impairments in attention, and anhedonia, or a loss of interest in usual activities. There may also be an accompanying deterioration in cognitive functioning. Obviously, all of these symptoms

---

[26] Paliperidone is the major active metabolite of risperidone. Study R076477-SCH-301 was conducted using paliperidone extended release tablets (ER OROS® paliperidone).

[27] Peter J. Weiden et al., *Partial Compliance and Risk of Rehospitalization among California Medicaid Patients with Schizophrenia*, 55 Psychiatric Servs. 886, 889 (2004) (Exh. 28).

can impair social and vocational functioning to a significant degree, lead to increased caregiver burden, as well as an increased possibility of suicidal and violent behaviors.[28]

Successive relapses can result in reduced periods of subsequent remission, with many patients unable to regain their previous level of functionality and cognitive capacity after each episode.[29] With each successive relapse, patients may experience an increase in the severity of their symptoms as the progression of their illness moves them further away from recovery.[30] The relapse rate for schizophrenia patients at two years, even with oral medications, is over 40%.[31] On the other hand, continuous medication, with accompanying maintenance of stable concentration of drug, has been shown to reduce this risk.[32]

2. Excessive Treatment May Have Adverse Clinical Impacts

The excessive release of paliperidone could have adverse effects on patients, including extrapyramidal symptoms ("EPS") and QTc interval prolongation.[33]

Specifically, acute dystonia, Parkinsonism, and akathisia are important safety and tolerability issues related to both higher and fluctuating plasma drug concentrations of typical and, to a lesser extent, atypical antipsychotic drugs.[34] These symptoms may occur

---

[28] S.W. Mikhail & H.G. Kennedy, *Homicide, Novel Antipsychotics, and Non-Compliance*, 355 Lancet 1189, 1189 (2000) (Exh. 29).

[29] D.A.W. Johnson et al., *The Discontinuance of Maintenance Neuroleptic Therapy in Chronic Schizophrenic Patients: Drug and Social Consequences*, 67 Acta Psychiatr. Scand. 339, 340 (1983) (Exh. 30); Vincente Molina et al., *Lower Prefrontal Gray Matter Volume in Schizophrenia in Chronic but Not in First Episode Schizophrenia Patients*, 131 Psychiatry Res. 45, 52 (2004) (Exh. 31).

[30] Jeffrey A. Lieberman et al., *The Early Stages of Schizophrenia: Speculations on Pathogenesis, Pathophysiology, and Therapeutic Approaches*, 50 Biol. Psychiatry 884, 885 (Dec. 2001) (Exh. 32).

[31] William T. Carpenter et al., *Continuous Versus Targeted Medication in Schizophrenic Outpatients: Outcome Results*, 147 Am. J. Psychiatry 1138 (1990) (Exh. 33).

[32] Kane & Garcia-Ribera *supra* note 13, at S65.

[33] In its citizen petition requesting specific parameters to evaluate the bioequivalence of proposed generic versions of RISPERDAL® CONSTA®, JRD summarized additional clinical impacts that may result from excessive release of risperidone, including orthostatic hypotension, sedation, and somnolence. Johnson & Johnson, *Citizen Petition of J&JPRD Requesting Adoption of Certain Parameters to Govern the Review of Bioequivalence of Proposed Follow-On Versions of RISPERDAL® CONSTA®*, at 22 (Feb. 10, 2011), *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0086-0001 (Exh. 34). Inasmuch as paliperidone is the major active metabolite of risperidone, such impacts would also be expected for INVEGA® SUSTENNA®. Indeed, the labeling for INVEGA® SUSTENNA® recognizes that paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha blocking activity. *See* Janssen Pharms., *supra* note 14, at § 5.7. Excessive release of paliperidone could also potentially increase the risk of sedation or somnolence and the complications associated with these events because paliperidone, like risperidone, has a high affinity for α1 adrenoceptors, which may partially regulate somnolence and sedation. *See* Massimo C. Mauri et al., *Clinical Pharmacokinetics of Atypical Antipsychotics: A Critical Review of the Relationship between Plasma Concentrations and Clinical Response*, 46 Clin. Pharmacokinet. 359, 362 (2007) (Exh. 35).

[34] Samuel Keith, *Advances in Psychotropic Formulations*, 30 Prog. Neuro-Psychopharmacology Biol. Psychiatry 996, 1002–03 (2006) (Exh. 36); Gary Remington, *Tardive Dyskinesia: Eliminated, Forgotten, or Overshadowed?*, 20 Curr. Op. Psychiatry 131, 134–35 (2007) (Exh. 37); Diederik E. Tenback et al.,

acutely in response to higher plasma drug concentrations.[35] While it is difficult to predict the occurrence of EPS for any individual patient, on a population level, D2 receptor occupancy levels >80% have been associated with higher rates of EPS.[36]

A pharmacodynamics model was developed relating the risk of having EPS-related adverse events with average steady-state plasma concentrations of paliperidone. The model was based on data from studies with a six-week treatment period using fixed oral doses of paliperidone (3-15 mg). EPS had a steep concentration-response profile for paliperidone ER. Half maximal effective concentration was estimated at 24 ng/mL. For plasma concentrations below 20 ng/mL, the EPS risk was similar to placebo. Between 20 and 40 ng/mL, this risk increased gradually to its maximum level, with a factor of about 2.8. For paliperidone ER, a plasma concentration of 20 ng/mL corresponded to a central D2 receptor occupancy of 80%.[37]

In a 13-week study of INVEGA® SUSTENNA® involving 234 mg initiation dosing, the incidence of any treatment-emergent EPS-related adverse events was similar to that of the placebo group (8%), but exhibited a dose-related pattern with 6%, 10%, and 11% in the INVEGA® SUSTENNA® 234/39 mg, 234/156 mg, and 234/234 mg groups, respectively.[38] A dose-related pattern in the incidence of treatment-emergent EPS-related adverse events has also been observed in pooled data from three placebo-controlled, six-week, fixed-dose studies in adult subjects with schizophrenia treated with paliperidone extended release tablets (overall percentage of patients with EPS-related adverse events was 11% in the placebo group, 13% in the 3 mg once daily group, 10% in the 6 mg once daily group, 25% in the 9 mg once daily group, and 26% in the 12 mg once daily group).[39] In addition, there was a dose-related increase observed for the 9 mg and

---

Evidence that Early Extrapyramidal Symptoms Predict Later Tardive Dyskinesia: A Prospective Analysis of 10,000 Patients in the European Schizophrenia Outpatient Health Outcomes (SOHO) Study, 163 Am. J. Psychiatry 1438, 1438 (2006) (Exh. 38).

[35] Peter J. Weiden, *EPS Profiles: the Atypical Antipsychotics are Not All the Same*, 13 J. Psychiatry Practice 13 (2007) (Exh. 39).

[36] Lars Farde et al., *Positron Emission Tomographic Analysis of Central D_1 and D_2 Dopamine Receptor Occupancy in Patients Treated with Classical Neuroleptics and Clozapine: Relation to Extrapyramidal Side Effects*, 49 Arch. Gen. Psychiatry 538, 543 (1992) (Exh. 40); Shitij Kapur et al., *Relationship Between Dopamine D_2 Occupancy, Clinical Response, and Side Effects: A Double-blind PET Study of First-episode Schizophrenia*, 157 Am. J. Psychiatry 514, 516 (2000) (Exh. 41); Svante Nyberg et al., *Suggested Minimal Effective Dose of Risperidone based on PET-measured D_2 and 5-HT_{2A} Receptor Occupancy in Schizophrenic Patients*, 156 Am. J. Psychiatry 869, 869 (1999) (Exh. 42); Gary Remington et al., *A PET Study Evaluating Dopamine D_2 Receptor Occupancy for Long-acting Injectable Risperidone*, 163 Am. J. Psychiatry 396, 398 (2006) (Exh. 43).

[37] F. De Ridder et al., *Evaluation of the Clinical Relevance of the Food Effect Observed with Paliperidone ER, Using a Pharmacokinetic/Pharmacodynamic Modeling Approach*, Poster at the 3rd Pharmaceutical Sciences World Congress (PSWC), Amsterdam, the Netherlands (April 22–25, 2007) (Exh. 44).

[38] Gahan J. Pandina, et al., *A Randomized, Placebo-Controlled Study to Assess the Efficacy and Safety of 3 Doses of Paliperidone Palmitate in Adults with Acutely Exacerbated Schizophrenia*, 30 Journal of clinical psychopharmacology 235 (2010) (Exh. 45).

[39] Herbert Y. Meltzer et al., *Efficacy and Tolerability of Oral Paliperidone Extended-Release Tablets in the Treatment of Acute Schizophrenia: Pooled Data From Three 6-Week, Placebo-Controlled Studies*, 69 J. Clin. Psychiatry 817 (2008) (Exh. 46).

12 mg doses for the Simpson-Angus Scale and use of anticholinergic medications whereas there was no difference observed between placebo and the 3 mg and 6 mg doses for these EPS measures.[40] Therefore, excessive release leading to sudden increases in plasma drug concentrations and D2 receptor occupancy could potentially increase the risk of EPS-related adverse events and the complications associated with these events.

QTc prolongation has also been identified as a potential safety concern with several atypical antipsychotics.[41] In a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder (n = 141), the 8 mg dose of immediate-release oral paliperidone (n = 50) showed a mean placebo-subtracted increase from baseline in QTcLD of 12.3 msec (90% confidence interval ("CI"): 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate release ($C_{max\ ss}$ = 113 ng/mL) was more than two-fold the exposure observed with the maximum recommended 234 mg dose of INVEGA® SUSTENNA® administered in the deltoid muscle (predicted median $C_{max\ ss}$ = 50 ng/mL). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which $C_{max\ ss}$ = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose.[42]

QTc prolongation[43] is of particular importance for patients with a history or presence of additional or pre-existing risk factors for a prolongation of the QTc interval, such as specific cardiac disorders (sick sinus syndrome, complete atrioventricular block, congestive heart failure, polymorphic ventricular tachycardia and congenital prolongation of the QT interval), clinically relevant hypocalcaemia, hypokalemia, or hypomagnesaemia, or concomitant use of other medications that prolong the QTc interval (particularly Class I or Class III antiarrhythmics).[44] Excessive release leading to sudden increases in plasma drug concentrations could potentially increase the risk of QTc prolongation and the complications associated with these events, particularly in at-risk patients.

---

[40] *Id.*

[41] Unpublished data, JRD, *A Study of QT and QTc Intervals in Patients Administered Immediate Release Paliperidone*, clinical study synopsis *available at*: http://www.clinicaltrials.gov/ct2/show/NCT00791349.

[42] *Id.*

[43] An undesirable property of some non-antiarrhythmic drugs is their ability to delay cardiac repolarization, an effect that can be measured as prolongation of the QT interval on the surface ECG. A delay in cardiac repolarization creates an electrophysiological environment that favors the development of cardiac arrhythmias, most clearly Torsade de Pointes. Torsade de Pointes can degenerate into ventricular fibrillation, potentially leading to sudden death. Center for Drug Evaluation and Research, FDA, *ICH Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* 2 (Oct. 2005), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129357.pdf.

[44] David M. Gardner, Ross J. Baldessarini, Paul Waraich, *Modern Antipsychotic Drugs: a Critical Overview*, 172 Can. Med. Ass'n J. 1703, 1708 (2005) (Exh. 47).

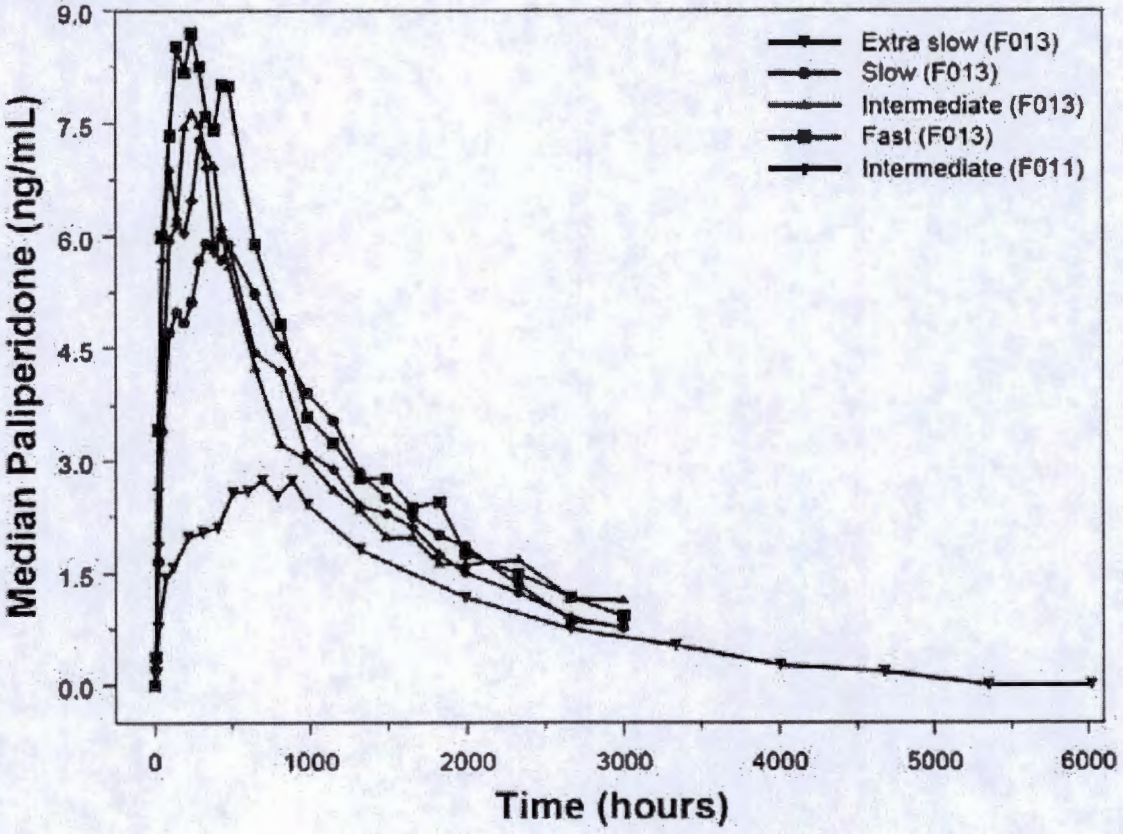
C. Particle Size and Distribution Control the Release Rate

In light of the clinical impacts that may result from inadequate or excessive treatment with paliperidone, it will be critical for FDA to ensure that any proposed generic product maintains a closely equivalent release profile to INVEGA® SUSTENNA®. As described above, the release of paliperidone palmitate is characterized by a biphasic release profile: an initial zero-order release phase (i.e., the same amount of drug is released per day) during the first two weeks, and subsequently a first-order release phase (i.e., the amount released per day diminishes, proportionally to the amount left at the injection site). As FDA recognized when it approved INVEGA® SUSTENNA®, the release profile is controlled by the particle size and distribution of paliperidone palmitate – the larger the particle size, the slower the release rate.

Indeed, when FDA reviewed the NDA for INVEGA® SUSTENNNA®, it stated that particle size is a main factor driving the release rate of paliperidone palmitate.[45] This is evident from early clinical studies (R092670-BEL-1, R092670-BEL-2, R092670-BEL-4), and was later confirmed in Study R092670-PSY-1002. There, the pharmacokinetic characteristics of four paliperidone palmitate formulations with different particle sizes (including the to-be-marketed formulation), were evaluated. As can been seen from Figure 1, the median C_{max} after injection of 50 mg eq. paliperidone palmitate decreased while the T_{max} occurred later with increasing particle sizes.

[45] FDA, *Application Number: 22-264: Clinical Pharmacology and Biopharmaceutics Review(s)* 12 (Feb. 3, 2009), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022264s000clinpharmr.pdf.

Figure 1: Median Plasma Concentration Profile for Different Treatments of 50 mg eq. Paliperidone[46]



The particle size distribution and particle morphology of INVEGA® SUSTENNA® is determined by the technology and operating conditions used to manufacture the product. If a different technology is used, it is likely that a different particle size distribution and morphology will be obtained. Such products, while having similar quantitative and qualitative composition, can be expected to have a significantly different pharmacokinetic profile while having similar C_{max} and AUC after a single-dose administration. For example, if, unlike INVEGA® SUSTENNA®, the generic product contains a fraction of very fine particles (e.g., 10%) this may theoretically lead to a burst release upon injection without impacting the single-dose C_{max} or AUC significantly.

Although FDA has proposed in the Draft Guidance that it will hold generic products to Q1/Q2 sameness,[47] this will not address potential differences in particle size distribution, and therefore PK.

---

[46] Identifying numbers have been redacted from this figure to protect trade secret information. Upon request from FDA, JRD can provide an unredacted figure, which would not be subject to public disclosure under the Freedom of Information Act.

[47] While adopting these bioequivalence metrics, FDA must also ensure that the proposed follow-on product contains the same inactive ingredients in the same concentration as INVEGA® SUSTENNA® ("Q1, Q2 Sameness"). 21 C.F.R. § 314.94(a)(9)(iii). To the very limited extent that differences are permitted under this regulation for such products, FDA must ensure that applicants identify and characterize any differences

D. Traditional Bioequivalence Parameters May Not Capture Clinically Meaningful Differences in Proposed Generic Products

As mentioned at the outset, FDA issued Draft Guidance in August 2011 outlining specific recommendations for measuring bioequivalence of paliperidone palmitate intramuscular injection products. That draft called for a single-dose, parallel, steady-state *in vivo* study evaluating the bioequivalence of test products at the 117 mg/0.75 mL strength. In this context, FDA did not specify any additional parameters that applicants should use in evaluating the bioequivalence of proposed generic products. As a result, it appears that the agency is prepared to accept bioequivalence determinations based solely on the traditional metrics of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.[48]

Yet, as JRD demonstrated in its comments on the Draft Guidance, the 72 hour time point in administration of INVEGA® SUSTENNA® reflects a turning point between a phase of increasing exposure to paliperidone and a phase of more stable exposure.[49] Indeed, this is the first time point for which an association with clinical effect has been shown in the clinical studies. In one Phase 3 study, treatment groups showed numerical improvement in PANSS total score over the placebo group as early as day 4 (72 hours after dosing).[50] Moreover, in a second Phase 3 study, mean PANSS total score improved significantly ($p<0.01$) from day 1–4 (72 hours after dosing).[51] Clinical improvement was associated with pharmacokinetic findings: mean paliperidone plasma concentrations exceeded a previously established antipsychotic efficacy threshold of 7.5 ng/mL from the first sampling point after dosing (day 4, i.e., 72 hours after dosing).[52]

Reliance solely on C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ to evaluate the bioequivalence of generic versions of INVEGA® SUSTENNA® may not, however, detect this potentially significant and clinically meaningful difference in such products. Moreover, the inability of C_{max} and AUC to capture potential differences in the PK profiles of proposed generic products could become especially problematic when and if such products are switched for INVEGA® SUSTENNA®. Upon switching treatment between INVEGA® SUSTENNA® and a generic product with different release properties, patients may be exposed to an excessive amount of paliperidone that, in turn, could lead to significant adverse events. Alternatively, such switching may cause patients to undergo periods with inadequate release of paliperidone that could result in decreased efficacy and clinically significant relapses.

---

in buffers, preservatives and antioxidants and demonstrate that these differences do not impact the safety/efficacy profile of the proposed drug product.

[48] Where FDA has recommended that additional metrics should be used, it has expressly specified them in its draft bioequivalence guidance documents. *See, e.g.*, FDA, *Guidance on Zolpidem* (Oct. 2011), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM175029.pdf.

[49] *See* Malchow, *supra* note 4, at 5.

[50] *See id.* at 9–10 (Summary of Efficacy Data From Study PSY-3007).

[51] *See id.* at 10–12 (Summary of Efficacy Data From Study PSY-3006).

[52] *See id.*

To investigate this possibility, JRD simulated different switching scenarios to determine if a product with different release properties but the same C_{max} and AUC after single dosing could, upon switching, have a different C_{trough}, C_{max} and AUC_{tau} during the next dosing cycles. These simulations were performed using the validated INVEGA® SUSTENNA® population PK model.[53] This population PK model was used to support the US Prescribing Information ("USPI") language regarding dosing window, management of missed doses, switching from other LAIs to INVEGA® SUSTENNA®, etc. Further information on the population PK model is located in the Appendix to this document.

Two different switching scenarios were simulated. Single-dose PK profiles are presented for both scenarios. In the first scenario, the consequences of switching between INVEGA® SUSTENNA® and a generic product with delayed release properties (start of release is delayed by a lag period of 1–5 weeks) but no other changes in the release characteristics were simulated. In the second scenario, the consequences of switching between INVEGA® SUSTENNA® and a generic product with altered release properties (lower first-order release rate [KA][54]) were simulated.

Scenario 1: Delayed Release

Simulations were performed to investigate the consequences of switching from INVEGA® SUSTENNA® to a generic product with the same C_{max} and AUC after a single dose, and the same release properties, except for an additional lag time (period without significant release) of 1–5 weeks (as is the case, e.g., for RISPERDAL® CONSTA®). This simulation demonstrated that potentially clinically relevant differences in minimum concentration ("C_{min}") are observed upon switching for generic products with a lag time of one week (–10%), two weeks (–19%), three weeks (–27%), four weeks (–34%), and five weeks (–41%) (Figure 2).

In addition, JRD conducted a simulation evaluating a switch from a generic product with the same C_{max} and AUC after a single dose, and the same release properties, except for a period without significant release of 1–5 weeks, to INVEGA® SUSTENNA®. This simulation revealed potentially clinically relevant differences in C_{max} for the proposed generic products with a lag time of two weeks (+15%), three weeks (+30%), four weeks (+36%), and five weeks (+36%) (Figure 3).

In these simulations, lag time has no influence on C_{max} and AUC after a single dose when switching from INVEGA® SUSTENNA® to a generic product or vice versa.

---

[53] Mahesh Samtani et al., *Population Pharmacokinetics of Intramuscular Paliperidone Palmitate in Patients with Schizophrenia: A Novel Once-Monthly, Long-Acting Formulation of an Atypical Antipsychotic*, 48 Clin. Pharmacokinet. 585, 586 (2009) (Exh. 48).

[54] A dual-absorption pharmacokinetic model best describes the complex pharmacokinetics of paliperidone after intramuscular administration of its palmitate ester. The absorption component of the model allows a fraction of the administered dose to enter relatively quickly into the central compartment via a zero-order process (i.e., the same amount of drug is released per day). Afterwards, the remaining fraction enters the systemic circulation via a first-order process (i.e., the amount released per day diminishes, proportional to the amount left at the injection site) characterized by the absorption rate constant KA.

C_{max} and AUC are not sufficiently sensitive to detect such generic products with delayed release.

These examples illustrate how switching between two seemingly identical drug products with the same C_{max} and AUC (after a single dose) can result in significant changes in the systemic drug concentrations for a significant time after switching.

Figure 2: Concentration-time Profile Upon Switching From INVEGA® SUSTENNA® to a Generic Product with Delayed Release

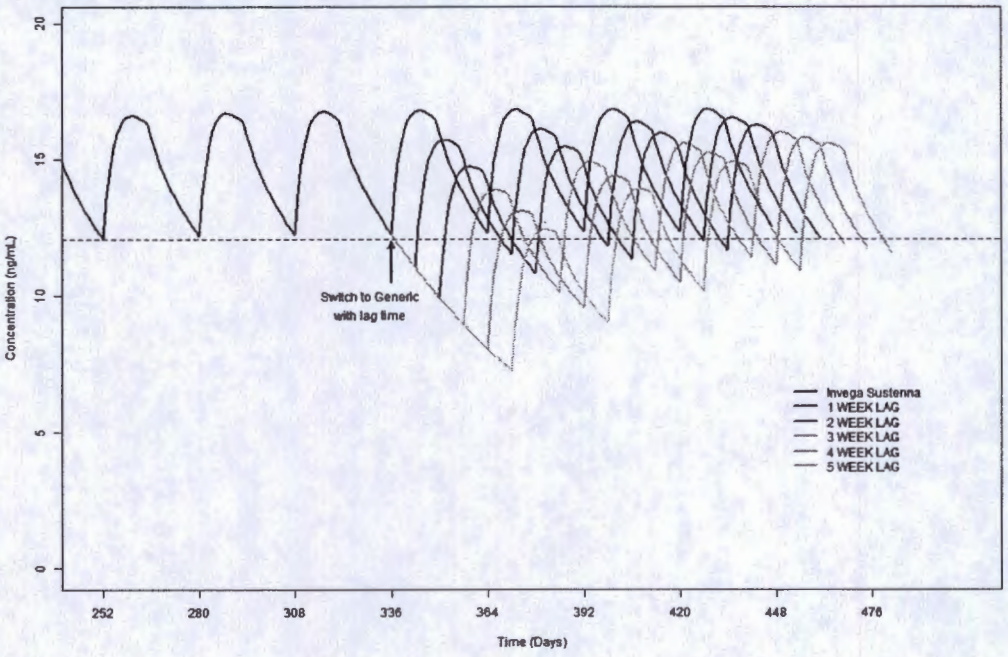
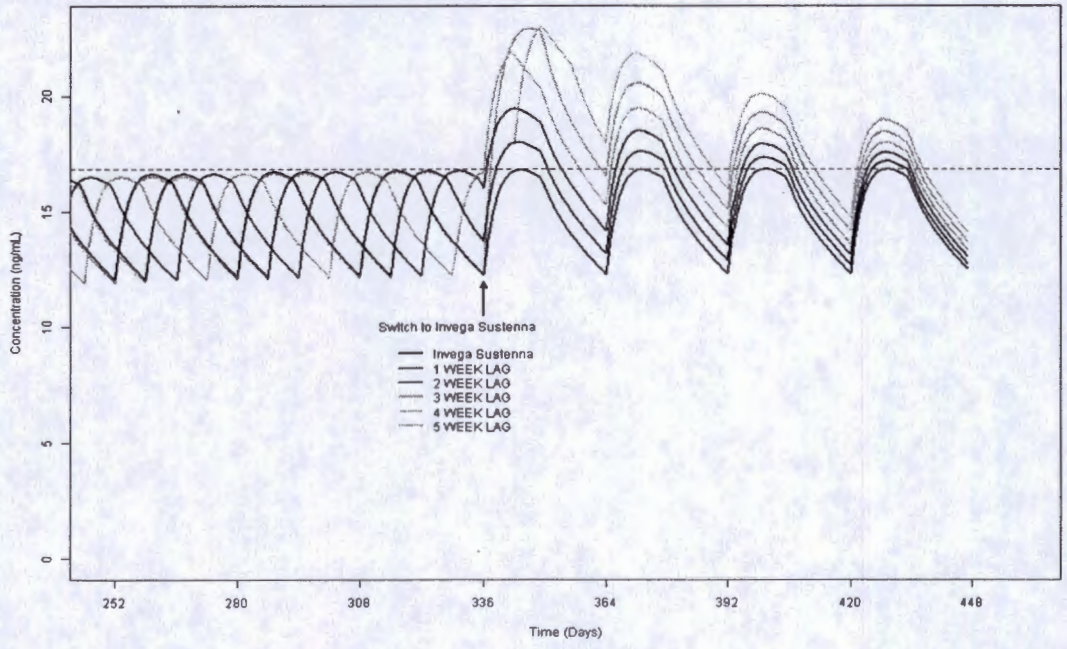


Figure 3: Concentration-time Profile Upon Switching From a Generic Product with Delayed Release to INVEGA® SUSTENNA®



Scenario 2: Altered Release

Simulations were performed to investigate the consequences of switching from INVEGA® SUSTENNA® to a generic product with the same C_{max} and AUC after a single dose but with altered release properties (lower first-order release rate characterized by absorption rate constant KA, presented as a percentage of KA of INVEGA® SUSTENNA®). Such a scenario is feasible as the zero-order and first-order release processes are independent, and could therefore occur in case of differences in the particle size distribution (see Section C). This simulation demonstrated that potentially clinically relevant differences in C_{min} are observed for generic products with 50% KA (–24%), 33.3% KA (–38%), 25% KA (–46%), 20% KA (–53%), and 10% KA (–69%) (Figure 4).

In addition, JRD conducted a simulation evaluating a switch from a generic product with the same C_{max} and AUC after a single dose, but with altered release properties, to INVEGA® SUSTENNA®. This simulation also revealed potentially clinically relevant differences in C_{max} for the proposed generic products with 50% KA (+18%), 33.3% KA (+27%), 25% KA (+34%), 20% KA (+38%), and 10% KA (+49%) (Figure 5).

In these simulations, the different absorption rate constant has no influence on C_{max} and AUC after a single dose when switching from INVEGA® SUSTENNA® to a generic product or vice versa. C_{max} and AUC are not sufficiently sensitive to detect such altered release in generic products.

These examples also illustrate how switching between two seemingly identical drug products with the same C_{max} and AUC after a single dose but with altered release properties (lower absorption rate constant KA) can result in significant changes in the systemic drug concentrations for a significant time after switching. It must be emphasized that the changes in steady-state PK parameters last for many months after switching.

Figure 4: Concentration-time Profile upon Switching from INVEGA® SUSTENNA® to a Generic Product with Lower Absorption Rate Constant (KA)

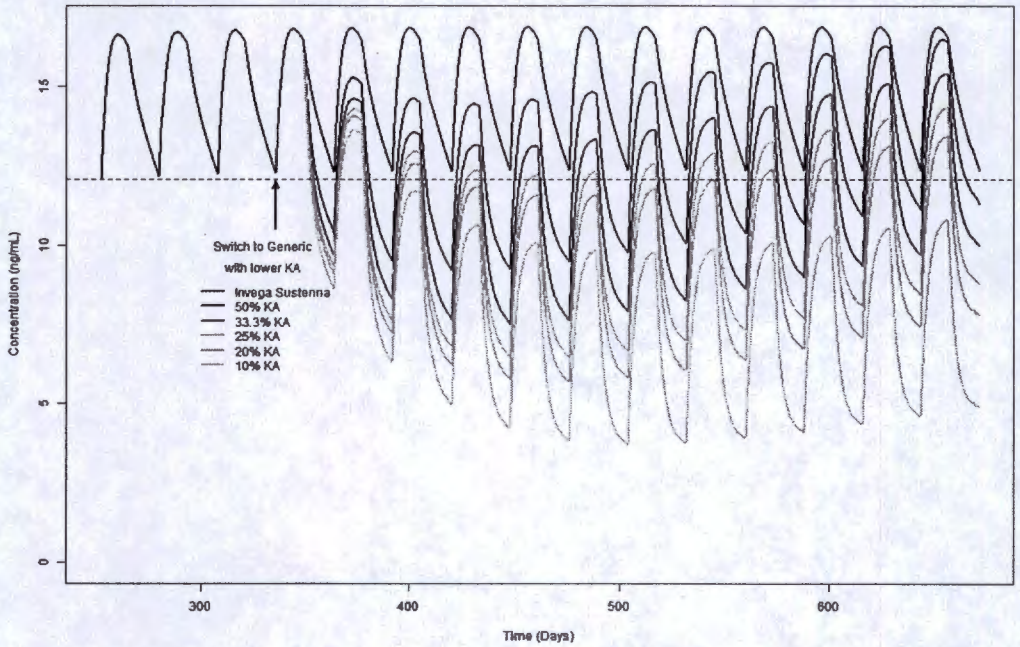
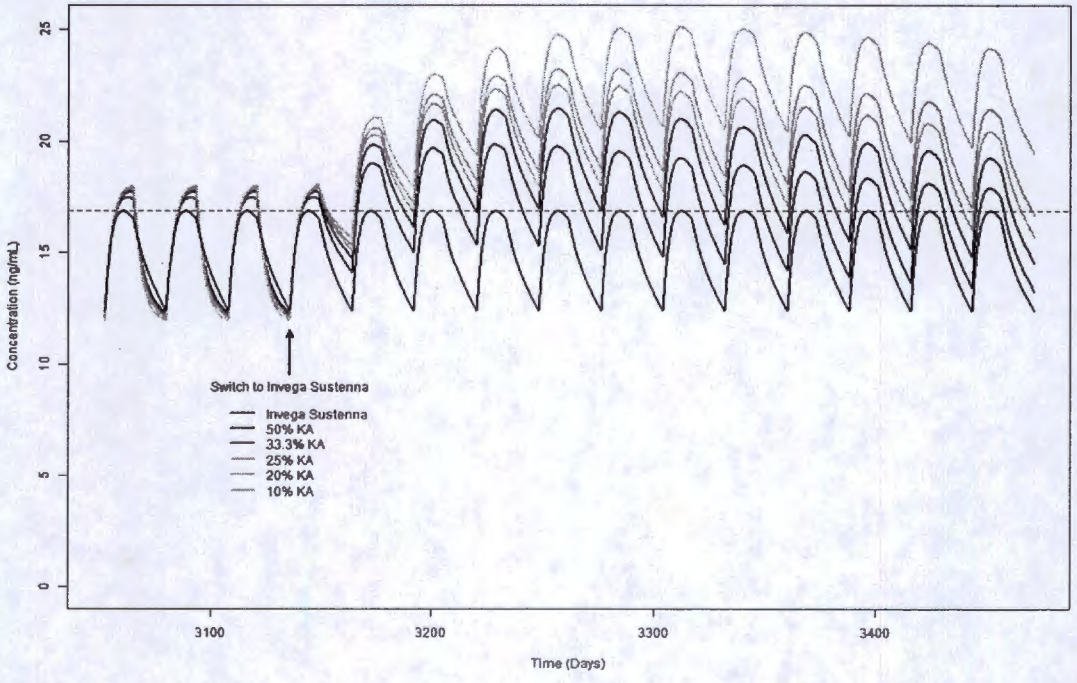


Figure 5: Concentration-time Profile upon Switching from a Generic Product with Lower Absorption Rate Constant (KA) to INVEGA® SUSTENNA®



Potential Clinical Consequences

Given the absence of a strong exposure-response relationship at the level of the population for paliperidone, it is difficult to predict the potential clinical consequences associated with the changes in pharmacokinetics simulated for the different scenarios.[55] However, at the level of the individual patient, an exposure-response relationship is applicable and is the basis for titrating individual patients to their individual optimal dose. As a consequence, a drop in the trough concentrations by approximately 50%, as depicted in Figures 2 and 4 above, corresponds to trough concentrations equal to the trough concentrations associated with approximately half of the optimal dose for that patient.

All of the Phase 2/3 clinical trials in the paliperidone palmitate program utilized a two-dose initiation sequence (days 1 and 8). Various doses of this regimen were studied in the Phase 2/3 program, and ultimately it was found that use of a 150 mg eq. dose on day 1 followed by 100 mg eq. dose on day 8 led to the most optimal PK profile.[56] The clinical efficacy data from these studies also closely mirrored the PK findings whereby those studies utilizing the optimal 150/100 initiation sequence had earlier onset of efficacy, compared with other initiation sequences. Use of lower doses was found to be detrimental to the speed of action of paliperidone palmitate in schizophrenia. In particular, in the studies that utilized lower initiation doses (25/50/100), onset of action was delayed until day 36 or later. Similarly in these studies, a higher percentage of subjects suffered from psychiatric-related adverse events (such as schizophrenia relapse and worsening of psychosis), compared with studies in which the optimal regimen was utilized. To illustrate this point, data from two active-controlled studies (PSY-3002 and PSY-3006) comparing paliperidone palmitate to RISPERDAL® CONSTA® are described below.

In the first active-controlled study (PSY-3002), subjects received either flexibly dosed paliperidone palmitate (25, 50, 75, or 100 mg eq.) following an initiation sequence of a 50 mg eq. dose on day 1 followed by 50 mg eq. dose on day 8 in the gluteal muscle, or flexibly dosed RISPERDAL® CONSTA® (25, 37.5, or 50 mg).[57] The primary efficacy endpoint in this study was the change from baseline in the PANSS total score to endpoint. Since no placebo group was used, a non-inferiority hypothesis was prespecified, and a non-inferiority margin of –5.0 points on the PANSS total score was declared prior to the start of the study. By the study endpoint, the efficacy difference between the two medications was evident as observed by the change in the PANSS total score from baseline to endpoint (see inset Figure 6). Results of the primary analysis exceeded the pre-specified margin for non-inferiority (non-inferiority margin was –5.0); therefore, this was considered to be a failed study. Upon closer examination, it was discovered that the plasma concentrations of subjects in the paliperidone palmitate group were considerably lower than expected (Figure 6). The plasma concentrations for the paliperidone palmitate

---

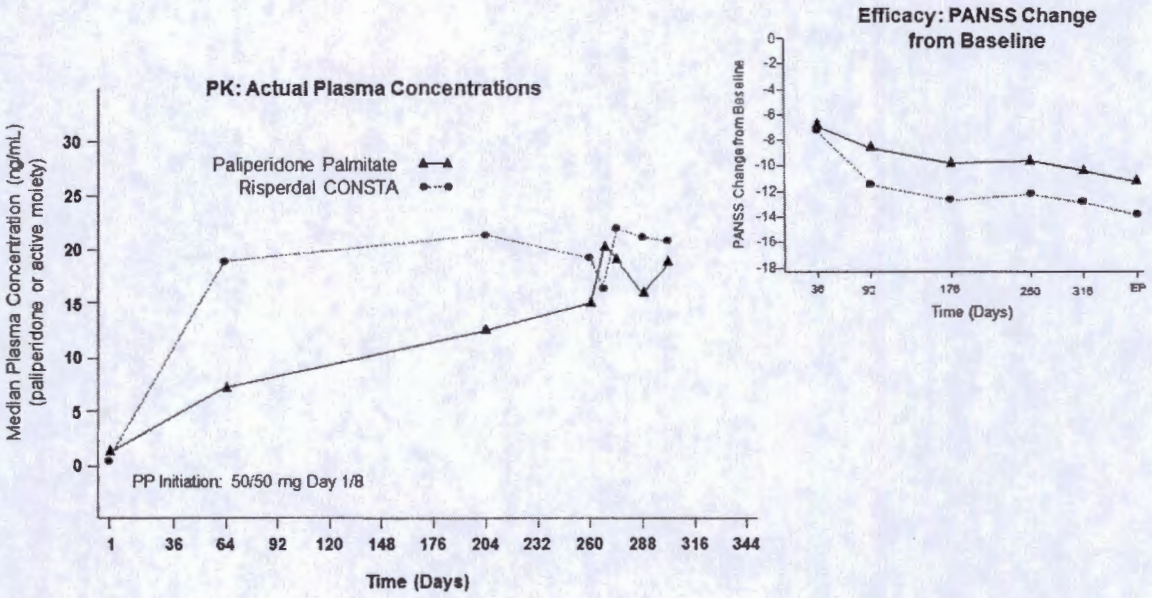
[55] JRD is currently exploring clinical data on switching between antipsychotic medications. Upon request from FDA, JRD can provide confidential information, which would not be subject to public disclosure under the Freedom of Information Act.

[56] *See* FDA, *supra* note 40, at 3 ("Starting the treatment with 150 mg eq. dose provides the benefit that the desirable exposure can be achieved within 1 week.").

[57] W. Wolfgang Fleischhacker et al., *A Randomized Trial of Paliperidone Palmitate and Risperidone Long-Acting Injectable in Schizophrenia*, 15 Int'l J. Neuropsychopharm. 107, 109 (2012) (Exh. 49).

group did not reach comparable levels to RISPERDAL® CONSTA® until day 260. Therefore, the observed delay in onset of efficacy was mirrored in the pharmacokinetic findings.

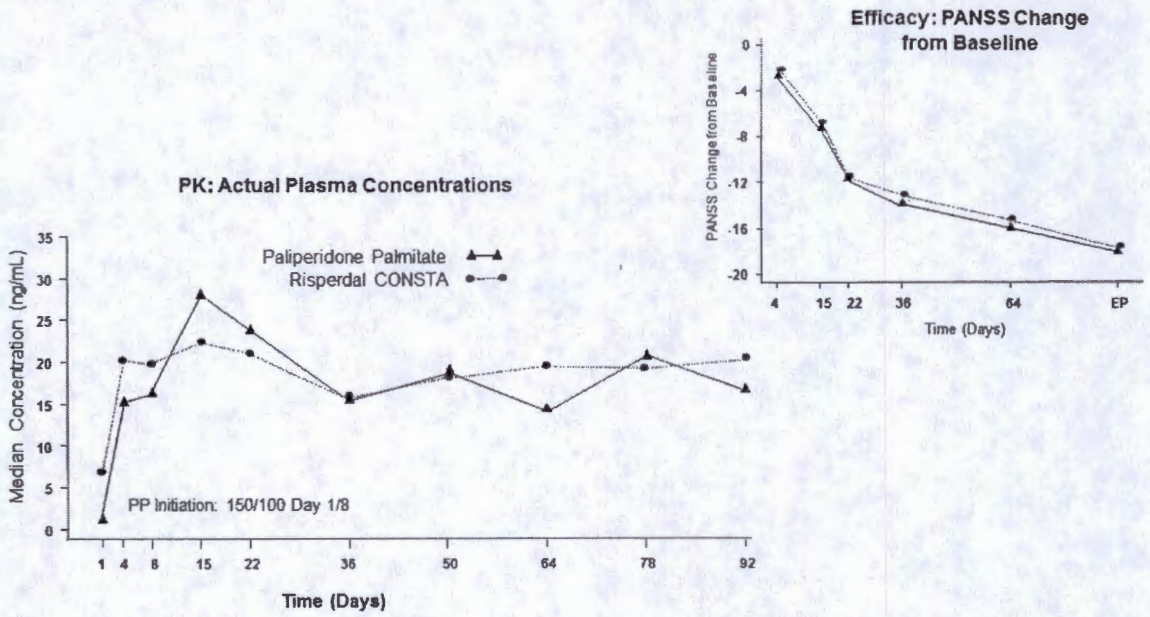
Figure 6: Relationship Between Plasma Concentration and Efficacy from Study R092670-PSY-3002



As a result, important modifications to the initiation sequence dosing regimen were implemented for the second-active controlled study (PSY-3006), which had a 150/100 initiation sequence required to be given in the deltoid muscle.[58] A similar non-inferiority analysis was used in both studies. Figure 7 summarizes the PK and efficacy over time for study PSY-3006. In contrast to PSY-3002, efficacy was numerically similar between both the paliperidone palmitate and RISPERDAL® CONSTA® groups at all time points. The results of the primary efficacy analysis conclusively demonstrated non-inferiority between the two medications.

[58] Gahan Pandina et al., *A Double-Blind Study of Paliperidone Palmitate and Risperidone Long-Acting Injectable in Adults with Schizophrenia*, 35 Prog. Neuropsychopharm. Biol. Psychiatry 218, 219 (2011) (Exh. 50).

Figure 7: Relationship Between Plasma Concentration and Efficacy from Study R092670-PSY-3006

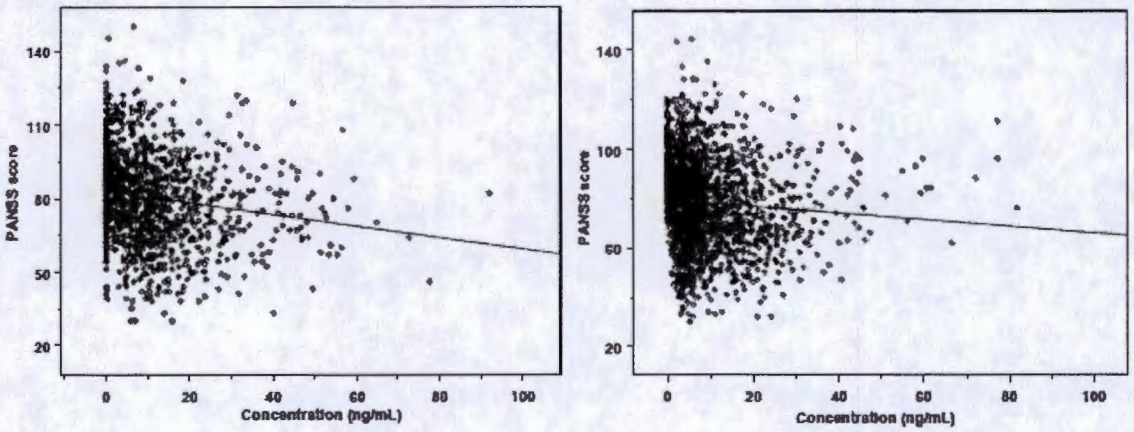


The results from active-controlled studies PSY-3002 and PSY-3006 suggest that there is a close relationship between PK levels and efficacy (as measured by PANSS). Small differences in the initiation regimens between the two studies likely contributed to the difference in efficacy profiles. This underscores the importance of the relationship between psychiatric symptom control and pharmacokinetic levels of paliperidone. If a generic version of paliperidone palmitate were made available that resulted in a different PK release profile, then it is likely that the efficacy observed would also be different. The efficacy observed during the initial period of treatment (i.e., the first eight days) is critical to ensure adequate control of symptoms.

Indeed, during the review of the paliperidone palmitate NDA by the FDA, a comprehensive examination of the relationship between plasma concentrations of paliperidone and efficacy as measured by PANSS was conducted. The Office of Clinical Pharmacology Review conducted an exposure response analysis using data submitted in the NDA from two fixed dose studies (PSY-3003 and PSY-3004). All of the paired values of plasma concentrations of paliperidone and the PANSS total score were plotted (Figure 8). FDA stated "It appears that the PANSS scores decrease when concentrations increase. Linear regression shows a significant relationship with $p<0.0001$."[59]

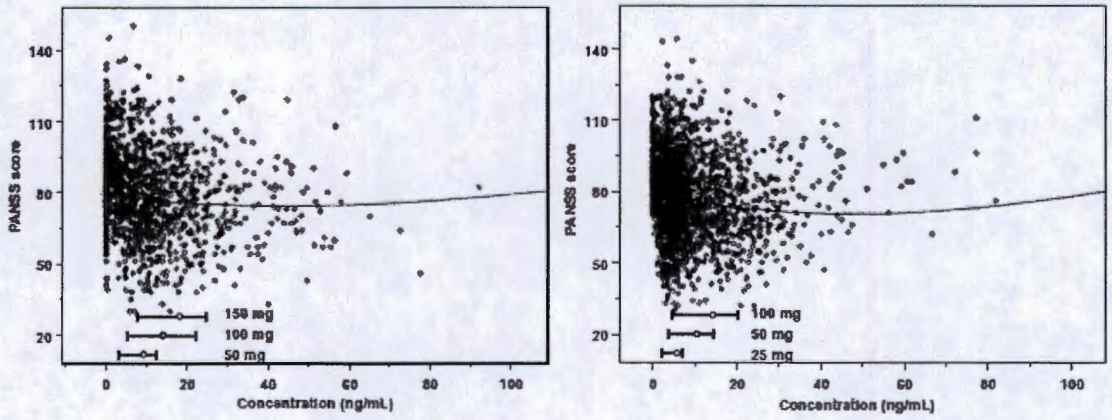
[59] *See* FDA, *supra* note 40, at 22–25.

Figure 8: Exposure Response Analysis Conducted by FDA Clinical Pharmacology Reviewer



The analysis was repeated using a local regression ("LOESS") method to understand if a nonlinear (i.e., polynomial) relationship between the two variables existed. A depiction of the LOESS regression between PANSS total score and paliperidone concentration conducted by the FDA reviewer is shown in Figure 9. FDA stated "They indicate that when the concentrations increase initially PANSS scores decrease considerably, while as the concentrations increase further, the PANSS scores do not change much (left panel for study 3003 and right for 3004)."

Figure 9: LOESS Relationship Between Plasma Concentration and PANSS Total Score



Looking at the data as a whole, the FDA reviewer concluded "From these observations, the initial concentrations seem to be important for the efficacy."

Accordingly, JRD believes that medications that do not follow the same early plasma concentration profile from the approved regimen are likely to have the same problems with achieving early onset of efficacy during treatment initiation. This will unnecessarily place patients at risk for psychiatric adverse events, the risks of which are well known, and include suicidal behaviors, suicide attempt, psychomotor agitation, and aggression.

E. FDA Should Require Partial AUCs to Evaluate the Bioequivalence of Proposed Generic Versions of INVEGA® SUSTENNA®

As an alternative to a long-lasting switching study, a single-dose bioequivalence study may control for differences in the release characteristics (such as the examples in the scenarios described in section D) if the concept of partial AUCs is applied. More details are presented below.

FDA has long recognized that pAUC should be used to evaluate bioequivalence in cases where C_{max} and $AUC_{0-\infty}$ will not capture clinically significant issues.[60] Indeed, in guidance issued by FDA in 2003 to govern bioequivalence studies of orally administered products, the agency declared that "an early exposure measure may be informative on the basis of appropriate clinical efficacy/safety trials . . . that call for better control of drug absorption into the systemic circulation (e.g., to ensure rapid onset of an analgesic effect or to avoid an excessive hypotensive action of an antihypertensive)."[61] In this context, FDA recommended use of pAUC as an early exposure measure.

More recently, FDA adopted this approach when evaluating bioequivalence of extended release products. Specifically, in October 2011, FDA issued recommendations calling for the use of pAUCs to evaluate bioequivalence of proposed generic and follow-on versions of AMBIEN CR® (zolpidem tartrate extended release).[62] Moreover, in November 2011, FDA issued draft guidance recommending that two pAUC parameters be used, in addition to traditional AUC metrics, to evaluate the bioequivalence of proposed generic and follow-on versions of RITALIN LA® (methylphenidate hydrochloride).[63] Subsequently, in response to citizen petitions involving CONCERTA® and ADDERALL XR®, the agency also agreed to adopt specific measures of pAUC to evaluate the bioequivalence of proposed generic versions of such products.[64]

---

[60] *See, e.g.*, FDA, *Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* 8–9 (Mar. 2003), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf.

[61] *Id.*

[62] FDA, *Guidance on Zolpidem*, *supra* note 43. AMBIEN CR is characterized by a multiphasic release profile with distinct and clinically relevant time intervals designed to induce sleep onset, maintain sleep, and prevent residual effects.

[63] FDA, *Draft Guidance on Methylphenidate Hydrochloride* (Nov. 2011), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM281454.pdf; *see* Jeanne Fourie Zirkelbach et al., *Use of Partial AUC (PAUC) to Evaluate Bioequivalence-A Case Study with Complex Absorption: Methylphenidate*, 30 Pharm. Res. 191, 192 (2013) (Exh. 51). In connection with issuance of this draft guidance, FDA explained that RITALIN LA® is a multiphasic modified-release formulation designed to release a bolus of methylphenidate followed by slower delivery later in the day.

[64] *See Citizen Petition Response Regarding CONCERTA® and METADATE® CD*, 2, Docket Nos. FDA-2004-P-0151 and FDA-2004-P-0290 (July 19, 2012), *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2004-P-0151-0011; *Citizen Petition Response Regarding ADDERALL XR®*, *supra* note 6.

The agency's approach to the use of pAUCs is reflected in the position that the agency took before the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology in April 2010. There, FDA indicated that it has "recently encountered several review examples of multiphasic modified-release (MR) products for which it was concluded that the generic and corresponding reference products may not be therapeutically equivalent (switchable), despite being deemed bioequivalent when the traditional metrics were compared."[65] For such products, FDA supported the use of pAUCs because there is a clear link between drug concentration and effect and there are clinically relevant time intervals that cannot be adequately measured by traditional bioequivalence parameters.

Accordingly, FDA has repeatedly affirmed that it supports the use of pAUCs for multiphasic drug products where there is a relationship between drug concentration and effect at each phase and there are clinically relevant time intervals that cannot be adequately or fully measured by the traditional bioequivalence parameters of C_{max}, AUC_t, and $AUC_{0-\infty}$.

To be sure, INVEGA® SUSTENNA® is not specifically designed to be a multiphasic product like those for which FDA has previously required additional pAUC metrics. That should make no difference, however. The key question before FDA is whether additional PK metrics are needed to evaluate bioequivalence of proposed generic versions to an RLD. Given the biphasic release profile of INVEGA® SUSTENNA®, and the potential clinical effects resulting from inadequate or excessive release of paliperidone from a generic product, FDA must require additional PK metrics here, as well.[66]

This is particularly relevant in the case of intramuscular paliperidone palmitate LAI. The rapid release of the reference drug (INVEGA® SUSTENNA®) allows it to achieve adequate plasma concentrations for the acute indication of schizophrenia without the need for oral supplementation, in addition to permitting the maintenance treatment of the disease. Because the release of the drug substance is affected by the physico-chemical properties of the drug formulation, such as particle size, measurement of pAUC is an essential PK parameter to ensure equivalent early release of paliperidone. Partial

---

[65] *See* FDA, *Briefing Information, Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology* (Apr. 13, 2010), *available at* http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM207955.pdf.

[66] FDA has previously declined to require measurements of pAUCs in particular bioequivalence studies. Those decisions, however, do not undermine FDA's position that pAUCs should be required where they will help elucidate potentially clinically meaningful differences in the PK profile of a test product that are not detected by C_{max} and $AUC_{0-\infty}$ alone. *See e.g.*, *Citizen Petition Response Regarding Morphine Sulfate*, at 7, Docket No. FDA-2010-P-0082 (July 19, 2010), *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2010-P-0082-0023; *Citizen Petition Response Regarding Temazepam*, at 6-7 n.16, Docket No. FDA-2009-P-0379 (Feb. 2, 2010), *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2009-P-0379-0009 (denying petitions calling for the use of pAUCs after finding that there was no evidence to suggest that differences in the PK profiles would have clinical significance). At the same time, FDA has declined to require pAUCs where the multi-peak PK profile of the RLD was not "consistently reproducible or medically significant." *See Citizen Petition Response Regarding Cardizem CD*, Docket No. 1998P-0145 (Oct. 22, 1999).

AUC metrics are needed to ensure that the reference drug and the test drug are therapeutic equivalents.

This is further demonstrated by the simulations presented in this document, showing the potential implications of switching between INVEGA® SUSTENNA® and a generic product that has the same release properties as INVEGA® SUSTENNA® except for delayed release (Scenario 1) or a lower absorption rate constant (Scenario 2). In both of these simulations, the same C_{max} and AUC were observed after a single dose but there was a different release rate (Scenario 1 and Scenario 2) and T_{max} (Scenario 1), and consequently different $C_{trough,ss}$, $C_{max,ss}$ and AUC_{tau} upon switching.

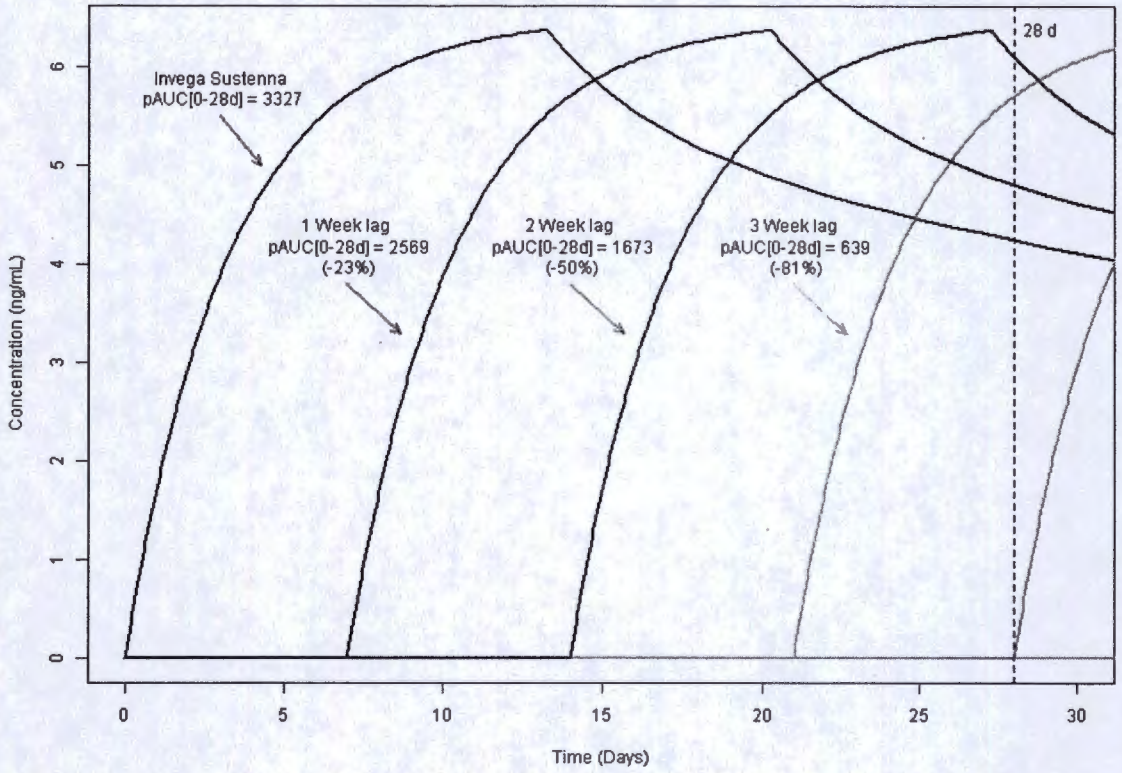
As described above, it is important to ensure that any proposed generic product does not release a substantially lower amount of drug during the zero-order release phase in order to achieve adequate plasma concentrations for the acute indication of schizophrenia without the need for oral supplementation. In Scenario 1, $pAUC_{0-72h}$ would capture the differences in the release profiles during the acute initiation treatment period (Table 1).[67]

In addition, it is important to ensure that any proposed generic product does not release a substantially lower amount of drug over the entire dosing interval, and especially to ensure that similar trough levels of paliperidone are released in order to maintain adequate dosing. In both of the simulations described above, $pAUC_{0-28d}$ would capture such differences in the release profiles (Table 1 and Figure 10 and Table 2 and Figure 11).

Partial AUC_{0-72h} and AUC_{0-28d} measurements will help to ensure that patients are not put at potential risk of relapse and its consequences from under-treatment for schizophrenia.

[67] The impact of lag time on AUC_{0-72h} is not graphically depicted because the effect is 100%: the absorption starts after the T = 72 hours.

Figure 10: Single-Dose, Percent Difference in $AUC_{0\text{-}28d}$ for INVEGA® SUSTENNA® and Generic Products with Delayed Release

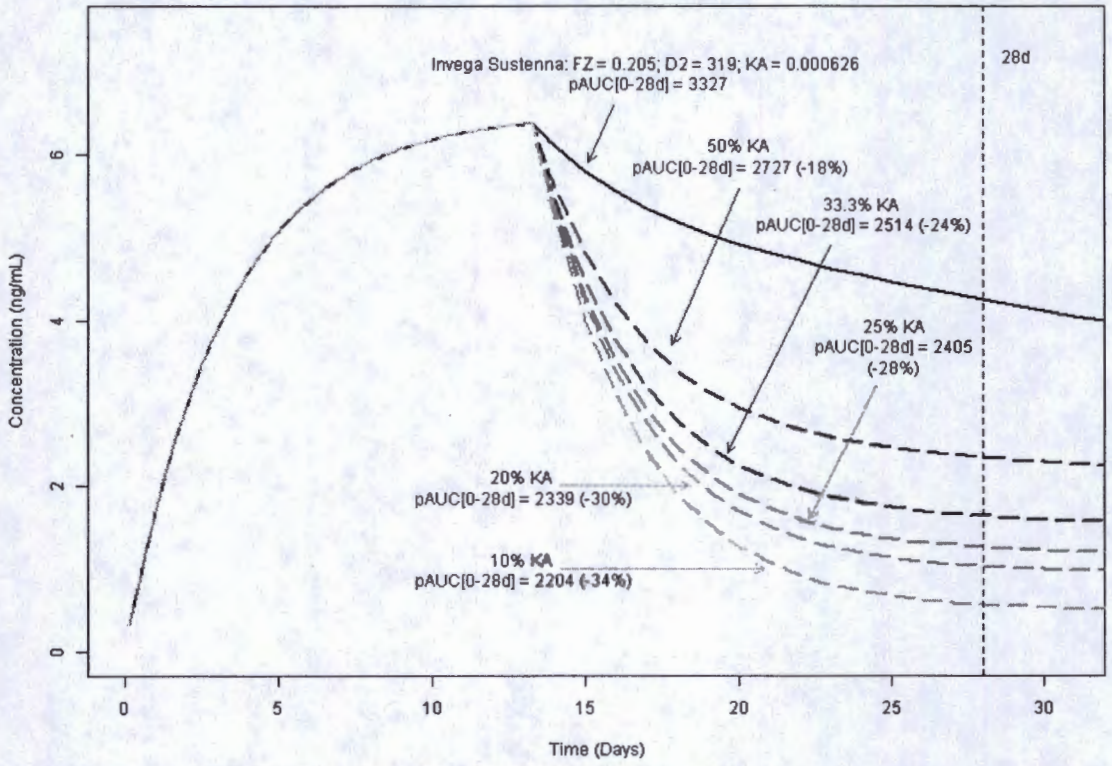


Note: Release of INVEGA® SUSTENNA® begins immediately following dosing. In the scenario where generic products have a delayed release "lag" of ≥1 week after dosing, C_{max} and AUC are equivalent to those of INVEGA® SUSTENNA® but $pAUC_{0\text{-}28d}$ identifies the differences in the release profiles.

Table 1: Single-Dose PK Parameters for INVEGA® SUSTENNA® and Generic Products with Delayed Release

	INVEGA® SUSTENNA®	1 Week Lag	2 Weeks Lag	3 Weeks Lag	4 Weeks Lag	5 Weeks Lag
C_{max} (ng/mL)	6.38	6.38	6.38	6.38	6.38	6.38
$AUC_{0\text{-}\infty}$ (ng/mL.h)	10100	10100	10100	10100	10100	10100
$AUC_{0\text{-}72h}$ (ng/mL.h)	160.7	0 (–100%)	0 (–100%)	0 (–100%)	0 (–100%)	0 (–100%)
$AUC_{0\text{-}28d}$ (ng/mL.h)	3327	2569 (–23%)	1673 (–50%)	639 (–81%)	0 (–100%)	0 (–100%)

Figure 11: Single-Dose, Percent Difference in AUC_{0-28d} for INVEGA® SUSTENNA® and Generic Products with Lower Absorption Rate Constant (KA)



Note: Release of INVEGA® SUSTENNA® and generic products begins immediately following dosing, and the same amount of drug is released per day during the initial phase of release (up to approximately day 13 in the graph for this scenario). Afterwards, the amount of drug released per day diminishes, proportional to the amount left at the injection site, which is characterized by the absorption rate constant KA. In the scenario where generic products have a lower KA, C_{max} and AUC are equivalent to those of INVEGA® SUSTENNA® but $pAUC_{0-28d}$ identifies the differences in the release profiles.

Table 2: Single-Dose PK Parameters for INVEGA® SUSTENNA® and Generic Products with Lower Absorption Rate Constant (KA)

	INVEGA® SUSTENNA®	50% KA	33.3% KA	25% KA	20% KA	10% KA
C_{max} (ng/mL)	6.38	6.38	6.38	6.38	6.38	6.38
$AUC_{0-\infty}$ (ng/mL.h)	10100	10100	10100	10100	10100	10100
AUC_{0-72h} (ng/mL.h)	160.7	160.7	160.7	160.7	160.7	160.7
AUC_{0-28d} (ng/mL.h)	3327	2727 (–18%)	2514 (–24%)	2405 (–28%)	2339 (–30%)	2205 (–34%)

Similarly, it can be inferred that $pAUC_{0\text{-}72h}$ and $pAUC_{0\text{-}28d}$ will help to ensure that patients are not put at potential risk of adverse events due to a substantially higher amount of drug being released during the acute initiation treatment period or during the subsequent release of the remaining fraction.

Thus, measurement of $pAUC_{0\text{-}72h}$ and $pAUC_{0\text{-}28d}$ after the injection will help to ensure that intramuscular paliperidone palmitate products manufactured with potentially different technologies will in fact demonstrate bioequivalence of test drugs and the reference drug (INVEGA® SUSTENNA®) during the acute initiation treatment period (measured by $pAUC_{0\text{-}72h}$) and over the entire dosing interval (measured by $pAUC_{0\text{-}28d}$). Partial $AUC_{0\text{-}72h}$ and $pAUC_{0\text{-}28d}$ are considered to be complementary as they characterize the release during the zero-order and first-order release phases, respectively. JRD is willing to discuss pAUC parameters with FDA if the agency considers this to be helpful.

III. ENVIRONMENTAL IMPACT

Under 21 C.F.R. §§ 25.30(h) and 25.31(a), this petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

IV. ECONOMIC IMPACT

Information regarding the economic impact of this proposal will be submitted upon request by FDA following review of this petition.

V. CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: September 1, 2011. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: None (however, as an employee of JRD, I receive compensation). I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Janssen Research & Development, L.L.C.

Donald L. Heald

Donald L. Heald, M.S., Ph.D.
Clinical Pharmacology Therapeutic Area Head for Neurosciences

cc: Joy Liu, Esq., Ropes & Gray LLP

APPENDIX

JRD conducted simulation modeling of single-dose-PK profiles in NONMEM® 7.2 to determine if a product with different release properties but similar C_{max} (maximum deviation of 10%) and AUC could, upon switching, have a different $C_{trough,ss}$, $C_{max,ss}$ and AUC_{tau}. These simulations were performed using the validated INVEGA® SUSTENNA® population PK model. [68]

The validated population PK model was used to evaluate the effect of altered absorption parameters (reflecting altered release characteristics, given the flip-flop kinetics of INVEGA® SUSTENNA®). The population PK model was built using pooled data from 1795 subjects from six Phase 1 trials and five Phase 2 and 3 trials. A total of 18,530 pharmacokinetic samples with valid concentration timepoints were available for this analysis. Nonlinear mixed-effects modeling of the pooled data was conducted using NONMEM® software. The concentration-time data for paliperidone following intramuscular administration of its palmitate ester were best fitted to a one-compartment model with first-order elimination. A dual-absorption pharmacokinetic model best described the complex pharmacokinetics of paliperidone after intramuscular administration of its palmitate ester. The absorption component of the model allowed a fraction of the administered dose (f2) to enter relatively quickly into the central compartment via a zero-order process (i.e., the same amount of drug is released per day). After a lag time, the remaining fraction then entered the systemic circulation via a first-order process (i.e., the amount released per day diminishes, proportional to the amount left at the injection site) characterized by the absorption rate KA. These subsequent processes are considered to be independent of each other. The final covariate model indicated that the following variables had a significant influence on KA: sex, age, injection volume (IVOL) and injection site (INJS). Similarly, the following variables had a significant influence on f2: sex, body mass index (BMI), needle length, INJS and IVOL. In addition, paliperidone clearance was related to creatinine clearance (CLCR), whereas volume of distribution was related to BMI and sex.

The population PK model was validated successfully on several different occasions using external validation datasets[69] and was used to support the USPI language regarding dosing window, management of missed doses, switching from other LAIs to INVEGA® SUSTENNA®, etc.

The single-dose profiles were estimated using NONMEM® 7.2, using the following assumptions:

---

[68] Samtani et al., *supra* note 48, at 586.

[69] *Id.*; W. Wolfgang Fleischhacker et al., *Optimization of the Dosing Strategy for the Long-Acting Injectable Antipsychotic Paliperidone Palmitate: Results of Two Randomized Double-Blind Studies and Population Pharmacokinetic Simulations*, Poster No. 21 at the 47th Annual Meeting of the American College of Neuropsychopharm. (ACNP), Scottsdale, Arizona, USA, December 7-11, 2008 (Exh. 52); Danielle Coppola et al., *A One-Year Prospective Study of the Safety, Tolerability and Pharmacokinetics of the Highest Available Dose of Paliperidone Palmitate in Patients with Schizophrenia*, BMC Psychiatry (Mar. 28, 2012), http://www.biomedcentral.com/content/pdf/1471-244X-12-26.pdf (Exh. 53).

- As an example, a dose of 50 mg (0.5 mL) INVEGA® SUSTENNA® was administered as a gluteal injection to a typical subject (age 42 years, BMI 26.8 kg/m^2 and CLCR 110.6 mL/min).
- INVEGA® SUSTENNA® parameter values: KA = 0.000626, FZ = 0.205, duration of input for the zero-order process = 319 h, t_{lag1} = 319 h (equivalent to duration of input for the zero-order process), V2 = 391 L and CL = 4.95 L/h where:
    - Fraction of the dose FZ is released by a zero-order process over a period D2 (h).
    - Remainder (1-FZ) is released by a first-order process at rate KA.
- Different paliperidone palmitate formulations were simulated by changing lag time or KA for each subject.

The single-dose profiles were used to estimate (applying noncompartmental superposition) the systemic exposure upon switching from INVEGA® SUSTENNA® to a generic drug product.