Janssen Research & Development, LLC
Global Regulatory Affairs

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janssen

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

July 27, 2015

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

Re: Second Supplement to Citizen Petition, Docket No. FDA-2011-P-0086-0001/CP

Dear Sir or Madam:

The above-referenced Citizen Petition was filed in February 2011 by Janssen Research & Development, LLC ("Janssen"), a company of Johnson & Johnson.[1]

As background, the Food and Drug Administration ("FDA") first issued "Draft Guidance on Risperidone" (Docket No. FDA-2007-D-0369) in February 2010 (the "First Draft Guidance"). Janssen submitted comments in response to safety and efficacy concerns raised by the First Draft Guidance in September of that year (the "September 2010 Comments"). Then, in February 2011, J&JPRD submitted the above referenced Citizen Petition requesting that FDA implement certain additional pharmacokinetic ("PK") standards when measuring the bioequivalence of any potential follow-on versions of RISPERDAL CONSTA® (risperidone) (the "Citizen Petition"). In August 2013, FDA released a revised Draft Guidance on Risperidone (the "Second Draft Guidance"), which did not appear to fully address the safety and efficacy concerns raised in the Citizen Petition. Thus, in October 2013, Janssen submitted comments in response to the Second Draft Guidance (the "October 2013 Comments"). In December 2013, Janssen submitted a supplement to the Citizen Petition, which incorporated by reference the October 2013 Janssen Comments (the "Citizen Petition Supplement").

Most recently, in May 2015, FDA released a further revised Draft Guidance on Risperidone (the "Third Draft Guidance"). The Third Draft Guidance does not address the majority of the concerns raised in the October 2013 Comments or Citizen Petition Supplement (or Citizen Petition). FDA has not yet responded to the Citizen Petition or Citizen Petition Supplement.

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[1] Janssen is the authorized regulatory agent for Janssen Pharmaceuticals, Inc. ("JPI"). JPI is the holder of the New Drug Application for RISPERDAL® CONSTA® (risperidone) Long-Acting Injection. The former holder of the NDA, Ortho-McNeil-Janssen Pharmaceuticals, Inc., was renamed JPI. Janssen was formerly named Johnson & Johnson Pharmaceutical Research & Development, L.L.C. ("J&JPRD"); the Citizen Petition was filed under the J&JPRD name.

Because the Third Draft Guidance does not address a number of key concerns raised in the Citizen Petition and Citizen Petition Supplement, Janssen resubmitted to the docket the Citizen Petition and Citizen Petition Supplement (incorporating the October 2013 Comments) as comments to the Third Draft Guidance (the "July 2015 Comments").

On behalf of Janssen, we request that the July 2015 Comments, which are attached hereto, be considered a second supplement to the Citizen Petition. Janssen continues to recommend FDA adoption of the PK suggestions in Janssen's original Citizen Petition, which address safety and efficacy concerns surrounding risperidone better than the methodology proposed in Janssen's October 2013 Comments. However, in the event FDA pursues the methodology set forth in the Third Draft Guidance, Janssen requests that, at a minimum, FDA adopt the recommendations presented by the company in the October 2013 Comments.

The undersigned makes the following verification for this submission, as required by 21 USC 355(q)(1)(I):

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about May 27, 2015, the date FDA released the Third Draft Guidance. 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: N/A. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

In addition, the undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information which are known to the petitioner and unfavorable to the petition.

Sincerely,

Amarnath Sharma, PhD
Vice President & Global Head Clinical Pharmacology & Pharmacometrics

cc: Mitchell V. Mathis, MD, CAPT., USPHS, Director, FDA Division of Psychiatry Products, Office of Drug Evaluation I, Office of New Drugs, CDER

Attachments

Janssen Research & Development, LLC
Global Regulatory Affairs

1125 Trenton-Harbourton Road, P.O. Box 200
Titusville NJ 08560

Janssen

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

July 27, 2015

Division of Dockets Management (HFA-305)
Docket No. #FDA-2007
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RLD Application Number: NDA 021346

Re: Docket No. FDA-2007-D-0369 "Draft Guidance on Risperidone" dated May 27, 2015; Request for Comments

Dear Sir or Madam:

These comments are submitted on behalf of Janssen Research & Development, LLC ("Janssen"), a company of Johnson & Johnson.[1]

As background, the Food and Drug Administration ("FDA") first issued "Draft Guidance on Risperidone" (Docket No. FDA-2007-D-0369) in February 2010 (the "First Draft Guidance"). Janssen submitted comments in response to safety and efficacy concerns raised by the First Draft Guidance in September of that year (the "September 2010 Comments"). Then, in February 2011, J&JPRD submitted a Citizen Petition requesting that FDA implement certain additional pharmacokinetic ("PK") standards when measuring the bioequivalence of any potential follow-on versions of RISPERDAL CONSTA® (risperidone) (the "Citizen Petition") (Docket No. FDA-2011-P-0086-0001/CP). In August 2013, FDA released a revised Draft Guidance on Risperidone (the "Second Draft Guidance"), which did not appear to fully address the safety and efficacy concerns raised in the Citizen Petition. Thus, in October 2013, Janssen submitted comments in response to the Second Draft Guidance (the "October 2013 Comments"). In December 2013, Janssen submitted a supplement to the Citizen Petition, which incorporated by reference the October 2013 Janssen Comments (the "Citizen Petition Supplement").

Most recently, in May 2015, FDA released a further revised Draft Guidance on Risperidone (the "Third Draft Guidance"). The Third Draft Guidance does not address the majority of the concerns raised in the October 2013 Comments or Citizen Petition Supplement (or Citizen Petition). FDA has not yet responded to the Citizen Petition or Citizen Petition Supplement.

[1] Janssen is the authorized regulatory agent for Janssen Pharmaceuticals, Inc. ("JPI"). JPI is the holder of the New Drug Application for RISPERDAL® CONSTA® (risperidone) Long-Acting Injection. The former holder of the NDA, Ortho-McNeil-Janssen Pharmaceuticals, Inc., was renamed JPI. Janssen was formerly named Johnson & Johnson Pharmaceutical Research & Development, L.L.C. ("J&JPRD").

Because the Third Draft Guidance does not address a number of key concerns raised in the Citizen Petition and Citizen Petition Supplement, Janssen is resubmitting the Citizen Petition and Citizen Petition Supplement (incorporating the October 2013 Comments) for consideration by FDA. Janssen continues to recommend FDA adoption of the PK suggestions in Janssen's original Citizen Petition, which address safety and efficacy concerns surrounding risperidone better than the methodology proposed in Janssen's October 2013 Comments. However, in the event FDA pursues the methodology set forth in the Third Draft Guidance, Janssen requests that, at a minimum, FDA adopt the recommendations presented by the company in the October 2013 Comments. Janssen also requests that the Division of Psychiatry Products and Office of Clinical Pharmacology be consulted in reviewing the Third Draft Guidance, the Citizen Petition and Citizen Petition Supplement, and these comments, and would appreciate confirmation that these reviews have occurred.

Janssen continues to believe that, as with the Second Draft Guidance, the proposed methodology in the Third Draft Guidance does not adequately evaluate safety and efficacy issues surrounding the release of risperidone and may pose a potential public health risk. RISPERDAL CONSTA® releases risperidone in three distinct phases: an initial release phase (<1% of the dose) following injection, a 3-week lag phase, and a main release phase. The methodology proposed in the Third Draft Guidance is not sufficiently sensitive to the phases of risperidone release, however. It is not designed to (1) detect uncontrolled early release (known as dose dumping) or (2) ensure equality of antipsychotic coverage during the lag phase. Thus, the methodology does not adequately test whether patients can safely switch between or start *de novo* on risperidone intramuscular products during the initiation period. Alternatively, patients switched from such drugs to RISPERDAL CONSTA® may experience symptomatic relapses.

Indeed, Janssen has recently become aware of an investigational risperidone intramuscular injection product that could be deemed bioequivalent to RISPERDAL CONSTA® based on the parameters set forth in the Third Draft Guidance, but which has a PK profile that is clearly quite different from that of RISPERDAL CONSTA®, and intentionally designed to be so. The product, LY03004, is being developed by Luye Pharma Group Ltd. ("Luye") and, according to a May 2015 press release (the "Press Release"), Luye has completed three PK studies of LY03004. One study compared the bioavailability of LY03004 and RISPERDAL CONSTA® in 108 patients over five consecutive injections (given once every two weeks). The Press release reports that the study "demonstrated pharmacokinetic bioequivalence of LY03004 compared to [RISPERDAL CONSTA®], based on the [FDA] standard method to assess bioequivalence, i.e., the 90% confidence interval for the ratio of [AUC] and [Cmax]. . . is within 80% to 125%".[2]

In a single-dose study of LY03004 and RISPERDAL CONSTA®, however, the results demonstrated that LY03004 commenced release of risperidone on the first day after injection and reached peak plasma levels at 14 days, while RISPERDAL CONSTA® did not reach peak plasma levels until 32 days (which is consistent with the fact that RISPERDAL CONSTA® has a three-week lag phase). Luye suggests that that this is advantageous because patients on LY03004 would not require oral antipsychotic supplementation during the three weeks after first

[2] Press Release, Luye Pharma Group Ltd., The Company has Successfully Completed Three Clinical Studies for LY03004 in the U.S. (May 15, 2015), *available at* http://www.luye.cn/en/news/?fid=1025&id=613.

injection.[3] Regardless of whether such supplementation is necessary, Luye's statements make clear that LY03004 was designed to have a different PK profile than RISPERDAL CONSTA®, such that the supplementation necessary with RISPERDAL CONSTA® would not be necessary with LY03004. And yet, despite this significant intended difference in the PK profile of LY03004, that product could very well satisfy the standards set forth in the Third Draft Guidance for demonstrating bioequivalence to RISPERDAL CONSTA®.

A follow-on product with a PK profile like that of LY03004 would present, however, significant safety and effectiveness concerns. As noted as a possibility in Janssen's prior comments, the follow-on product might release so much risperidone during what is supposed to be the lag phase that oral supplementation might not be necessary – but the follow-on product would have an identical label as RISPERDAL CONSTA®, which would *require* oral supplementation. Patients receiving too much risperidone during the initial release phase, when coupled with oral supplementation, could experience significant adverse effects, including extrapyramidal symptoms, hypotension, somnolence and sedation, and QTc interval prolongation. Similarly, a follow-on product such as LY03004, which releases risperidone early, may expose patients to risks upon switching from RISPERDAL CONSTA® to the follow-on product. As explained in the Citizen Petition, switching from RISPERDAL CONSTA® to a follow-on product with a shorter lag phase (but bioequivalent in terms of C_{max} and AUC) would result in an increase in C_{max} at steady state during the second cycle of the follow-on product (i.e. a lag phase of 1 week instead of 3 weeks would result in a 79% increase in C_{max} at steady state). This could raise significant safety concerns that occur when patients receive too much risperidone – namely, extrapyramidal symptoms, hypotension, somnolence and sedation, and QTc interval prolongation.

In light of the concerns raised by Janssen in the filings referenced above, in addition the problematic, real-world example presented herein, Janssen urges FDA to adopt the PK suggestions in its original petition. In the event FDA does not adopt the petition's suggestions, the proposed methodology may be an adequate alternative if the *in vitro* and *in vivo* studies contain additional endpoints to detect improper release profiles, as set forth in the October 2013 ~~Comments incorporated by reference in the Citizen Petition Supplement.~~

Thank you for the opportunity to review and comment on the Third Draft Guidance. Should you have any questions or comments, please contact me directly at (609) 730-3063.

Sincerely,

Jacqueline Brown

Jacqueline Brown, R.Ph.
Associate Director, North American Regulatory Leader
Janssen Research and Development, L.L.C.

cc: Mitchell V. Mathis, MD, CAPT., USPHS, Director, FDA Division of Psychiatry Products, Office of Drug Evaluation I, Office of New Drugs, CDER

[3] *Id.* (stating that "LY03004 has several advantages over [RISPERDAL CONSTA®], for example, there is no need to administer oral formulation [sic] during the three weeks after the first injection of LY03004 compared to [RISPERDAL CONSTA®]. The stable plasma drug level can also be reached much faster with LY03004[.]").

Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

DATE STAMP
&
RETURN

4195 11 FEB 10 P2:10

February 10, 2011

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 Johnson & Johnson Pharmaceutical 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 follow-on versions of RISPERDAL® CONSTA®. 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:

Bruce S. Manheim, Jr.
Ropes & Gray, LLP
One Metro Center, Suite 900
700 12th Street, N.W.
Washington, D.C. 20005
(202) 508-4696
(202) 383-8332 (facsimile)

Thank you in advance.

Sincerely,

Donald L. Heald

Donald L. Heald, Ph.D.
Vice-President
Clinical Pharmacology Therapeutic Area Head for
Neurosciences

CITIZEN PETITION OF J&JPRD REQUESTING ADOPTION OF CERTAIN PARAMETERS TO GOVERN THE REVIEW OF BIOEQUIVALENCE OF PROPOSED FOLLOW-ON VERSIONS OF RISPERDAL® CONSTA®

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CITIZEN PETITION

I. ACTIONS REQUESTED

On behalf of Janssen Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. ("OMJPI"), Johnson & Johnson Pharmaceutical Research & Development, L.L.C. ("J&JPRD") submits this Citizen Petition pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act"), 21 U.S.C. § 355, and FDA's regulations implementing the Act, including agency procedures published at 21 C.F.R. § 10.30 governing the filing of citizen petitions.[1]

This petition requests the Food and Drug Administration ("FDA" or "agency") to require specific bioequivalence parameters to govern the review and approval of any product that is the subject of an abbreviated new drug application ("ANDA") under Section 505(j) of the FDCA, 21 U.S.C. § 355(j), where the reference listed drug is RISPERDAL® CONSTA® (risperidone) Long-Acting Injection ("LAI"). This petition also requests FDA to utilize these bioequivalence parameters in connection with any bioequivalence study that is required of a product that is the subject of an application under Section 505(b)(2) of the FDCA, 21 U.S.C. § 355(b)(2), and for which FDA refers to or otherwise relies on its findings of safety and efficacy for RISPERDAL CONSTA.[2]

As described in more detail below, RISPERDAL CONSTA is a parenteral drug product. In order for FDA to approve an ANDA, it must find that that the generic product contains the same active ingredient as the reference listed drug.[3] Moreover, for drug products intended for parenteral use, the generic formulation must also generally contain the same inactive ingredients in the same concentration as the reference listed drug.[4] To the limited extent that differences in preservatives, buffers and antioxidants are

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[1] J&JPRD is the authorized regulatory agent for OMJPI. OMJPI is the holder of the New Drug Application for RISPERDAL® CONSTA® (risperidone) Long-Acting Injection.

[2] In its draft guidance on applications covered by Section 505(b)(2), FDA indicated that applications for proposed drug products where the rate and/or extent of absorption exceed, or are otherwise different from, the 505(j) standards for bioequivalence compared to a listed drug may be submitted pursuant to Section 505(b)(2). As FDA stated, such a proposed product may require additional clinical studies to document safety and efficacy at the different rate and extent of delivery and a 505(b)(2) application should not be used as a route of approval for generic drug products unable to meet the 505(j) standards for bioequivalence. In that guidance document, FDA further indicated that a 505(b)(2) application should include a bioavailability/bioequivalence study comparing the proposed product to the listed drug. *See* FDA, *Draft Guidance for Industry, Applications Covered by Section 505(b)(2)* (Oct. 1999), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf.

[3] 21 U.S.C. § 355(j)(4)(C).

[4] *See* 21 C.F.R. § 314.94(a)(9)(iii). These requirements for parenteral products were echoed in FDA's response to a citizen petition involving Eloxatin. There, the agency declared: "As a threshold matter, we think it is important to review the requirements for an ANDA for a parenteral drug product. A drug product intended for parenteral use generally must contain both the same active and inactive ingredients in the same concentration as the reference listed drug." *See Citizen Petition Response, Eloxatin*, Docket No. FDA-2006-P-0025 (May 22, 2009).

permitted under this regulation, FDA must ensure that applicants identify and characterize those differences and demonstrate that they do not affect the safety or efficacy of the proposed generic drug product. In the event that a proposed product does not satisfy these requirements, then the applicant would need to seek approval of its product under Section 505(b)(2) of the FDCA and provide additional studies necessary to support the change or modification from RISPERDAL CONSTA in the application. To the extent that a proposed product may be considered for approval under Section 505(j) or 505(b)(2), J&JPRD believes that FDA must utilize the bioequivalence parameters requested in this citizen petition. Accordingly, for the purposes of this petition, a product that is the subject of either an ANDA or 505(b)(2) application involving RISPERDAL CONSTA is hereafter collectively referred to as a "follow-on product."[5]

In February 2010, FDA issued draft guidance containing recommendations for a study to evaluate the bioequivalence of risperidone intramuscular injection products (RISPERDAL CONSTA would be the reference listed drug for such a study).[6] J&JPRD submitted comments on that draft guidance on September 13, 2010. To date, FDA has not issued final guidance. The agency has previously indicated that it is not required to publish draft or final product-specific bioequivalence recommendations before it approves an ANDA for the drug product.[7] In light of the critical importance of this issue to patients, and following additional and more detailed analysis, J&JPRD herewith submits this petition formally requesting FDA to refrain from approving follow-on products unless the agency adopts, at a minimum, the bioequivalence requirements set

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[5] As of the date of this petition, J&JPRD is not aware of any application for 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. OMJPI has not received a paragraph IV certification from any applicant seeking approval of a follow-on version of RISPERDAL CONSTA. As a result, 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* (Jan. 2009), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079353.pdf.

[6] *See* FDA, *Draft Guidance on Risperidone* (Feb. 2010), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201272.pdf.

[7] *See Guidance for Industry, Bioequivalence Recommendations for Specific Products* (June 2010), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072872.pdf. In this guidance, FDA also stated 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. FDA went on to declare that such coordination may involve coordinating the consideration of a pending citizen petition with the development and publication of a product-specific bioequivalence recommendation. J&JPRD believes that FDA should do so in the instant case and that any final bioequivalence guidance on risperidone intramuscular injection products should include the PK parameters requested in this citizen petition.

forth herein.[8] J&JPRD further emphasizes that such requirements should be included in any final bioequivalence guidance document that the agency issues for risperidone intramuscular injection products.

J&JPRD believes that FDA must adopt these requirements in light of the complex pharmacokinetic ("PK") profile of RISPERDAL CONSTA. RISPERDAL CONSTA is characterized by a PK profile with three distinct phases: an initial release phase (<1% of the dose) following injection, a lag phase, and a main release phase (see Section II.B.1). J&JPRD accepts the general applicability of bioequivalence concepts for risperidone LAI follow-on products. However, in the absence of adequate PK measures and studies to ensure bioequivalence of proposed follow-on products, both the safety and efficacy of such products may be substantially compromised.

J&JPRD requests FDA not to approve a follow-on product unless the agency has assured bioequivalence by requiring applicants to conduct, at a minimum, a 2-strength single dose study that, in addition to the traditional bioequivalence metrics of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, utilizes the following PK metrics to evaluate bioequivalence:

(1) *$pAUC_{0-24h}$:* Applicants should measure $pAUC_{0-24h}$ to ensure that the early systemic exposure due to the initial release of risperidone[9] immediately following injection does not exceed that of RISPERDAL CONSTA. This will help to ensure that patients are not exposed to an excessive amount of risperidone shortly after injection that potentially may lead to significant adverse events.

(2) *$pAUC_{0-24d}$:* Applicants should also measure $pAUC_{0-24d}$ to ensure that any follow-on product does not release an excessive amount of drug during the expected lag phase (accelerated main release). This will help to ensure that patients are not exposed to an excessive amount of risperidone that potentially may lead to significant adverse events.

(3) *$pAUC_{24d-t}$:* Applicants should calculate $pAUC_{24d-t}$ to ensure that any follow-on product does not release a substantially lower amount of drug during the expected main release phase (either due to excessive release of risperidone during the initial release or expected lag phases, or due to a delayed main release). This will help to ensure that there is not inadequate

[8] J&JPRD continues to believe that FDA should adopt all of the recommendations outlined in its earlier comments on the draft guidance. It will be especially important, however, for the agency to take the actions requested herein in its review of follow-on products. Indeed, J&JPRD believes that the specific actions outlined in this petition for evaluating bioequivalence of follow-on products are required, at a minimum, to ensure the safety and efficacy of such products under the FDCA and the agency's implementing regulations.

[9] Upon injection of RISPERDAL CONSTA, "unencapsulated" risperidone present on the surface of the microspheres is immediately released. Similarly, dose dumping may occur through different mechanisms for follow-on products where the release of risperidone is driven by a different release mechanism.

release of risperidone and consequent under-treatment, which potentially could lead to patients being put at increased risk of relapse and associated consequences.

J&JPRD believes that if FDA does not adopt these additional bioequivalence requirements, the agency will not be able to ensure that proposed follow-on versions of RISPERDAL CONSTA do not raise potentially significant safety and efficacy issues for patients. Accordingly, J&JPRD respectfully urges FDA to grant this citizen petition.

II. STATEMENT OF GROUNDS

A. BACKGROUND

1. The Importance of RISPERDAL CONSTA in the Treatment of Schizophrenia and Bipolar I Disorder

RISPERDAL CONSTA is an LAI product indicated for the treatment of schizophrenia, and as a monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder.

(a) Schizophrenia and Bipolar Disorder[10]

Schizophrenia and bipolar disorder are chronic, debilitating psychiatric disorders. The clinical courses of these diseases entail frequent symptomatic relapses and hospitalizations that inflict a terrible toll on patients, family members, caregivers, and society.[11] Schizophrenia is characterized by disorganized and bizarre thoughts, delusions, and hallucinations that affect work, interpersonal relations, or self-care.[12] Bipolar disorder, previously referred to as manic-depressive disorder, is a cyclical psychiatric disorder with recurrent fluctuations in mood, energy, and behavior.[13] Patients with this disease experience mood swings, which are often severe in intensity and alternate between mood elevation and depression or their variable admixtures.[14] Bipolar disorder is subdivided into four subtypes: bipolar I, bipolar II, cyclothymic disorder, and

[10] RISPERDAL CONSTA is indicated as a monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder. This section of the citizen petition provides a more general description of bipolar disorder due to the epidemiological information that is available; NIMH statistics are not broken down into bipolar disorder subtypes.

[11] B. Müller-Oerlinghausen, A. Berghöfer, & M. Bauer, *Bipolar Disorder*, 359 Lancet 241 (2002) (Exh. 1); R. Wyatt, *Neuroleptics and the Natural Course of Schizophrenia*, 17 Schizophr. Bull. 325 (1991) (Exh. 2).

[12] Am. Psychiatric Ass'n, *Diagnostic and Statistical Manual of Mental Disorders* 297-344 (4th ed. 2000) [hereinafter "DSM-IV-TR"] (Exh. 3).

[13] Joseph T. Dipiro, *et al.*, *Pharmacotherapy: A Pathophysiologic Approach* 1161 (4th ed. 1999) (Exh. 4).

[14] *Id.* at 1164.

bipolar disorder not otherwise specified.[15] Bipolar I disorder presents as fluctuations between major depressive episodes with manic or mixed episodes.[16]

Schizophrenia affects approximately 2.4 million Americans annually, which represents 1.1% of the adult population in a given year.[17] Bipolar disorder affects approximately 5.7 million Americans annually or almost 2.6% of the adult population in a given year.[18] Although antipsychotic medications often help alleviate the symptoms of patients suffering from schizophrenia and bipolar disorder, one of the major impediments to improvement and remission is patient non-adherence to recommended treatment interventions, particularly pharmacotherapy. Indeed, non-adherence has been shown to be among the most frequent reasons for relapse in both of these disorders.[19] With relapse, there is an exacerbation of symptoms, which often include severely impaired insight, leading to further non-adherence, and a downwardly spiralling course resulting in poor clinical outcome, overall deterioration of psychosocial functioning, high resource utilization, and potential fatalities.[20]

LAI products have been developed to address the problem of non-adherence in this patient population by providing continuous therapeutic concentrations of antipsychotic medication, with a professionally administered delivery mechanism. Current practice guidelines recommend offering an LAI antipsychotic to patients in whom non-adherence has been demonstrated and linked to repeated relapse.[21] With such medications, physicians and other mental health care professionals gain an earlier

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[15] DSM-IV-TR, *supra* n. 12, at 345-428.

[16] *Id.* A major depressive episode is two weeks or more of either depressed mood or loss of interest or pleasure in normal activities and additional symptoms of depression; a manic episode is a week or more of abnormal and persistent elevated mood with additional symptoms of grandiosity; and a mixed episode is a fluctuation between major depressive and manic episodes daily for at least one week. *Id.*

[17] Nat'l Inst. of Mental Health, *The Numbers Count: Mental Disorders in America*, http://tinyurl.com/c7evb6.

[18] *Id.* In 1990 dollars, the total economic impact of schizophrenia in the United States was $38 billion, with a disproportionate amount directed toward relapse and crisis management instead of outpatient focused maintenance efforts. Dipiro, *supra* note 13, at 1135-36. By comparison, in the same year the total costs for anxiety disorders, which are more than ten times more prevalent than schizophrenia, were $46.6 billion. D.P. Rice, *The Economic Impact of Schizophrenia*, 60 J. Clin. Psychiatry 28 (1999) (Exh. 5). The annual costs of bipolar disorder, in 1991 dollars, were estimated at $45.2 billion. L. Kleinman, *et al.*, *Costs of Bipolar Disorder*, 21 Pharmacoeconomics 601 (2003) (Exh. 6).

[19] L. Berk, *et al.*, *Enhancing Medication Adherence in Patients with Bipolar Disorder*, 25 Hum. Psychopharmacol. Clin. Exp. 1 (2010) (Exh. 7); D. Robinson, *et al.*, *Predictors of Relapse Following Response from a First Episode of Schizophrenia or Schizoaffective Disorder*, 56 Arch. Gen. Psychiatry 241 (1999) (Exh. 8).

[20] J. Clatworthy, *et al.*, *Understanding Medication Non-Adherence in Bipolar Disorders Using a Necessity Concerns Framework*, 116 J. Affective Disorders 51 (2008) (Exh. 9).

[21] J.M. Kane & C. Garcia-Ribera, *Clinical Guideline Recommendations for Antipsychotic Long-Acting Injections*, 195 Br. J. Psychiatry S63 (2009) (Exh. 10).

knowledge and awareness of non-adherence through missed injections. 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.[22]

(b) RISPERDAL CONSTA: An Injectable Product Developed to Help Address the Problem of Non-adherence

On October 29, 2003, FDA approved a New Drug Application ("NDA") authorizing OMJPI to market RISPERDAL CONSTA in the United States. The active ingredient in RISPERDAL CONSTA is risperidone, an atypical antipsychotic agent. Risperidone is extensively metabolized in the liver following oral and LAI administration. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone, mainly by the enzyme CYP2D6. A minor metabolic pathway is through N-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity to risperidone. As a result, the clinical effect of the drug results from the combined concentrations of risperidone plus 9-hydroxyrisperidone (*i.e.*, the active antipsychotic fraction or "active moiety"). RISPERDAL CONSTA is available in dosage strengths of 12.5 mg, 25 mg, 37.5 mg, and 50 mg risperidone per vial.[23]

RISPERDAL CONSTA is a complex LAI formulation designed to release risperidone at particular periods of time over the course of several weeks. Specifically, the product consists of extended-release microspheres made up of polylactide co-glycolide ("PLG"). Risperidone is encapsulated within these microspheres at a concentration of 381 mg risperidone per gram of microspheres. These microspheres are suspended in a diluent (which is specifically formulated for reconstituting and administering the microspheres) shortly before injection.[24] Following a single intramuscular injection of RISPERDAL CONSTA, there is a small initial release of unencapsulated drug present on the surface of the microspheres (<1% of the dose), followed by a lag time of three weeks. The main release of the drug starts three weeks after the injection, continues from four to six weeks, and then subsides by seven weeks after injection. The labeling for RISPERDAL CONSTA provides that "[o]ral Risperdal (or another antipsychotic medication) should be given with the first injection of

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[22] J.M. Kane, *et al.*, *Expert Opinion Paper and Literature Review on the Need for an LAI Injectable Formulation of a Second-Generation Antipsychotic for the Treatment of Schizophrenia* (2003) (white paper) (Exh. 11).

[23] RISPERDAL CONSTA is provided as a dose pack, comprising a vial containing the microspheres, a syringe containing the diluent, a SmartSite® Needle-Free Vial Access Device, and 1 Needle-Pro® (2-inch, 20-G safety needle for gluteal administration; or 1-inch, 21-G safety needle for deltoid administration).

[24] The microspheres used in RISPERDAL CONSTA are manufactured by Alkermes, Inc., which developed the product's unique modified release formulation. The diluent is manufactured by Vetter Pharma Fertigung GmBH & Co. KG. or Cilag AG, Schaffhausen, Switzerland or Ortho Biotech Products, L.P., Raritan, NJ.

[RISPERDAL CONSTA], and continued for 3 weeks (and then discontinued) to ensure that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site."[25]

Biweekly intramuscular injections of RISPERDAL CONSTA have been developed to increase adherence and improve clinical outcomes for its intended patient population.[26] As described above, RISPERDAL CONSTA is a complex LAI formulation designed to release risperidone at particular periods of time over the course of several weeks. Healthcare providers administer RISPERDAL CONSTA injections to their patients. These biweekly injections help to alleviate healthcare providers' concerns that patients are non-adherent, thereby allowing physicians to more confidently diagnose symptom exacerbation and make dosing adjustments. Thus, treatment with RISPERDAL CONSTA can be easily monitored and non-adherence readily identified, allowing for rapid intervention prior to clinical deterioration.[27] There is evidence from outcomes studies and modelling that the assured delivery of RISPERDAL CONSTA may lead to improved patient outcomes and reduced healthcare costs.[28]

2. The Statutory and Regulatory Framework Governing Approval of Generic Drug Products

(a) Review and Approval of Generic Drug Products Under Section 505(j) of the FDCA

In connection with its consideration of any application seeking approval of a new drug product, 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. While the 1984 Hatch-Waxman Amendments to the FDCA created an abbreviated approval scheme for generic drug products,[29] they did not override the most fundamental objective

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[25] *See* RISPERDAL CONSTA Prescribing Information (December 2010).

[26] Pierre Chue, *Long-Acting Risperidone Injection: Efficacy, Safety, and Cost-effectiveness of the First Long-Acting Atypical Antipsychotic*, 3 Neuropsychiatric Dis. Treat. 13, 16, 35 (2007) (Exh. 12); Kane & Garcia, *supra* n. 21.

[27] M.K. Rainer, *Risperidone Long-Acting Injection: A Review of Its Long-Term Safety and Efficacy*, 4 Neuropsychiatric Dis. Treat. 919 (2008) (Exh. 13).

[28] Chue, *supra* note 26, at 35; Pierre Chue, *et al.*, *Hospitalization Rates in Patients During Long-term Treatment with Long-Acting Risperidone Injection*, 5 J. Applied Res. 266 (2005) (Exh. 14); L. Beauclair, *et al.*, *Impact of Risperidone Long-Acting Injectable on Hospitalization and Medication Use in Canadian Patients with Schizophrenia*, 10 J. Medical Economics 427 (2007) (Exh. 15); N.C. Edwards, *et al.*, *Cost Effectiveness of Long-Acting Risperidone Injection Versus Alternative Antipsychotic Agents in Patients with Schizophrenia in the USA*, 23 Pharmacoeconomics 75 (suppl. 1 2005) (Exh. 16).

[29] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

of the FDCA. Indeed, that "essential purpose pervades the FDCA."[30] Accordingly, while FDA is authorized to approve follow-on products under Section 505(j) and Section 505(b)(2) of the FDCA, the entry of such products into the marketplace is "subsumed by the overriding necessity of ensuring public access to safe commercial drugs."[31]

Under Section 505(j) of the FDCA, a generic drug applicant need not conduct human clinical trials to demonstrate that its proposed product is safe and effective. Rather, through the filing of an ANDA, the manufacturer may rely on FDA's findings of safety and effectiveness for a previously approved drug product ("reference listed drug" or "RLD"). The ANDA process, therefore, permits generic drug applicants to reference the clinical findings that FDA has already approved for the RLD. To rely on those findings, however, the generic drug manufacturer must demonstrate that its proposed product is both pharmaceutically equivalent and bioequivalent to the RLD. 21 U.S.C. § 355(j)(2)(A)(i)-(v). Indeed, if the proposed follow-on product cannot make this showing (or otherwise qualify for a suitability petition) then there would be no way to ensure that FDA's findings of safety and efficacy for the RLD are applicable to the generic drug product.[32]

Strict compliance with the foregoing requirements is critical because, upon approval of an ANDA, 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").[33] 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."[34] Physicians and pharmacists consider the "A" rating to mean that a generic drug is fully substitutable for

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[30] *See FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000). *See also 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.")

[31] 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 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 follow-on drug." *Schering Corp. v. Food and Drug Admin.*, 51 F.3d 390, 396 (3d Cir. 1995).

[32] A 505(b)(2) application shares certain features of both an ANDA and a full New Drug Application. FDA has indicated that such an application is similar to an ANDA because it may rely, in part, on FDA's finding that the listed drug it references is safe and effective as evidence in support of the proposed product's own safety and effectiveness. The agency has further indicated that, depending on the nature of a 505(b)(2) application, a demonstration of bioequivalence to the referenced drug may be needed. *See Citizen Petition Response Regarding Carvedilol Phosphate*, at 3, Docket No. FDA-2010-P-0216 (Oct. 15, 2010).

[33] *See* FDA, *Approved Drug Products with Therapeutic Equivalence Evaluations* (30th ed. 2010), *available at* http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[34] FDA, *Approved Drug Products with Therapeutic Equivalence Evaluations*, at vii (29th ed. 2009).

the RLD. 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.[35]

(b) FDA's General Approach to Evaluating Bioequivalence of Systemically Absorbed Drug Products

Before FDA may approve an ANDA and assign an A rating to the proposed generic product, the agency must determine, among other things, that the product is bioequivalent to the RLD. Under the FDCA, a generic drug is considered bioequivalent to the listed drug if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent 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."[36] In its regulations implementing these statutory provisions, FDA directs all ANDA applicants to "conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available" among certain methodologies set forth in the regulations.[37]

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.[38] 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 the maximum concentration ("C_{max}") and the area under the curve ("AUC"), both from dosing until the last measured time point ("AUC_{0-t}") and extrapolated to infinity ("$AUC_{0-\infty}$"). C_{max} is believed to reflect the rate of

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[35] One review found that thirty-one states, along with the District of Columbia, require reference to the *Orange Book* for the selection of generic drugs that may be legally substituted for brand-name products. Those states are Alabama, Arizona, Arkansas, Delaware, Hawaii, Idaho, Illinois, Indiana, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Mississippi, Missouri, Nevada, New Hampshire, New Jersey, New Mexico, New York, Pennsylvania, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Wisconsin, Wyoming, and West Virginia. *See Summary of State Regulations on Generic Substitution* (April 2009), *available at* http://pharmacistsletter.therapeuticresearch.com/pl/ArticleDD.aspx?nidchk=1&cs=&s=PL&pt=2&fpt=31&dd=220901&pb=PL&cat=2986&segment=1186&AspxAutoDetectCookieSupport=1.

[36] *See* 21 U.S.C. § 355(j)(8)(B)(i). The FDA has indicated that two drug products will be considered bioequivalent if they "display comparable bioavailability when studied under similar experimental conditions." FDA, *supra* n. 33. Bioavailability is, in turn, defined as "the rate and extent to which the active drug ingredient or therapeutic ingredient is absorbed from a drug product and becomes available at the site of the drug action." 21 U.S.C. § 355(j)(8)(A).

[37] 21 C.F.R. § 320.24(a).

[38] 21 C.F.R. § 320.24(b)(1)(i).

the drug's absorption into the systemic circulation, while AUC_{0-t} and $AUC_{0-\infty}$ are believed to reflect the extent of the drug's absorption.[39]

B. C_{max}, AUC_{0-t}, AND $AUC_{0-\infty}$ WILL NOT CAPTURE ALL POTENTIALLY SIGNIFICANT DIFFERENCES IN THE PK PROFILES OF FOLLOW-ON PRODUCTS

1. RISPERDAL CONSTA is Characterized by a Complex PK Profile

As stated in its labeling and presented below in Figure 1, RISPERDAL CONSTA is characterized by a complex PK profile that is broken down into three phases: an initial release phase, a lag phase, and a main release phase.[40] Specifically, in the initial release phase, a small amount of risperidone, which is present on the surface of the formulation's microspheres, is immediately absorbed into systemic circulation upon injection of the product. The labeling for RISPERDAL CONSTA declares that "there is a small initial release of the drug (<1% of the dose)" following injection. Next, there is a lag phase that lasts for three weeks in which a minimal amount of risperidone is released. To ensure that patients maintain adequate antipsychotic coverage during this period, the labeling for RISPERDAL CONSTA directs that patients should receive oral antipsychotic supplementation for the first three weeks of treatment following the initial injection.

Following the initial release and lag phases, there is a main release phase in which the microspheres in the formulation degrade and allow the encapsulated risperidone to be absorbed into systemic circulation. The rate and extent to which the microspheres erode during this phase are critically important because they are closely linked to the cessation of oral antipsychotic supplementation. As provided in the labeling for RISPERDAL CONSTA, the main release phase of the drug begins at three weeks, is maintained from weeks four to six, and then subsides relatively rapidly by seven weeks following injection, with an apparent half-life of three to six days. The label provides that "[t]he combination of the release profile and the dosage regimen . . . results in sustained . . . [s]teady-state plasma concentrations . . . after 4 injections [or 8 weeks] and are maintained for 4 to 6 weeks after the last injection."[41]

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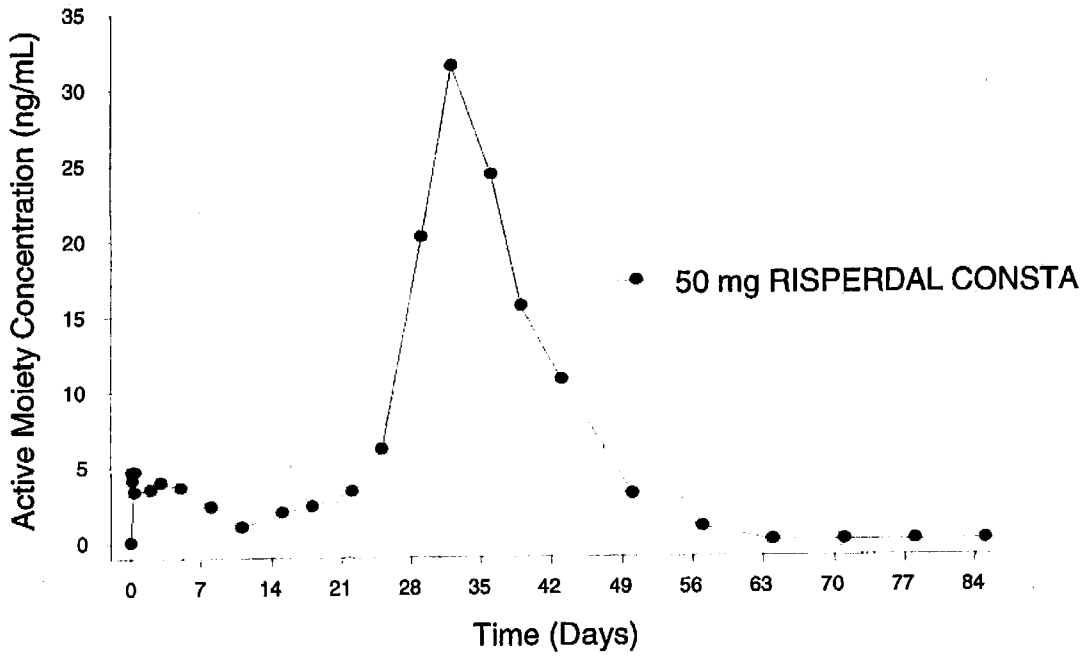
[39] *See* 21 C.F.R. § 320.26(c); FDA, *Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (Mar. 2003), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf.

[40] RISPERDAL CONSTA Prescribing Information, *supra* n. 25.

[41] *Id.*

Figure 1: The PK Profile for RISPERDAL CONSTA[42]



2. Differences in Manufacturing Processes May Yield Different PK Profiles for Follow-On Products

The PK profile for RISPERDAL CONSTA is a function of a complex interplay between the active drug substance, formulation, excipients (including those of the diluent), solvents used in the microspheres manufacturing process, and injection site. Follow-on products with a different manufacturing process could result in significantly altered exposure during the period of the initial and/or expected lag phases and consecutive main release phase. Moreover, if proposed follow-on products use different solvents and excipients (or excipients with a different impurity profile), these may have the potential to cause an injection site reaction, resulting in a significantly increased initial release (dose dumping) or potentially leading to a sharp drop in local pH that could result in greater uptake of water by the microspheres, an accelerated hydrolysis, and acceleration of the main release of encapsulated drug during the expected 3-week lag

[42] E. Mannaert, *et al.*, *Pharmacokinetic Profile of Long-Acting Injectable Risperidone at Steady State: Comparison with Oral Administration*, 31 L'Encephale 609 (2005) (Exh. 17). This figure presents median active moiety (risperidone + 9-hydroxyrisperidone) concentration observed after administration of 50 mg RISPERDAL CONSTA.

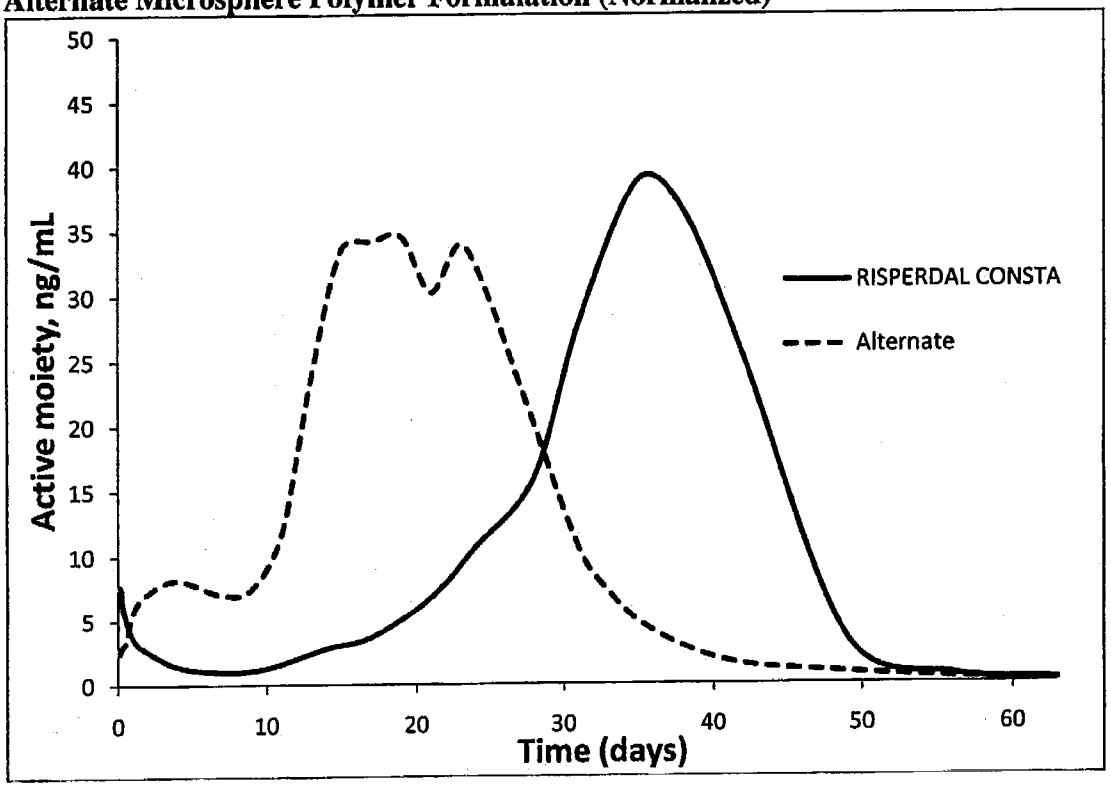
time period.[43] As a result, potential variables in follow-on products, such as polymer composition, excipients, impurity profile, (residual) solvents, and actual concentration of active drug substance in the polymer, may affect the release phases and, thus, yield a plasma time-concentration profile different from RISPERDAL CONSTA.

For example, as depicted in Figure 2, follow-on products that utilize a slightly different polymer formulation for the microspheres may have a substantially different PK profile.[44] In this example, the "alternate polymer" consists of a blend of 6535 and 7525 high inherent viscosity (IV) PLG copolymers rather than the single 7525 PLG, which is used in RISPERDAL CONSTA. The numbers 6535 and 7525 refer to the mole ratio of lactide:glycolide in the polymer. This formulation was made using the same manufacturing process as RISPERDAL CONSTA at the same 20 kg commercial scale. Each of these polymers was evaluated in individuals by injection of a single dose of 75 mg risperidone. Median single dose PK profiles for the active moiety (risperidone + 9-hydroxyrisperidone) are presented in Figure 2 for both formulations. Because of the small sample size in both studies, the average clearance was different for the comparison groups resulting in differences in AUC. However, by correcting for the difference in clearance, this confounding factor was eliminated. As shown in Figure 2, a small change in the polymer composition may result in a vastly different PK profile between the two products but comparable C_{max} and AUC_t, within the bioequivalence acceptance criteria.

[43] An increased proportion of patients may encounter increased release immediately upon injection of drug, for example, due to excipient or solvent-mediated inflammatory reactions, as observed in pilot formulations of long-acting injectable risperidone. *See* CDER, *Clinical Pharmacology and Biopharmaceutics Reviews, available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21346_Risperdal%20Consta%20Long-Acting%20Injection_biopharmr.PDF.

[44] Products with a polymer formulation or excipients different from those of RISPERDAL CONSTA would not be eligible for an ANDA under 21 C.F.R. § 314.94(a)(9)(iii). Nevertheless, this example is useful as an illustration of how sensitive the PK profile of RISPERDAL CONSTA is to its microsphere-based formulation and why additional PK metrics are necessary for any bioequivalence study under Section 505(b)(2) of the FDCA.

Figure 2: The PK Profile of a RISPERDAL CONSTA Product Compared with an Alternate Microsphere Polymer Formulation (Normalized)[45]



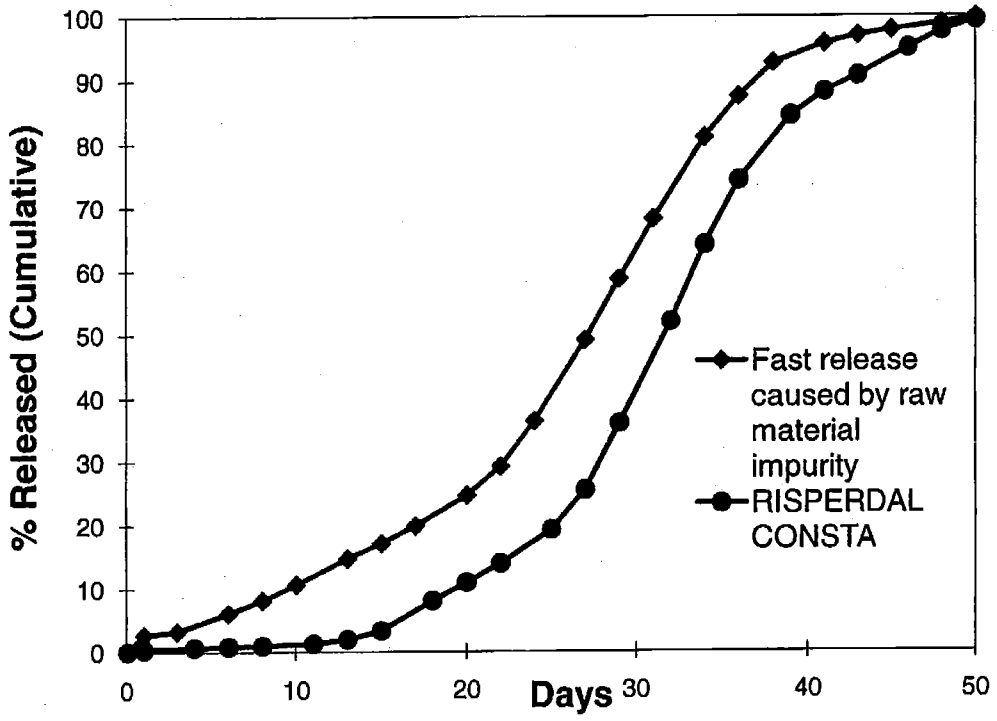
J&JPRD's experience with altering the quality and quantity of the constituents of the pilot formulations of RISPERDAL CONSTA led to a demonstrable variation in systemic exposure that was highly sensitive to the quality and quantity of each solvent used in the manufacturing of the product, and to the quality and quantity of residual solvents and excipients (including the impurity profile) in the finished products. This sensitivity can result in an increased initial release exposure or as an accelerated main release following a shorter lag time.

Early studies with pilot formulations of LAI risperidone show that small changes in amounts of residual solvents or excipients can cause a significant increase in early

[45] Figure 2 presents median active moiety (risperidone + 9-hydroxyrisperidone) concentrations observed after administration of 75 mg RISPERDAL CONSTA versus normalized median active moiety concentrations after 75 mg of the formulation using the alternate polymer. PK profiles were obtained in 2 separate small-scale studies (n=14 and 20 for RISPERDAL CONSTA and alternate formulation, respectively). Small differences in total exposure observed, despite the identical 75-mg dose, are likely to be due to the nature of a cross-study comparison, the small sample sizes, and the high inter-subject variability in PK. To correct for the difference in clearance between the 2 groups (4.51 L/h and 5.35 L/h for RISPERDAL CONSTA and alternate formulation, respectively), PK profiles were normalized to the same clearance by dividing the median active moiety concentrations of the alternate formulation by the clearance ratio (0.84=4.51/5.35).

release of drug.[46] The sensitivity to minor differences in the excipients is additionally illustrated in Figure 3 below. Here, the *in vitro*[47] release profile of RISPERDAL CONSTA is compared with a formulation from a batch in which benzyl alcohol was found to have degraded and contained measurable levels of impurities, particularly benzaldehyde. As can be seen, the impurities from this solvent were responsible for a shift in the profile yielding a higher initial release, no apparent lag phase and an accelerated main release.

Figure 3: *In Vitro* Release Profile Comparison of RISPERDAL CONSTA with a Formulation with Impurities[48]



Still other differences in the manufacturing process may have an impact on the release profile of follow-on products. In one batch produced at the small 125 g clinical manufacturing scale, an alternative drying process was utilized at one phase of the manufacturing process. Specifically, a cold drying step was shortened by six-fold; no other changes were made in the manufacturing process. As can be seen from Figure 4

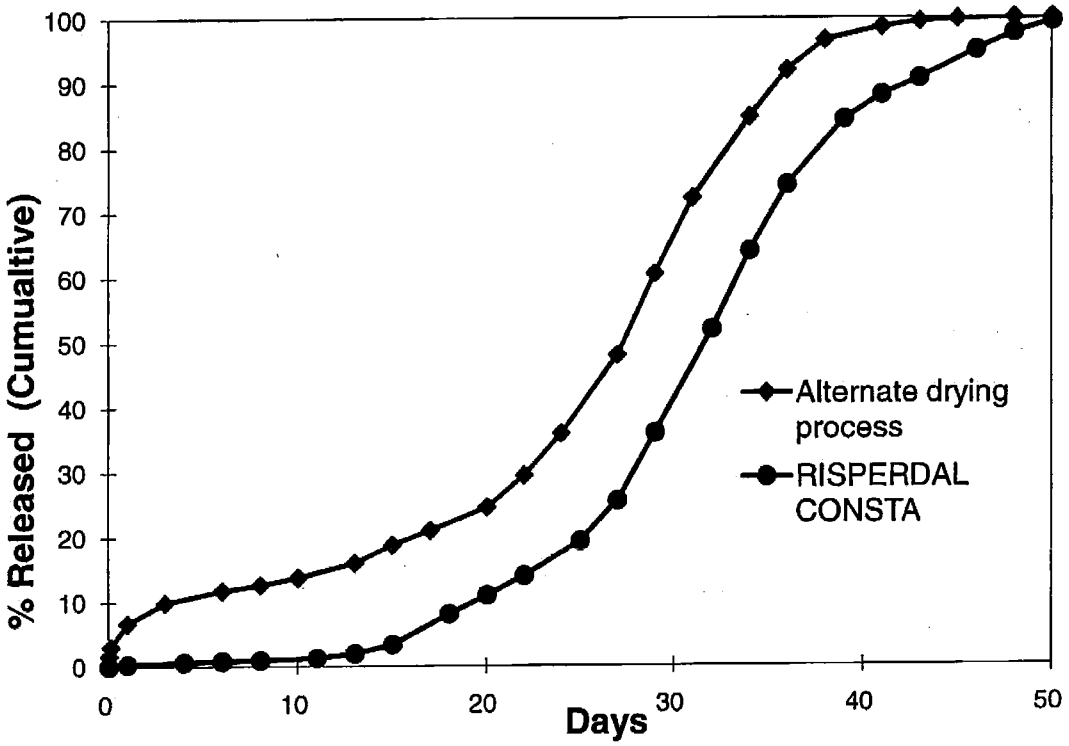
[46] FDA, *Drug Approval Package, Risperdal Consta Long-Acting Injection* (June 2005), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21346_RisperdalTOC.cfm.

[47] The *in vitro* dissolution method was correlated with human PK. The Day 1 and Day 15 *in vitro* values were shown to be predictive of the initial release, lag phase, and main release phase in humans.

[48] Data from a 20 kg scale batch made during Phase 3 development. This batch of microspheres was never tested in humans.

below, this slight change in the manufacturing process resulted in an *in vitro*[49] release profile characterized by a higher initial release, and an increased release during the expected lag phase (accelerated main release), compared with batches manufactured from the standard manufacturing process.

Figure 4: *In Vitro* Release Profile Comparison of RISPERDAL CONSTA Following a Manufacturing Change[50]



These two examples demonstrate that minor differences in the manufacturing process can dramatically alter the three distinct release phases by increasing the initial release rate, reducing the lag phase, and/or accelerating the main release phase, the last resulting in a shift in the main release phase which may not be detectable as a change in C_{max} or AUC_{0-t} and $AUC_{0-\infty}$ alone, as discussed in the next section.

[49] The *in vitro* dissolution method was correlated with human PK. The Day 1 and Day 15 *in vitro* values were shown to be predictive of the initial release, lag phase, and main release phase in humans.

[50] Data from an intramuscular (gluteal) injection of 50 mg risperidone in microspheres from a 125-g production process (no. 147-1197). This batch was subsequently used in clinical study RIS-INT-54 (Treatment E).

3. C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ Will Not Detect All Potentially Significant Differences in the PK Profiles of Follow-On Products

As mentioned earlier, FDA issued draft guidance in February 2010 outlining specific recommendations for measuring bioequivalence of risperidone intramuscular injection products. That draft called for a single-dose, two-way crossover *in vivo* fasting study evaluating the bioequivalence of a follow-on risperidone intramuscular formulation at the 25 mg/vial strength. FDA indicated that it would waive *in vivo* testing for other strengths (12.5 mg/vial, 37.5 mg/vial and 50 mg/vial) based on an acceptable bioequivalence study on the 25 mg/vial strength, proportional similarity of the formulations across all strengths, and acceptable *in vitro* dissolution testing of all strengths. In this context, FDA did not specify a set of PK parameters that applicants should use in evaluating the PK profile of proposed follow-on products. As a result, it appears that the agency is prepared to accept bioequivalence determinations for follow-on versions of RISPERDAL CONSTA based solely on the traditional metrics of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.[51]

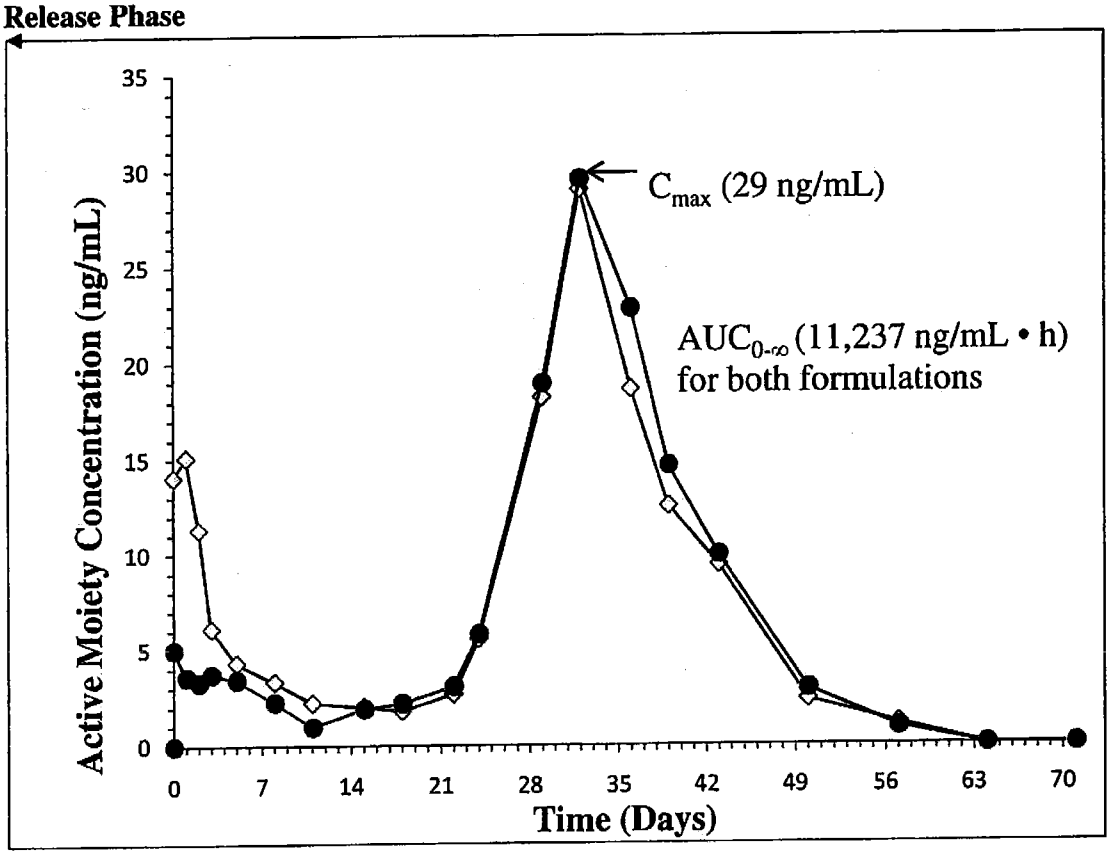
However, reliance solely on C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ to evaluate the bioequivalence of follow-on products for RISPERDAL CONSTA, with its complex LAI formulation designed to release risperidone at particular periods of time over the course of several weeks, will not detect potentially significant and clinically meaningful differences in such products. This problem is illustrated by Figures 5 and 6, which compare the PK profile of RISPERDAL CONSTA with PK profiles of possible follow-on products whose release profiles may differ slightly because of a different diluent, polymer composition, or a manufacturing change.[52]

[51] 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, *Draft Guidance on Zolpidem* (Aug. 2009), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM175029.pdf.

[52] Although the examples of possible follow-on products in Figures 5 and 6 are based on hypothetical data, these are realistic scenarios, given the experience of J&JPRD whereby altering the quality and quantity of the constituents of the pilot formulations of RISPERDAL CONSTA led to a demonstrable variation in systemic exposure that was highly sensitive to the quality and quantity of each solvent used in the manufacturing of the product, and to the quality and quantity of residual solvents and excipients (including the impurity profile) in the finished products (see Section II.B.2).

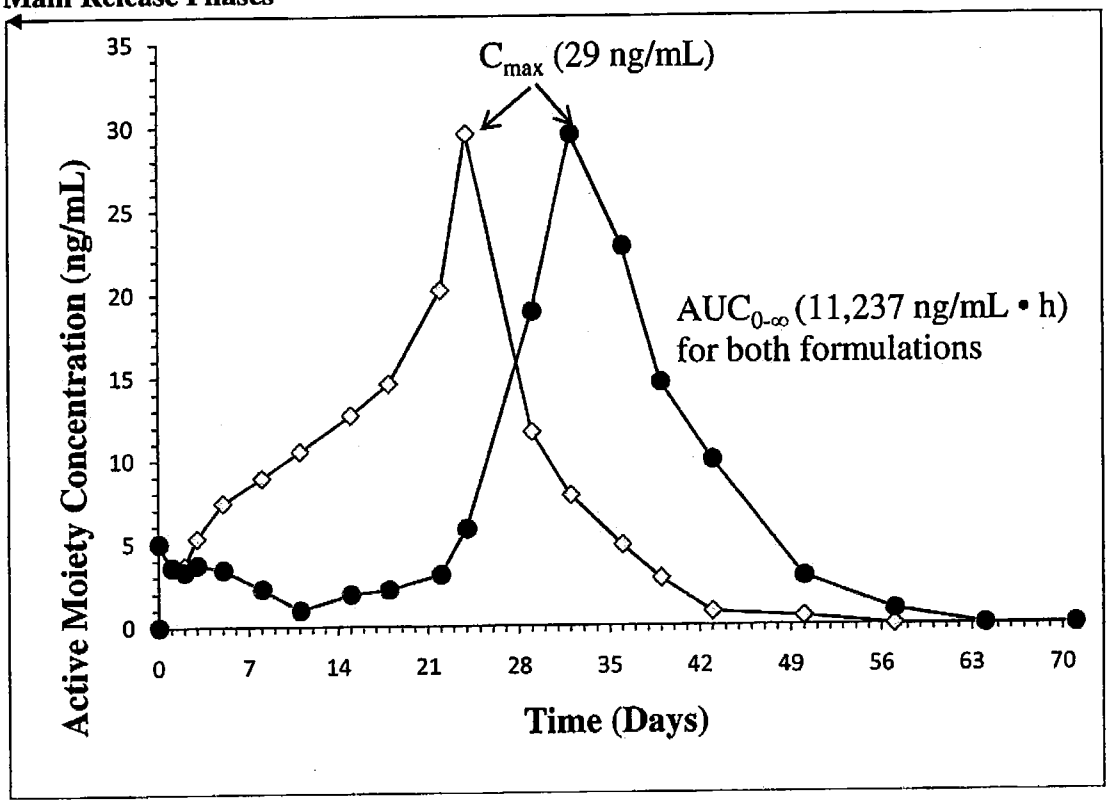
As demonstrated in Figure 5, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ are the same even though, at the initial release phase, the concentration of risperidone released from the possible follow-on product is three times that of RISPERDAL CONSTA.

Figure 5: C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ Do Not Capture Differences in the Initial Release Phase



In Figure 6, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ are also the same but the possible follow-on product releases excessive amounts of risperidone during the expected lag phase (accelerated main release) and, correspondingly, inadequate concentrations during the expected main release phase.

Figure 6: C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ Do Not Capture Differences in the Lag and Main Release Phases



Figures 5 and 6 show that demonstration of bioequivalence only in terms of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ does not guarantee that both drug products will be equivalent.

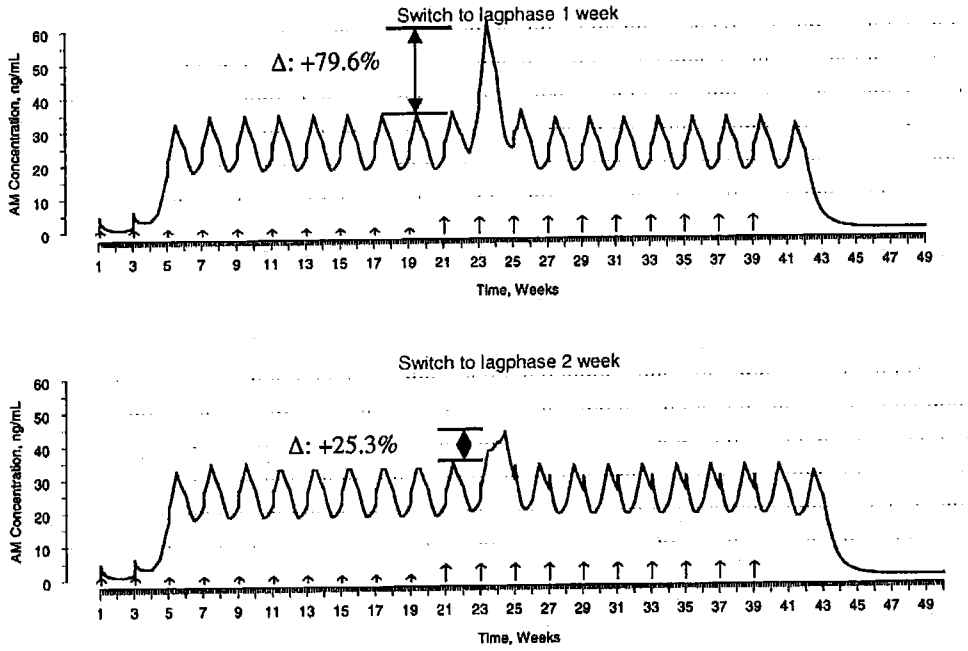
4. Differences in the PK Profiles of Follow-On Products May be Pronounced in a Switching Context

The inability of C_{max} and AUC to capture potential differences in the PK profiles of follow-on products becomes especially problematic when such products are switched for RISPERDAL CONSTA. Upon treatment initiation with a follow-on product that releases too much drug substance during the initial release phase, patients may be exposed to an excessive amount of risperidone that may lead to significant adverse events, both for patients who are starting risperidone LAI and therefore receiving oral risperidone supplementation, and for patients with steady state drug exposure who are switching from RISPERDAL CONSTA to the follow-on product. Similarly, a follow-on product that releases risperidone too early (accelerated main release after a shortened lag

phase) may expose patients to an excessive amount of risperidone, either when starting risperidone LAI and therefore receiving oral risperidone supplementation, or upon switching from RISPERDAL CONSTA to the follow-on product.

As an example, Figure 7 below presents the median plasma active moiety concentrations for a scenario in which patients are exposed to repeated (n=10) administrations of 50 mg RISPERDAL CONSTA prior to being switched to a sequence of ten biweekly injections of 50 mg of a follow-on product with an accelerated main release phase. The top graph presents a switching scenario from RISPERDAL CONSTA to a follow-on product with a one-week lag time. The bottom graph presents a switching scenario from RISPERDAL CONSTA to a follow-on product with a two-week lag time.

Figure 7: Switching to a Follow-on Product with Shorter Lag Phases (Accelerated Main Release)[53]



From Figure 7 it can be concluded that patients would be exposed to significantly higher (*i.e.*, out of the bioequivalence acceptance criteria of [–20% to +25%]) active moiety steady-state peak concentrations ($C_{max,ss}$) upon switching to a follow-on product with accelerated main release. It must be re-emphasized that the simulations are based on the same single dose PK profile (same C_{max}, same AUC_{0-t} and $AUC_{0-\infty}$, different lag phase) for RISPERDAL CONSTA and the follow-on product. The simulation shows that

[53] PK profiles were calculated by non-parametric superposition of the single dose PK data obtained for 50 mg RISPERDAL CONSTA in RIS-INT-54 (treatment B). For the alternate formulation, the same data were used after shortening the lag period.

bioequivalence in terms of single-dose C_{max} and AUC alone does not guarantee equivalence in terms of peak exposure upon switching to a follow-on product unless the two products have a similar lag phase.

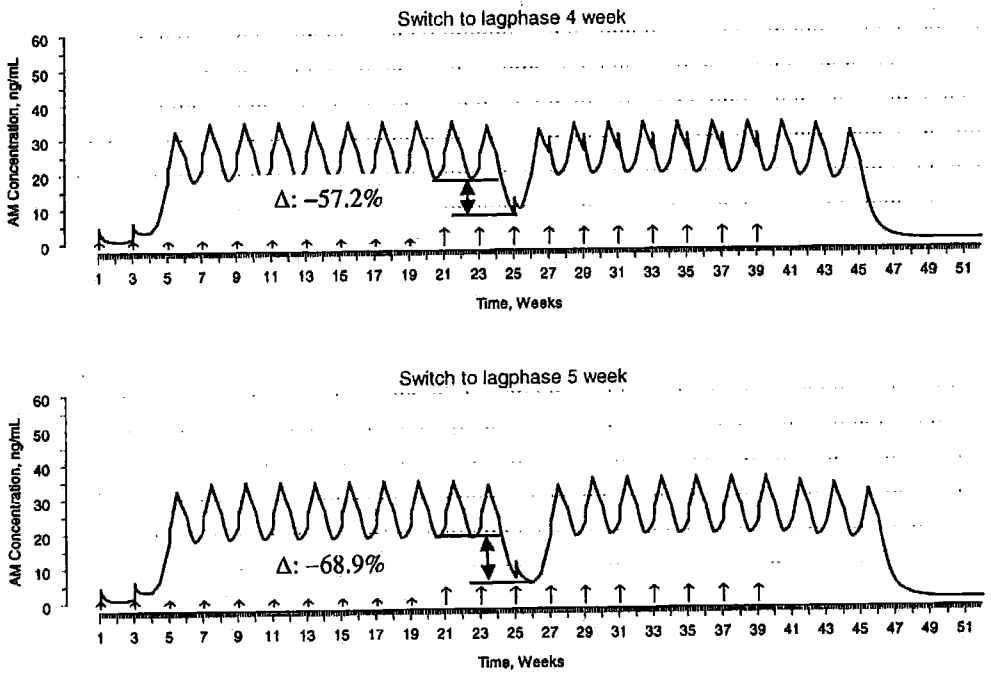
If an increased amount of risperidone is released from a follow-on product due to excessive initial release or accelerated main release, less drug will be available for absorption during the expected main release phase. This scenario is applicable both to patients starting their treatment with LAI risperidone (at the time when the three-week oral antipsychotic supplementation period has ended in accordance with the label), and to patients with steady state drug exposure who switch from RISPERDAL CONSTA to a follow-on product.

Moreover, even if a follow-on product does not release excessive amounts of risperidone during the initial release and lag phases, a longer lag time than RISPERDAL CONSTA (delayed main release) would result in an insufficient release of risperidone during the expected main release phase.[54]

As an example, Figure 8 presents the median plasma active moiety concentrations for a scenario in which patients are exposed to repeated (n=10) administrations of 50 mg RISPERDAL CONSTA prior to being switched to a sequence of ten biweekly injections of 50 mg of a follow-on product with a delayed main release phase. The top graph presents a switching scenario from RISPERDAL CONSTA to a follow-on product with a four-week lag time. The bottom graph presents a switching scenario from RISPERDAL CONSTA to a follow-on product with a five-week lag time.

[54] Similarly, when switching from a follow-on product with longer lag time to RISPERDAL CONSTA, increased $C_{max,ss}$ would be observed, potentially resulting in a higher incidence of the adverse events described herein.

Figure 8: Switching to a Follow-On Product with Longer Lag Phases[55]



From Figure 8 it can be concluded that patients would be exposed to significantly lower (*i.e.*, out of the bioequivalence acceptance criteria of [–20% to +25%]) active moiety steady-state trough concentrations ($C_{min,ss}$) upon switching to a follow-on product with a delayed main release. It must be re-emphasized that the simulations are based on the same single dose PK profile (same C_{max}, same AUC_{0-t} and $AUC_{0-\infty}$, different lag phase) for RISPERDAL CONSTA and the follow-on product. As before, this simulation also shows that bioequivalence in terms of single-dose C_{max} and AUC alone does not guarantee equivalence in terms of minimal exposure upon switching to a follow-on product unless the two products have a similar lag phase.

From the simulations above, it is clear that differences in a lag time of one week (compared with a three-week lag time of RISPERDAL CONSTA) can potentially result in significantly different active moiety steady-state trough or peak concentrations upon switching. In a scenario in which multiple follow-on products would be approved based on equivalence solely on C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, even smaller differences in lag time could become clinically relevant when switching between different products (*e.g.*, follow-on A with a 2½-week lag time and follow-on B with a 3½-week lag time) will be possible, potentially exacerbating the safety and efficacy concerns described herein.

[55] PK profiles were calculated by non-parametric superposition of the single dose PK data obtained for 50 mg RISPERDAL CONSTA in RIS-INT-54 (treatment B). For the alternate formulation, the same data were used after prolonging the lag period.

C. FOLLOW-ON PRODUCTS WITH DIFFERENT PK PROFILES MAY PRESENT SIGNIFICANT SAFETY AND EFFICACY ISSUES

Subtle differences in the plasma time-concentration profiles of follow-on versions of RISPERDAL CONSTA may have adverse impacts for patients. This section describes the potential clinical issues associated with excessive initial release or accelerated main release (see Section II.C.1) or delayed main release (see Section II.C.2) of risperidone from the follow-on product. Given that a generic product would be regarded as "therapeutically equivalent" (see Section II.A.2(a)), RISPERDAL CONSTA and the product could be used interchangeably. Therefore, there may be a repeated risk if there were significantly increased plasma drug concentrations prior to the expected main release phase, with the potential for both acute adverse events and tolerability issues, or a repeated risk of periods without adequate antipsychotic coverage, with the potential for relapse.

1. Potential Clinical Issues Associated With Excessive Initial Release or Accelerated Main Release of Risperidone From a Proposed Follow-on Product

The excessive initial release or accelerated main release of risperidone from a proposed follow-on product that is different from RISPERDAL CONSTA could have adverse effects when patients are starting risperidone LAI treatment and therefore receiving oral antipsychotic supplementation, or when patients are switched from RISPERDAL CONSTA to the follow-on version. The most clinically important of these adverse effects, potentially related to a sudden increase in systemic exposure, may include extrapyramidal symptoms ("EPS"), hypotension, sedation and somnolence, and QTc interval prolongation.

EPS: 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.[56] These symptoms may occur acutely in response to higher plasma drug concentrations.[57] While it is difficult to predict the occurrence of EPS symptoms for any individual patient, on a population level, D2

[56] S. Keith, *Advances in Psychotropic Formulations*, 30 Prog. Neuropsychopharmacol. Biol. Psychiatry 996 (2006) (Exh. 18).

[57] D.E. Tenback, P.N. van Harten, C.J. Slooff, J. van Os, & SOHO Study Group, *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 (2006) (Exh. 19); G. Remington, *Tardive Dyskinesia: Eliminated, Forgotten, or Overshadowed?*, 29 Curr. Opin. Psychiatry 131 (2007) (Exh. 20).

receptor occupancy levels >80% have been associated with higher rates of EPS.[58] Studies have shown that EPS symptoms have a steep concentration-response profile for risperidone. The EC50 in plasma is approximately 32 ng/mL for the active moiety (sum of risperidone and active metabolite); therefore, the risk of developing EPS increases significantly as the concentration of risperidone in plasma increases.[59]

Other published studies have reached the same conclusion. In comparison with daily immediate-release oral therapy, LAI risperidone reduces peak blood drug concentrations and decreases plasma drug peak-to-trough ratios. It is believed that these release characteristics help to maintain optimal dopamine receptor occupancy, thereby reducing associated side effects.[60] Dose-related increase in the incidence of EPS-related adverse events has been observed with up to 75 mg of LAI risperidone over a 12-week double-blind period.[61] Therefore, excessive initial release or accelerated main 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.

Orthostatic Hypotension: RISPERDAL CONSTA may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope (syncope was reported in 0.8% [12/1499 subjects] in patients treated with RISPERDAL CONSTA in multiple dose studies), especially during the initial dose-titration period with oral risperidone, probably reflecting its alpha-adrenergic antagonistic properties. It is recommended that RISPERDAL CONSTA should be used with caution in patients with known cardiovascular disease (*e.g.*, heart failure, history of MI or ischemia, conduction abnormalities), cerebrovascular disease or conditions that would predispose patients to hypotension (*e.g.*, dehydration, hypovolemia) and, additionally, elderly patients and those with renal or hepatic impairment. Monitoring should be considered in patients for whom this may be of concern.[62] If managed with careful dose adjustment, patients can become

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[58] L. 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 (1992) (Exh. 21); S. Nyberg, B. Eriksson, G. Oxenstierna, C. Halldin, & L. Farde, *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 (1999) (Exh. 22); S. Kapur, R. Zipursky, C. Jones, G. Remington, & S. Houle, *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 (2000) (Exh. 23); G. Remington, *et al.*, *A PET Study Evaluating Dopamine D_2 Receptor Occupancy for Long-Acting Injectable Risperidone*, 163 Am. J. Psychiatry 396 (2006) (Exh. 24).

[59] F. De Ridder, A. Vermeulen, A. Cleton, M. Kramer, & M. Eerdekens, *Evaluation of the Clinical Relevance of 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 2007) (Exh. 25).

[60] R. Yoshimura, *et al.*, *Fluctuating Plasma Levels of the Active Moiety of Risperidone is Related to Occurrence of Extrapyramidal Symptoms*, 13 Int. J. Psychiatry Clin. Practice 21 (2009) (Exh. 26).

[61] Kane, *et al.*, *supra* note 22.

[62] RISPERDAL CONSTA Prescribing Information, *supra* n. 25.

partially or fully tolerant to this adverse effect.[63] Excessive initial release or accelerated main release of risperidone leading to sudden increases in plasma drug concentrations could potentially increase the risk of orthostatic hypotension and the complications associated with these events. The labeling for RISPERDAL CONSTA recognizes the dose-dependent risk of orthostatic hypotension in patients on risperidone, and notes that "clinically significant" hypotension has been seen in patients taking risperidone concomitantly with other drugs.

Sedation and Somnolence: Risperidone has a high affinity for α1 adrenoceptors, which may partially regulate somnolence and sedation.[64] Sedation and somnolence, which are often observed early in the course of antipsychotic treatment and tend to be dose related, can lead to a potential for cognitive and motor impairment, falls (with resultant injuries), sleep cycle disruption, and inability to participate in normal activities, including impairments in work, study, or social functioning.[65] This problem is of particular concern in elderly patients who are more prone to adverse consequences from falls, such as bone fractures, injuries, functional decline, dependency, and death.[66] The incidence of somnolence with LAI risperidone over a 12-week double-blind period was similar for the 25 mg (5%) and 50 mg (6%) dose groups, but further increased in the 75 mg dose group (10%) versus placebo (3%).[67] Accordingly, excessive initial release or accelerated main release leading to sudden increases in plasma drug concentrations could potentially increase the risk of sedation or somnolence and the complications associated with these events.

QTc Prolongation: QTc prolongation has been identified as a potential safety concern with several atypical antipsychotics,[68] and it has been observed in overdoses of

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[63] P.M. Haddad & S.G. Sharma, *Adverse Effects of Atypical Antipsychotics: Differential Risk and Clinical Implications*, 21 CNS Drugs 911 (2007) (Exh. 27).

[64] M.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 (2007) (Exh. 28).

[65] J. Muench & A.M. Hamer, *Adverse Effects of Antipsychotic Medications*, 81 Am. Fam. Physician 617 (2010) (Exh. 29); Haddad &Sharma, *supra* note 63; J.M. Kane, *et al.*, *Long-Acting Injectable Risperidone: Efficacy and Safety of the First Long-acting Atypical Antipsychotic*, 160 Am. J. Psychiatry 1125 (2003) (Exh. 30).

[66] S.M. Maixner, A.M. Mellow, & R. Tandon, *The Efficacy, Safety, and Tolerability of Antipsychotics in the Elderly*, 60 J. Clin. Psychiatry 29 (suppl. 8 1999) (Exh. 31).

[67] Kane, *et al.*, *supra* note 65.

[68] 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. *See* FDA, *Guidance for Industry, E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Aniarrhythmic Drugs* (Oct. 2005), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129357.pdf.

both oral risperidone and 9-hydroxyrisperidone. One case study of risperidone overdose describes correlation of serum drug concentration with QTc prolongation, which resolved as exposure to the drug fell.[69] This risk factor 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 AV block, congestive heart failure, polymorphic ventricular tachycardia and congenital prolongation of the QT interval), clinically relevant hypocalcaemia, hypokalaemia, or hypomagnesaemia, or concomitant use of other medications that prolong the QTc interval (particularly Class I or Class III antiarrhythmics).[70] Excessive initial release or accelerated main 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.

2. Potential Clinical Issues Associated with Inadequate Amounts of Risperidone at the Expected Main Release Phase

Treatment of patients with insufficient amounts of risperidone during the critical expected main release phase could cause decreased efficacy and clinically significant relapse for patients suffering from schizophrenia or bipolar I disorder. Exploratory analysis of data from a randomized, double-blind, withdrawal-of-treatment study designed to evaluate the efficacy of flexibly dosed ER OROS paliperidone in the prevention of the recurrence of the symptoms of schizophrenia[71] suggests that even short periods of treatment interruption can lead to an increase in the number of patients who relapse. Study subjects who met the protocol-specified eligibility criteria with regard to symptom control on a stable dosage regimen of ER OROS paliperidone were eligible for entry into the double-blind phase. Subjects who entered the double-blind phase were randomly assigned, in a 1:1 ratio, to receive flexibly dosed ER OROS paliperidone (3 to 15 mg/day, starting at the dose maintained during stabilization) or placebo. Following one week of treatment in the double-blind phase, recurrence (as defined per protocol) 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 due to switching to a follow-on product with a four-week or five-week lag phase, respectively (see Figure 8).

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[69] P.T. Pollack, A.W. Lyon, & Z.H. Verjee, *Risperidone Induced QT Prolongation Following Overdose Correlates with Serum Drug Concentration and Resolves Rapidly with No Evidence of Altered Pharmacokinetics*, 7 Clin. Pharm. Ther. PII-6 (suppl. 1 2010) (Exh. 32).

[70] D.M. Gardner, R.J. Baldessarini, & P. Waraich, *Modern Antipsychotic Drugs: A Critical Overview*, 172 CMAJ 1703 (2005) (Exh. 33).

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

This situation is also 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 one to ten days were associated with increased risk of hospitalization (odds ratio = 1.98); the risk of hospitalization increased further with increasing medication coverage gap.[72]

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, as described for schizophrenia and bipolar I disorder, below. We acknowledge that not all patients will relapse due to short interruptions in treatment, even if these interruptions recur due to RISPERDAL CONSTA and a follow-on product being used interchangeably. However, for those patients who are susceptible and who are being prescribed risperidone LAI therapy because non-adherence has been demonstrated and linked to repeated relapse, the consequences of further relapse may be severe.

Schizophrenia: 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 can impair social and vocational functioning to a significant degree, lead to increased caregiver burden, as well as an increased risk of suicidal and violent behaviors.[73]

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.[74] With each successive relapse, patients may experience an increase in the severity of their symptoms as the progression of their illness moves them further

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[72] P.J. Weiden, C. Kozma, A. Grogg & J. Locklear, *Partial Compliance and Risk of Rehospitalization Among California Medicaid Patients with Schizophrenia*, 55 Psychiatric Services 886 (2004) (Exh. 34).

[73] S.W. Mikhail & H.G. Kennedy, *Homicide, Novel Antipsychotics, and Non-Compliance*, 355 Lancet 1189 (2000) (Exh. 35).

[74] D.A. Johnson, *et al.*, *The Discontinuance of Maintenance Neuroleptic Therapy in Chronic Schizophrenic Patients: Drug and Social Consequences*, 67 Acta Psychiatr. Scand. 339 (1983) (Exh. 36); V. Molina, *et al.*, *Lower Prefrontal Gray Matter Volume in Schizophrenia in Chronic but Not in First Episode Schizophrenia Patients*, 131 Psychiatry Res. 45 (2004) (Exh. 37).

away from recovery.[75] A substantial percentage of patients (60% to 75%) with schizophrenia relapse within one to two years without antipsychotic medication. Even with oral medications this rate is still over 40%.[76] On the other hand, continuous medication, with accompanying maintenance of stable concentration of drug, has been shown to reduce this risk.[77] Thus, it is critical to ensure that any proposed follow-on version of RISPERDAL CONSTA has a comparable release profile during the main release phase.[78]

Bipolar I Disorder: The natural history of bipolar disorder is also characterized by relapses and recurrences. More than 90% of individuals who have a single manic episode will have future episodes, and 10% to 15% of patients will have more than ten episodes in their lifetime. Typically, functioning and well being are impaired even after symptomatic recovery, meaning bipolar disorder is a cause of significant disability, morbidity, and mortality and is one of the leading causes of disability in young adults. Consequently, bipolar disorder is increasingly recognized as a chronic and debilitating, recurrent illness that requires long-term maintenance treatment following alleviation of the acute symptoms of the disease.[79]

Much as with schizophrenia, there is a high rate of poor treatment adherence among patients with bipolar disorder, which is a significant problem: nearly 50% of bipolar disorder patients are partially adherent or non-adherent.[80] Hence, as described previously, RISPERDAL CONSTA offers potentially significant benefits to patients with schizophrenia or bipolar I disorder by reducing the rates of recurrent episodes.[81] Yet, any change of treatment leading to a consequent decrease in the plasma levels of active medication can increase the risk of such relapses. Accordingly, as with schizophrenia, it

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[75] J.A. Lieberman, *et al.*, *The Early Stages of Schizophrenia: Speculations on Pathogenesis, Pathophysiology, and Therapeutic Approaches*, 50 Biol. Psychiatry 884 (2001) (Exh. 38).

[76] J.G. Csernansky, R. Mahmoud, & R. Brenner, *A Comparison of Risperidone and Haloperidol for the Prevention of Relapse in Patients with Schizophrenia*, 346 N. Engl. J. Med. 16 (2002) (Exh. 39).

[77] Kane, *et al.*, *supra* n. 22.

[78] *Id.*

[79] P.D. Harvey, *et al.*, *Cognition and Disability in Bipolar Disorder: Lessons From Schizophrenia Research*, 12 Bipolar Disorders 364 (2010) (Exh. 40); G.S. Malhi, *et al.*, *The Management of Individuals With Bipolar Disorder: A Review of the Evidence and its Integration Into Clinical Practice*, 69 Drugs 2063 (2009) (Exh. 41); P.E. Keck, Jr., R.C. Kessler, & R. Ross, *Clinical and Economic Effects of Unrecognized or Inadequately Treated Bipolar Disorder*, 14 J. Psychiatric Practice 31 (suppl. 2 2008) (Exh. 42); S. Derry & R.A. Moore, *Atypical Antipsychotics in Bipolar Disorder: Systematic Review of Randomized Trials*, 7 BMC Psychiatry 40 (2007) (Exh. 43); P. Oswald, *et al.*, *Current Issues in Bipolar Disorder: A Critical Review*, 17 European Neuropsychopharmacology 687 (2007) (Exh. 44); N. Huxley & R.J. Baldessarini, *Disability and its Treatment in Bipolar Disorder Patients*, 9 Bipolar Disorders 183 (2007) (Exh. 45).

[80] *See* FDA, *Guidance for Industry*, *supra* n. 39.

[81] M. Sajatovic, *et al.*, *Treatment Adherence With Antipsychotic Medications in Bipolar Disorder*, 8 Bipolar Disorders 232 (2006) (Exh. 46); M. Sajatovic, M. Davies, & D.R. Hrouda, *Enhancement of Treatment Adherence Among Patients With Bipolar Disorder*, 55 Psychiatr. Serv. 264 (2004) (Exh. 47).

is critical that FDA ensure that the rate and extent of release of risperidone in a follow-on product be comparable with that of RISPERDAL CONSTA, thereby reducing the potential for an increased rate of relapse among patients with these diseases.

D. ADDITIONAL PK METRICS ARE NEEDED TO CAPTURE CLINICALLY SIGNIFICANT DIFFERENCES IN FOLLOW-ON PRODUCTS

1. FDA Has Relied on Partial AUCs to Evaluate the Bioequivalence of Multiphasic Drug Products

FDA has long recognized that non-traditional metrics, such as T_{max} and partial AUC ("pAUC"), should be added to evaluate bioequivalence in certain cases, particularly in those where C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ will not capture potentially, clinically significant issues.[82] In August 2009, FDA issued draft bioequivalence recommendations calling for the use of pAUCs to evaluate proposed follow-on versions of Ambien CR® (zolpidem tartrate extended release).[83] 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. These distinct phases in the PK profile prompted FDA to recommend specific pAUC measures for any related ANDA to ensure that "the pharmacokinetic profiles of test and reference products are sufficiently similar that there will be no significant difference in sleep onset, sleep maintenance, and lack of residual effects between the test and reference products."[84]

FDA had previously declined to require use of pAUCs as an additional metric to evaluate proposed follow-on versions of another multiphasic drug product, Cardizem CD. But, even there, the agency based that conclusion on its finding that Cardizem CD's PK profile was not "consistently reproducible or medically significant."[85] Indeed, in this

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[82] *See, e.g.*, FDA, *Guidance for Industry*, *supra* n. 39, at 8-9.

[83] FDA, *Draft Guidance on Zolpidem* (Aug. 2009), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM175029.pdf.

[84] *Id.* FDA's approach to Ambien CR reflects its current position with respect to the use of partial AUC. Thus, the agency's earlier decision in 2003 denying Pharmacia's petition concerning the use of additional bioequivalence metrics to evaluate proposed follow-on versions of Covera-HS is fully distinguishable and does not reflect the agency's current views towards the use of pAUC. *See Citizen Petition Response, Covera-HS*, Docket No. 2001P-0546 (Nov. 21, 2003).

[85] *See Citizen Petition Response, Cardizem CD*, Docket No. 1998P-0145 (Oct. 22, 1999). FDA found Cardizem CD's multi-peak PK profile to be variable and inconsistent, and it declined to require ANDA filers to comply with heightened bioequivalence standards when Cardizem CD itself was not able to reproduce the multi-peak PK profile consistently in its clinical studies. FDA found that Cardizem CD's failure to include its multi-peak PK profile in its labeling suggested it was unaware of any clinical benefits. Here, in contrast, the labeling for RISPERDAL CONSTA expressly describes the three intended drug release phases, provides guidance on administering concomitant oral antipsychotic medication, and states when steady-state plasma drug levels are expected.

context, FDA declared that complex PK profiles may be medically significant and will be assessed on a case-by-case basis, and if differences in profiles are shown to be medically significant, two products will not be deemed bioequivalent. In the case of Ambien CR, FDA appears to have reached that conclusion. Thus, notwithstanding its earlier decisions, FDA has now clearly recognized that additional bioequivalence parameters should be required where, as here, those metrics will help elucidate potentially clinically meaningful differences in the PK profile of a proposed follow-on product that are not detected by C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ alone.[86]

This approach is further confirmed by the position that the agency took before the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology in April 2010.[87] That Advisory Committee was convened to review the need for additional bioequivalence metrics for products with complex PK profiles. In its briefing document for this meeting, FDA indicated that it has "recently encountered several review examples of multiphasic products for which it was concluded that the follow-on and corresponding reference products may not be therapeutically equivalent (switchable), despite being deemed [bioequivalent] when the traditional metrics were compared."[88] 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 the traditional bioequivalence parameters of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.[89] The agency indicated that pAUC may be applied to time intervals

[86] It is in this respect that FDA's 2002 response to a citizen petition involving Adderall should be understood. There, the petitioner asserted that non-traditional bioequivalence metrics were necessary to evaluate any follow-on product's PK profile because a failure to mimic Adderall's absorption phase will have a higher potential for abuse. While acknowledging the utility of partial AUC in certain cases, FDA rejected that request after finding that there was no clinical significance to the petitioner's arguments concerning abuse potential for this product. *See* Citizen Petition Response, Adderall, Docket No. 2001P-0585 (Aug. 1, 2002).

[87] *See* FDA, *Briefing Information, Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology* (Apr. 13, 2010), *available at* http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm207736.htm.

[88] *Id.*

[89] During the Advisory Committee, Dr. Buehler supported this conclusion, stating that "as the products become more complex and more specialized and more directed to the particular diseases, and as they're designed to release at certain times for these diseases, we felt it was critical that follow-on products mimic those products more closely than we were looking at before." Transcript of Advisory Comm. Meeting at 391 (April 13, 2010).

that are not related to early exposure if there is a need to ensure equivalent drug exposure over a particular time interval.[90,91]

2. FDA Should Require Partial AUCs to Evaluate the Bioequivalence of Follow-On Products

Against this background, FDA should also require the use of pAUCs to evaluate the bioequivalence of proposed follow-on products to RISPERDAL CONSTA. Like Ambien CR, RISPERDAL CONSTA is characterized by a complex and predictable PK profile where each phase of that profile has clinical significance. The labeling for RISPERDAL CONSTA expressly reflects the consistency of its PK profile. Just as with Ambien CR and other multiphasic products, FDA will only be able to ensure that proposed follow-on versions of RISPERDAL CONSTA will not have clinically meaningful differences through the use of pAUCs. Specifically, here, J&JPRD urges FDA to require applicants for follow-on products to utilize, in addition to C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, three pAUCs (*i.e.*, $pAUC_{0-24h}$, $pAUC_{0-24d}$, and calculated $pAUC_{24d-t}$) to evaluate bioequivalence.[92] The ability of these pAUCs to detect clinically meaningful differences in follow-on products that are not captured by C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ is depicted in Figures 9 to 11. These figures compare the PK profile for RISPERDAL CONSTA to the possible release profiles of follow-on products. These are not hypothetical possibilities; rather, they may arise from the types of manufacturing changes previously described herein.[93]

First, applicants should be required to measure the partial area from 0 to 24 hours ("$pAUC_{0-24h}$") to ensure that the total amount of unencapsulated risperidone released during this period does not exceed that of RISPERDAL CONSTA. This pAUC metric will help to ensure that patients are not put at risk of receiving an excessive exposure in the amount of drug product during the initial release phase, either when starting

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[90] Elsewhere, in the context of responding to two citizen petitions, FDA echoed this position, stating that additional parameters for assessing bioequivalence would be required in cases of complex extended or modified release products for which there were known and clinically significant connections between release characteristics and performance. *See Citizen Petition Response regarding Morphine Sulfate*, at 7, Docket No. FDA-2010-P-0082 (July 19, 2010); *Citizen Petition Response regarding Temazepam*, at 6-7 n.16, Docket No. FDA-2009-P-0379 (Feb. 2, 2010). Although FDA declined these citizen petitions, it did so only after finding that there was no evidence to suggest that differences in PK profiles of proposed follow-on products would have clinical significance. In the case of RISPERDAL CONSTA, J&JPRD has presented such evidence.

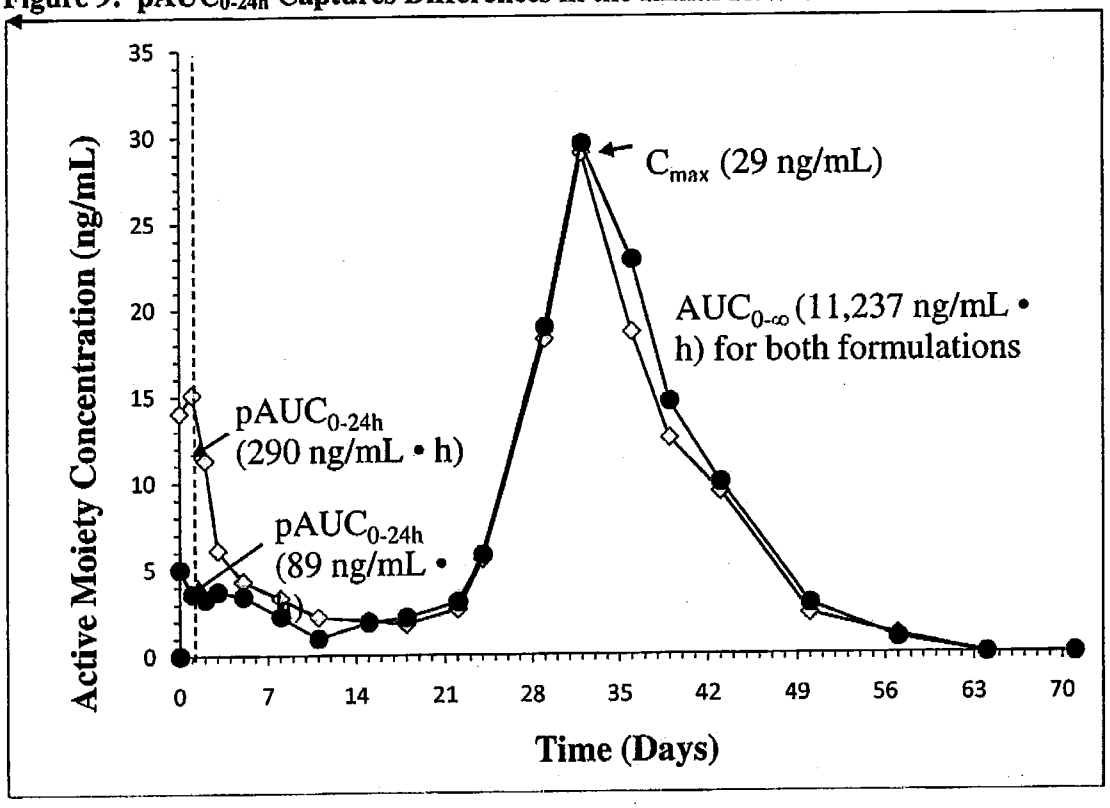
[91] It is acknowledged that the concept of partial AUC has been accepted by FDA to ensure timely onset of action for follow-on products. Nevertheless, J&J considers the same concept to be useful to ensure equivalence in terms of the safety profile.

[92] FDA did not require pAUCs in its assessment of the bioequivalence of deltoid and gluteal intramuscular injections of RISPERDAL CONSTA. It did not need to utilize these additional PK metrics since the same product was used in these studies. In contrast, additional bioequivalence metrics will be necessary to ensure that potentially distinct release profiles of follow-on products do not have clinical significance.

[93] *See* Section II.B.2, *supra* p. 11.

risperidone LAI treatment and receiving oral supplementation of risperidone or another oral antipsychotic medication, or when switching from RISPERDAL CONSTA to a follow-on product. As can be seen from Figure 9 (which presents the PK curve previously presented in Figure 5 plus representation of $pAUC_{0\text{-}24h}$ for ease of reference), in contrast to relying solely on C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$, $pAUC_{0\text{-}24h}$ would allow FDA to determine whether the initial release of risperidone for follow-on products does not exceed that of RISPERDAL CONSTA. Indeed, the pAUC for 0-24 hours between the two release profiles is substantially different, while C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ are the same.

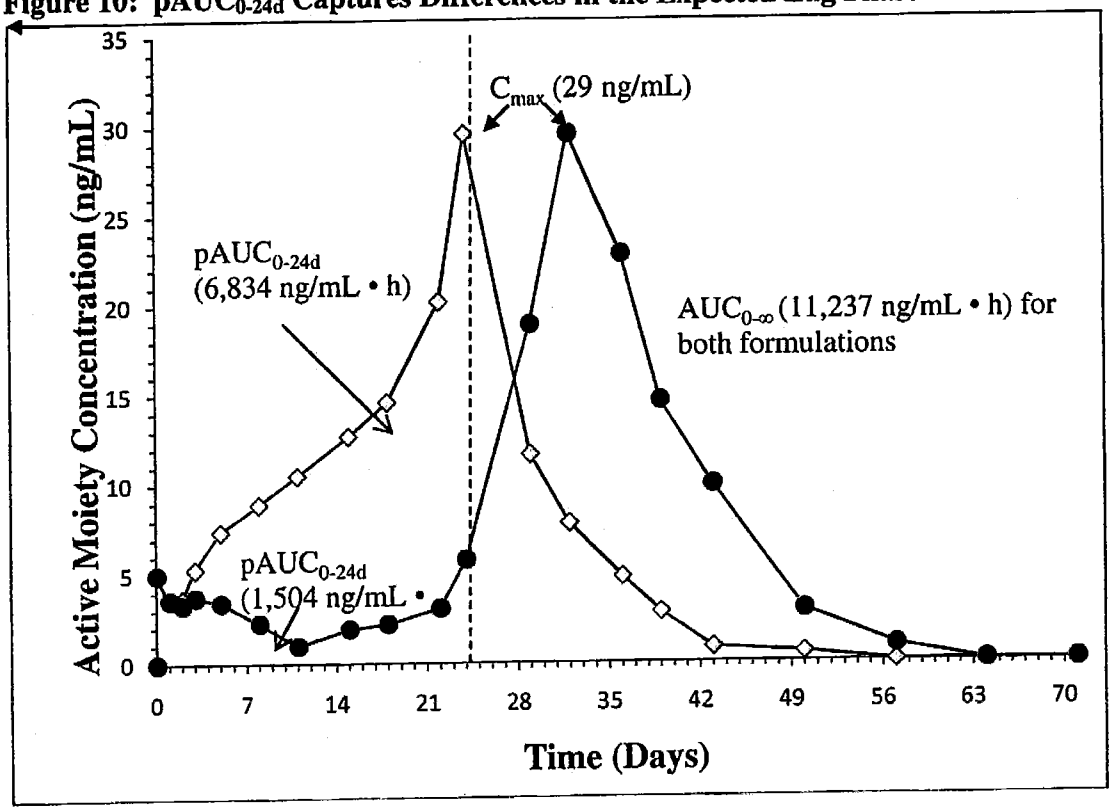
Figure 9: $pAUC_{0\text{-}24h}$ Captures Differences in the Initial Release Phase



Second, to ensure that any proposed follow-on product does not release an excessive amount of drug during the expected lag phase (accelerated main release), FDA should also require applicants to evaluate the partial area from initial dosing until day 24 ("$pAUC_{0\text{-}24d}$"). A thorough assessment of this phase is critical since there are obviously risks related to an earlier release of encapsulated risperidone that is meant to be released over several weeks following a three-week lag period. As before, in contrast to reliance solely on C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$, use of this additional metric will allow applicants and FDA to ensure that the release of risperidone during the lag phase is equivalent to that of RISPERDAL CONSTA. This is demonstrated below in Figure 10 (which presents the PK curve previously presented in Figure 6 plus representation of $pAUC_{0\text{-}24d}$ for ease

of reference). This figure shows vastly different pAUCs for 0-24 days between the two release profiles even though AUC and C_{max} are the same.

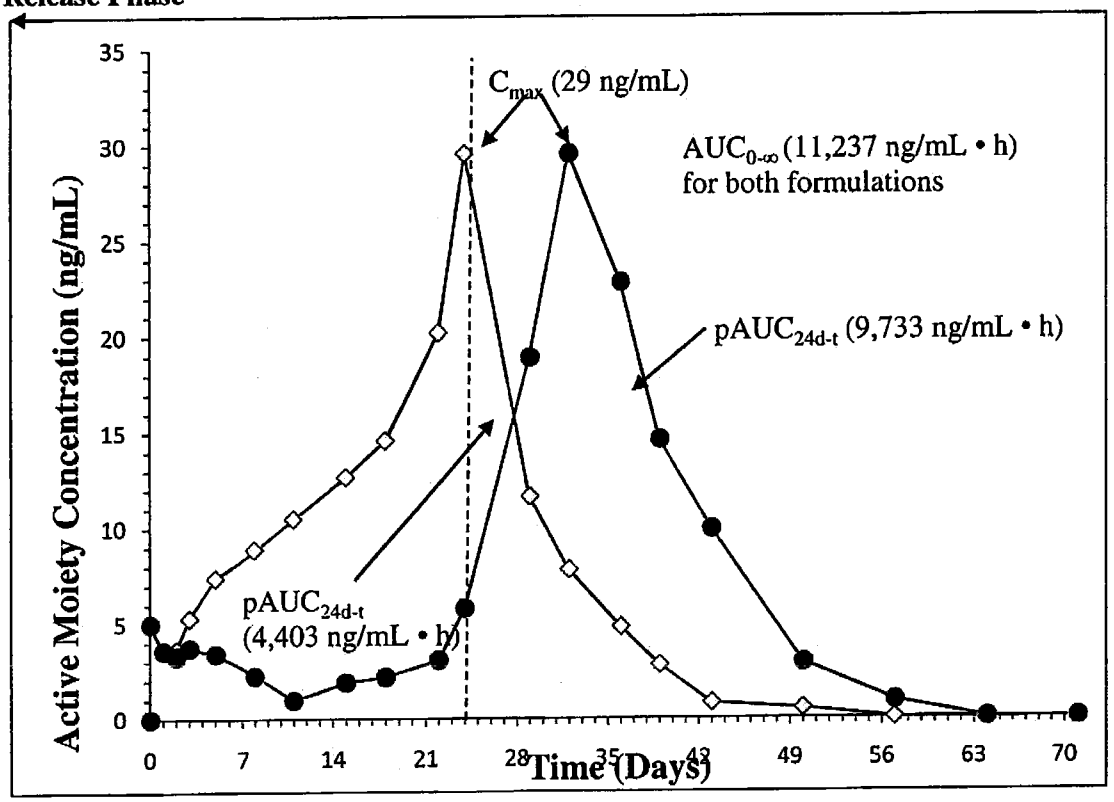
Figure 10: $pAUC_{0\text{-}24d}$ Captures Differences in the Expected Lag Phase



Third, to ensure that any proposed follow-on product does not release a substantially lower amount of drug during the expected main release phase (either due to excessive release of risperidone during the initial release or expected lag phases, or due to a delayed main release), FDA should also require applicants to calculate the partial area under the curve from day 24 until the last measured time point ("$pAUC_{24d\text{-}t}$"). This measurement will ensure that patients are not put at potential risk of relapse and its consequences from under-treatment for schizophrenia and bipolar I disorder. Applicants could calculate this figure by measuring AUC_t and then subtracting the partial area from 0 to 24 days ($pAUC_{0\text{-}24d}$). Figure 11 (which presents the PK curve previously presented in Figure 6 plus representation of $pAUC_{24d\text{-}t}$ for ease of reference) demonstrates that, when $pAUC_{0\text{-}24d}$ values between two release profiles are not equivalent, $pAUC_{24d\text{-}t}$ will also not be equivalent. This partial area should capture at least a period of 85 days because truncation to a time point when the drug release is not complete is unacceptable for products such as RISPERDAL CONSTA. Indeed, for compounds with a long half-life, truncated AUC_{72h} has been proposed as an alternative for AUC_t. However, the terminal half-life of LAI antipsychotics is not driven by their elimination rate but, rather, by the slow release rate of drug from the formulation (flip-flop kinetics). The absorption phase continues for a long period of time (several months for RISPERDAL CONSTA)

after injection. Truncation to a time point when the drug release is not complete would not allow characterization of the entire release/absorption phase.

Figure 11: $pAUC_{0\text{-}24d}$ and AUC_t Allow for Assessment of the Expected Main Release Phase



J&JPRD must emphasize that RISPERDAL CONSTA is intended to be administered for chronic treatment of schizophrenia and bipolar I disorder. It will be critical for FDA to ensure that any follow-on product is bioequivalent to RISPERDAL CONSTA over an extended period of time. The PK profile of RISPERDAL CONSTA is characterized by a three-week lag time and relatively short apparent half-life, driven by the release rate (flip-flop kinetics). Small changes in the release rate may cause significant changes in the apparent half-life and, therefore, in the steady-state PK parameters ($C_{min,ss}$, $C_{max,ss}$ and/or peak/trough ratio). Yet, reliance solely on C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ in a single dose study to ensure bioequivalence would not allow one to infer bioequivalence at steady-state, and to ensure safety and therapeutic equivalence. Accordingly, in the event that FDA does not require applicants for follow-on products to utilize the foregoing bioequivalence metrics, the agency should require such applicants to conduct multiple dose studies.

E. BIOEQUIVALENCE SHOULD BE DEMONSTRATED AT LEAST AT THE LOWEST AND HIGHEST DOSE STRENGTHS

In its draft guidance for intramuscular risperidone, FDA proposed to require applicants to conduct a single-dose study at 25 mg, accepting waivers for the 12.5, 37.5 and 50 mg strengths if they satisfied certain conditions.[94] The guidelines on the Investigation of Bioequivalence[95] state that it may be sufficient to establish bioequivalence at only one or two strengths, provided that the strengths are proportionally similar in composition and appropriate comparative dissolution data are available. In the case of linear PK (AUC-based) a biowaiver can be conditionally granted for all lower strengths (criteria specified in the applicable guideline).

For drugs with non-linear PK characterized by a less than dose-proportional increase in PK parameters caused by limited solubility, bioequivalence should be demonstrated at the most critical dose, *i.e.*, the highest strength. The kinetics of risperidone after oral administration of risperidone and after intramuscular administration of RISPERDAL® CONSTA® are dose-proportional in the 12.5-50 mg range. However, because of the complex interplay between the drug (product), excipients, and injection site, the dose proportionality may be dependent on characteristics other than the intrinsic physicochemical properties of the active pharmaceutical ingredient (*e.g.*, chemical composition of the polymer, excipients and residual solvents) or, as observed for other antipsychotics,[96] particle size (distribution) and injection site, which may affect the PK profile of the drug (dependent on the applied manufacturing technology). Therefore, FDA should also require demonstration of bioequivalence at least at the lowest and the highest strength. Biowaivers may be acceptable for the intermediate strengths of LAI antipsychotics provided that both bioequivalence is minimally demonstrated at the highest and the lowest strength and dose-proportionality for the follow-on version is demonstrated for the dose range.

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.

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[94] FDA, *Draft Guideline on Risperidone, supra* n. 5.

[95] FDA, *Guidance for Industry, supra* n. 39, at 8-9.

[96] FDA, *Clinical Pharmacology and Biopharmaceutics Review(s), INVEGA SUSTENNA* (Feb. 2009), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022264s000clinpharmr.pdf.

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: February 2010. 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 J&JPRD, 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,

Johnson & Johnson Pharmaceutical Research & Development

Donald L. Heald

Donald L. Heald, Ph.D.
Vice-President
Clinical Pharmacology
TA Head for Neuro Sciences

cc: Bruce Manheim, Esq., Ropes & Gray LLP

VI. LIST OF EXHIBITS IN ADDENDUM

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Janssen Research & Development, LLC.
Global Regulatory Affairs
Neuroscience

janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

December 10, 2013

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

Re: Submission of Supplement to Docket No. FDA-2011-P-0086-0001/CP

Dear Sir or Madam,

The above-referenced Citizen Petition was filed in February 2011 by Johnson & Johnson Pharmaceutical Research & Development, LLC, requesting that FDA implement certain additional pharmacokinetic ("PK") standards when measuring the bioequivalence of any potential follow-on versions of RISPERDAL® CONSTA® (risperidone). While FDA has not yet responded to the petition, it has released a revised "Draft Guidance on Risperidone" (Docket No. FDA-2007-D-0369) in August 2013 (the "Revised Draft Guidance"). This Revised Draft Guidance addressed some of the same concerns raised in the petition, but did not fully address all of them. On October 24, 2013, Janssen Research & Development, LLC[1] ("Janssen") submitted comments to the Revised Draft Guidance docket.

Janssen hereby requests that the comments submitted to the Revised Draft Guidance docket, which are attached hereto, be considered a supplement to the Citizen Petition. Janssen believes that the PK suggestions in the original petition are preferable to the requirements set forth in the August 2013 Revised Draft Guidance, but is submitting this supplement for consideration by FDA in the event FDA does not accept those suggestions.

The undersigned makes the following verification for this submission, as required by 21 USC 355(q)(1)(I):

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about August 23, 2013. 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: __N/A_____ I verify

[1] Johnson & Johnson Pharmaceutical Research & Development, LLC was renamed Janssen Research & Development, LLC.

under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

In addition, the undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition which are unfavorable to the petition.

Sincerely,

Donald L. Heald

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

Docket # FDA-2007-D-0369

Janssen Research & Development, LLC
Global Regulatory Affairs
Neuroscience Therapeutic Area

1125 Trenton-Harbourton Road
Titusville, NJ 08560

October 24, 2013

Division of Dockets Management (HFA-305)
Docket No. # FDA-2007-D-0369
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RLD Application Number: NDA 021346

Re: Docket No. FDA-2007-D-0369 "Draft Guidance on Risperidone" dated August 2013; Requests for Comments.

Dear Sir/Madam:

On behalf of Janssen Research & Development, L.L.C.[1] ("Company"), a company of Johnson & Johnson, we are providing the following comments and recommendations in response to the U.S. Food and Drug Administration ("FDA") revised guidance entitled "Draft Guidance on Risperidone," initially released in February 2010 and revised in August 2013 ("Revised Draft Guidance"), for risperidone intramuscular injection.

In response to the FDA's release of the original draft bioequivalence Guidance in February 2010, the Company had submitted comments on 13 September 2010.

In February 2011, the Company (formerly Johnson & Johnson Pharmaceutical Research & Development, L.L.C. ["J&JPRD"]), submitted "A Citizen Petition Requesting Adoption of Certain Parameters to Govern the Review of Bioequivalence of Proposed Follow-On Versions of RISPERDAL® CONSTA®" ("Citizen Petition") to the FDA. The primary requests, based on the complex pharmacokinetic ("PK") profile of RISPERDAL® CONSTA® (risperidone), were to implement additional PK measures. Specifically, J&JPRD requested that FDA not approve a follow-on product unless the agency has assured bioequivalence by requiring applicants to conduct, at a minimum, a 2-strength single dose study that, in addition to the traditional bioequivalence metrics of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, utilizes the following PK metrics to evaluate bioequivalence: $pAUC_{0-24h}$, $pAUC_{0-24d}$, and $pAUC_{24d-t}$.

[1] The Company is the authorized regulatory agent for Janssen Pharmaceuticals, Inc. ("JPI"). JPI is the holder of the New Drug Application for RISPERDAL® CONSTA® (risperidone) Long-Acting Injection. The former holder of the NDA, Ortho-McNeil-Janssen Pharmaceuticals, Inc. was renamed JPI.

The Company evaluated the new bioequivalence study design in the Revised Draft Guidance. These comments address areas in which the new proposal does not appear to fully address the safety and efficacy concerns raised in the Citizen Petition, or are unclear. The Company is planning to submit a supplement to the Citizen Petition to address these concerns, in addition to submitting these comments.

Given the three distinct phases of release for RISPERDAL® CONSTA® and the historical experience gained in its development program, the Company believes the studies recommended in the Revised Draft Guidance, including one *in vitro* and one *in vivo* study, may be appropriate but the end points are not adequate to detect inadequate and/or non-robust release profiles necessary to allow patients to safely switch between or start *de novo* on risperidone intramuscular products.

1. BACKGROUND

As described in more detail in the Citizen Petition, the release of risperidone from RISPERDAL® CONSTA® is characterized by three distinct phases: an initial release phase (<1% of the dose) following injection, a 3-week lag phase and a main release phase. To ensure that patients maintain adequate antipsychotic coverage during this period, the labeling for RISPERDAL® CONSTA® directs that patients should receive oral antipsychotic supplementation for the first three weeks of treatment following the initial injection. The main release phase of the drug begins at three weeks after the injection, is maintained from weeks four to six, and then diminishes relatively rapidly by seven weeks following injection, with an apparent half-life of 3 to 6 days.

If treated with a follow-on product that releases an excessive amount of risperidone during the initial release phase (referred to as dose dumping), patients may experience significant dose-related adverse effects. This would be expected both for patients who are starting risperidone intramuscular for the first time (and therefore receiving oral risperidone supplementation), and for patients with steady state drug exposure who are switching from RISPERDAL® CONSTA® to the follow-on product. Similarly, a follow-on product that releases risperidone too early (accelerated main release after a shortened lag phase) may expose patients to excessive risks, either when starting risperidone intramuscular (and therefore receiving oral risperidone supplementation), or upon switching from RISPERDAL® CONSTA® to the follow-on product.

Accordingly, while the Revised Draft Guidance appears to recognize implicitly the importance of the release phases on safety and efficacy, the actual measures proposed do not evaluate and control for all three phases. A small increase in initial release or a slightly earlier start of the main release phase may cause significant changes in the duration of the oral supplementation required when initiating patients *de novo* on the follow-on risperidone intramuscular injection and in the key PK parameters (C_{min}, C_{max} and/or peak/trough ratio) upon switching between

drugs (reference/follow-on or follow-on/reference). Therefore, any bioequivalence study design should evaluate and control for all three release phases, either by the use of the pAUC parameters in a single-dose study recommended in the Citizen Petition, or by implementing appropriate parameters at the right timepoints in the *in vitro* and *in vivo* bioequivalence studies proposed in the Revised Draft Guidance.

2. RECOMMENDATIONS FOR THE REVISED DRAFT GUIDANCE

2.1 General Comments

In the event that FDA does not adopt the recommendations set forth in the Citizen Petition, the Company is concerned that the study design proposed in the Revised Draft Guidance is not sufficiently sensitive to adequately measure all three release phases. Specifically, the design proposed may not (1) detect uncontrolled early release (dose dumping) during the initial release phase; or (2) ensure equality in terms of the lag phase. Evaluating the potential for both of these effects is considered critically important both for *de novo* initiation of the follow-on drug and in the context of switching as described in Section 1 above and the Citizen Petition.

The potential risks related to dose dumping were extensively discussed in the Citizen Petition. In summary, the extensive initial release of drug product could have adverse effects potentially related to a sudden increase in systemic exposure, such as extrapyramidal symptoms (EPS), hypotension, somnolence and sedation, and QTc interval prolongation.

Evaluating the potential for dose dumping in the initial release phase is important when patients are initiated *de novo* on the follow-on drug (to avoid excessive exposure due to early burst on top of the orally supplemented risperidone), as well as upon switching (to ensure that no excessive exposure is provided by simultaneous early release from the new injection and main release from prior injections).

Evaluating the 3-week lag phase is important when patients are initiated *de novo* on the follow-on drug (to ensure that the 3-week oral supplementation is adequate for the follow-on drug) and also upon switching (to ensure there is no increase in peak exposure or drop in minimal exposure upon switching - see simulations provided in the Citizen Petition). The collective evaluation proposed in the *in vitro* and *in vivo* studies set forth in the Revised Draft Guidance are not an adequate alternative to the implementation of partial AUCs in a single-dose bioequivalence study as set forth in the Citizen Petition because the early release and lag phase are neither evaluated nor controlled by specified criteria in the Revised Draft Guidance. However, the Company recognizes that the proposed studies may provide an adequate alternative to the recommendations set forth in the Citizen Petition if endpoints measuring the initial and lag phases are implemented in both studies.

If a switching study is pursued as an alternative to a more sensitive single-dose bioequivalence study, the Company recommends that a number of important adjustments be made to evaluate the follow-on product in order to maximize the likelihood of detecting uncontrolled early release and ensuring equality in the lag phase. Detailed rationale for each of the Company's recommendations is provided in Sections 2.2 through 2.4 of this document. Besides these critical recommendations related to the characterization of the initial release, and directly relevant to patients' safety, some additional comments are provided to help improve clarity of the Revised Draft Guidance.

2.2 *In Vitro* Study

2.2.1 Recommendation: Implement Dissolution Criteria at All Critical Timepoints

The Revised Draft Guidance recommends comparing the dissolution characteristics of the follow-on drug product to RISPERDAL® CONSTA® *in vitro*, applying the biorelevant dissolution method, as an alternative to a single dose *in vivo* bioequivalence study. Bioequivalence is to be demonstrated in terms of T50%. This approach does not adequately control for follow-on products sensitive to dose dumping because the timing of the main release phase is not necessarily predictive of the early release phase and dose dumping. Given the potential clinical consequences of uncontrolled dose dumping, described in the Citizen Petition and in Section 2.1 above, recommendations for endpoints that the Company believes would control for dose dumping under the study design proposed in the Revised Draft Guidance are presented below.

The 37°C dissolution test applied to release the reference drug uses two timepoints to characterize the initial release phase and lag phase (Day 1 and Day 15, respectively). The 45°C test (accelerated temperature/release conditions) uses an estimate of the midpoint of release to confirm the shape of the *in vitro* release profile, and an end timepoint for greater than 80% drug release (Day 8). The selection of these timepoints was based on the correlations with the cumulative (*in vivo*) release during each of the 3 critical release phases and, therefore, the combination of specifications, collectively, ensures that each of these release phases is adequately controlled for individual batches.

The implementation of criteria for the midpoint (T50%) release only is not adequately sensitive to detect early burst release. Adequate release at T50% is not necessarily predictive of the absence of excessive early release (dose dumping) if there are small changes in the amount or type of excipients or residual solvents, particularly given that the formulation is sensitive to such small differences (see Citizen Petition).[2]

Therefore, it is recommended that acceptance criteria be implemented for the percentage of drug released at all critical dissolution timepoints in the 37°C and the 45°C dissolution tests, in addition to the criteria for T50% currently implemented in the Revised Draft Guidance. In the absence of a single-dose bioequivalence study as recommended in the Citizen Petition, a thorough evaluation of the initial release phase and the lag phase of the *in vitro* release profile is needed in order to avoid dose dumping and ensure that the 3-week period of oral supplementation is adequate when patients start *de novo* on treatment with the follow-on product or when being switched between the follow-on product and RISPERDAL® CONSTA®.

2.2.2 Comment: Replace Day 21 with Day 15 Evaluation

The 37°C dissolution test for release of the reference drug uses two early timepoints to characterize the initial release phase and lag phase (day 1 and day 15, respectively). The selection of the timepoints was based on the correlation with the cumulative (*in vivo*) release. Specifically, day 15 *in vitro* release was correlated with *in vivo* release at day 24, representing the onset of the main release phase of the drug. It is unclear to the Company why a different timepoint (day 21) was selected in the Revised Draft Guidance.

2.3 *In Vivo* Study

2.3.1 Recommendations

2.3.1.1 Study Design

The *in vivo* study design as set forth in item 2 of page 1 requires performance of a steady-state cross-over study. From this description, it is not clear whether FDA intends a cross-over multiple dose bioequivalence study, simply comparing steady-state PK parameters $AUC_{tau,ss}$, $C_{max,SS}$ and $C_{min,SS}$ for reference and follow-on drug product, or a cross-over switching study (with direct switch between drug products), evaluating also the changes in exposure upon switching. The cross-over multiple dose bioequivalence study design, evaluating solely steady-state PK parameters, will not enable detection of inadequate risperidone intramuscular drug products with a different lag phase (see simulations in Citizen Petition), whereas the switching study may

[2] As noted in the Citizen Petition, products with a polymer formulation or excipients different from those of RISPERDAL CONSTA would not be eligible for an ANDA under 21 C.F.R. § 314.94(a)(9)(iii). Nevertheless, examples were provided in the Citizen Petition about how sensitive the PK of RISPERDAL CONSTA are given its microsphere-based formulation to even small changes in the amounts of excipients or residual solvents and why additional PK metrics would be necessary for a bioequivalence study under Section 505(b)(2) of the FDCA.

enable detection of risperidone intramuscular drug products with a different lag phase, provided that the pharmacokinetics are thoroughly evaluated by extensive PK sampling during the period after switching (see simulations in Citizen Petition). The Revised Draft Guidance, page 2, last bullet provides that "in period 2 (when patients are switched from reference to test or vice versa)....", which suggests that FDA indeed intends a switching study, such that patients stabilized on the reference drug before enrollment in the study will be randomized to one of the two sequences (reference/follow-on or follow-on/reference) in a randomized, two-way, 2-sequence cross-over switching study. The Company agrees that a 2-sequence, 2-way cross-over switching study, evaluating the pharmacokinetics in all critical cycles upon switching is appropriate. Given the critical importance of detecting inadequate risperidone intramuscular drug products with a different lag phase, it is recommended that the expected study design be clarified in more detail to avoid potential misinterpretation.

2.3.1.2 PK Parameters to be Assessed

The Revised Draft Guidance specifies that the 90% confidence interval for the ratio of geometric means of AUC and C_{max} should be within 80-125%. No criteria were specified for C_{min}. Although the Revised Draft Guidance states that individual and average $C_{min,SS}$ should be submitted for review, the Revised Draft Guidance does not state that the 90% confidence interval for the ratio of geometric means of $C_{min,SS}$ should be within 80-125%.

As outlined in Citizen Petition, even small and temporary reductions in exposure to risperidone could lead to significant risks of clinical relapse and the consequent need for hospitalization. While not all patients will relapse due to short interruptions in treatment - even if these interruptions recur due to RISPERDAL® CONSTA® and follow-on product being used interchangeably - for those patients who are susceptible and who are being prescribed risperidone intramuscular therapy because non-adherence has been demonstrated and linked to repeated relapse, the consequences of further relapse may be severe. Therefore, therapeutic equivalence in terms of efficacy requires sustained exposure during the entire dosing interval, and it is accordingly essential to ensure bioequivalence in terms of $C_{min,SS}$.

In addition, it is unclear how to estimate $C_{max,SS}$ and $C_{min,SS}$. Given that $C_{min,SS}$ and $C_{max,SS}$ may be different in the first three to four cycles after switching, it is recommended that these PK parameters be estimated in each cycle and that how to estimate $C_{min,SS}$ and $C_{max,SS}$, be defined based on minimum and maximum exposure values estimated in each cycle. Given the importance to patient safety of ensuring that peak exposure does not change significantly upon switching - and given the importance to efficacy in ensuring that minimal exposure does not change - it is important to characterize these parameters adequately. Therefore, the Company recommends that FDA define how to estimate $C_{min,SS}$ and $C_{max,SS}$.

Finally, the multiple dose set-up is not optimal to characterize the release rate during the initial burst phase, or during the lag phase, which is important to avoid dose dumping and ensure that

the 3-week period of oral supplementation is adequate when patients start *de novo* on treatment with the follow-on product or when being switched between a follow-on product and RISPERDAL® CONSTA®. However, even in a switching study, which is less sensitive than the measures proposed in the Citizen Petition, the release rate can be evaluated to some extent by evaluating T_{max}. This is especially important because the *in vitro* study alone may not enable detection of significant *in vivo* changes in release rate effected by small changes in the amount or type of excipients or residual solvents. For example, indirect effects, mediated through local tolerability issues and physiological changes at the injection site, e.g. pH changes (see Citizen Petition), will not be detectable in the *in vitro* study. Therefore, the Company recommends that the Revised Draft Guidance be modified to specify that T_{max} should be carefully evaluated for each of the dosing cycles in the *in vivo* study.

2.3.1.3 Intensive PK Sampling in Multiple Cycles

The Revised Draft Guidance requires intensive PK sampling during the third dosing interval of Period 2. As described in the Citizen Petition (see Figures 7 and 8 of the Citizen Petition), sudden increase in C_{max} can occur in the 2nd or 3rd cycle upon switching between RISPERDAL® CONSTA® and a follow-on product. Thus, the proposed sampling procedure may not enable detection of significant changes in peak or minimal exposure upon switching and, therefore, will not ensure bioequivalence for certain drug products.

In addition, as discussed above, careful evaluation of the potential for dose dumping after the first injection of a follow-on product is warranted, given the potential safety consequences of excessive release. A careful evaluation of peak exposure and time to peak exposure in each of the cycles upon switching is especially important because the *in vitro* study alone may not detect indirect effects caused by small changes in the amount or type of excipients or residual solvents on drug release, mediated by local tolerability and physiological changes, as discussed above.

2.3.1.4 Demonstration of Bioequivalence at Least at the Lowest and the Highest Strengths

As noted in the Citizen Petition - because of the complex interplay between the drug, excipients and the injection site - dose-proportionality may be dependent on characteristics other than the intrinsic physicochemical properties of the active pharmaceutical ingredient. For example, the composition of the polymer, excipients, residual solvents, particle size distribution, and injection site reactions, all may affect the PK of the drug, and may be dependent not on Q1/Q2, but on the applied manufacturing technology. Some of these factors may affect the extent of early release, and, therefore, the safety profile of the drug product in a dose-related manner. Therefore, the Company repeats its request set forth in the Citizen Petition that FDA should also require demonstration of bioequivalence at least at the lowest and the highest strengths.

2.3.1.5 Evaluation of Bioequivalence after Deltoid and Gluteal Injections

Differences in physiology between deltoid and gluteal muscle, and differences in tolerability between these injection sites, may directly or indirectly affect the release characteristics of long-acting injectable antipsychotics. As noted in the Citizen Petition, FDA did not require additional PK measures in its assessment of the bioequivalence of deltoid and gluteal intramuscular injections of RISPERDAL® CONSTA®. It did not need to utilize these additional PK metrics since the same product was used in these studies. In contrast, additional bioequivalence metrics will be necessary to ensure that potentially distinct release profiles of follow-on products do not have clinical significance. Accordingly, the Company recommends that bioequivalence be evaluated both after deltoid and gluteal injection to ensure therapeutic equivalence can be inferred for both injection sites.

2.3.2 Comment: BE Assessment under Fasting Conditions

The scientific rationale for the requirement to study bioequivalence under fasting conditions for this intramuscular drug product is not clear to the Company.

2.4 Recommendation: PK Study

It is generally accepted that a single-dose PK study is more sensitive than a multiple dose PK study to detect differences in the release rate. This is especially important for a long-acting injectable antipsychotic given that different early release rates may reflect a higher sensitivity for uncontrolled release (dose dumping) and reveal that a formulation is sensitive to small changes in the amount or type of excipients or residual solvents. For RISPERDAL® CONSTA® specifically, this would allow for evaluation of changes in the lag phase. As noted above, the Company recognizes that this may not be critical if adequate measures for early release are incorporated in the proposed *in vitro* and *in vivo* studies.

3. SUMMARY AND CONCLUSION

The Company believes that the Revised Draft Guidance would not fully address the safety and efficacy issues raised in the Citizen Petition; however, with the addition of additional endpoints, the methodology proposed in the Revised Draft Guidance may be adequate to detect such differences.

Accordingly, the Company recommends that FDA modify the Revised Draft Guidance to:

- Implement acceptance criteria for the percentage of drug released at all critical dissolution timepoints in the 37°C and at 45 °C dissolution tests, i.e., for all *in vitro* time points which are correlated with critical timepoints in the *in vivo* release profile and PK curve. Specifically, this would entail demonstration of equivalence of the formulations at each individual timepoint (day 1 and day 15 at 37 °C and day 8 at 45 °C) in addition to the criteria for T50% currently implemented in the Revised Draft Guidance;

- Clarify that a randomized, 2-sequence (reference/follow-on and follow-on/reference sequences) cross-over switching study is recommended;
- Indicate the minimum number of cycles in period 1 and period 2: patients stabilized on RISPERDAL® CONSTA® will need to be stabilized for multiple cycles in period 1, given that half of the patients will be randomized to the follow-on/reference sequence;
- Specify PK sampling times during cycles of extensive PK sampling (to ensure peak and trough levels are well defined);
- Specify that the bioequivalence limit of 80-125% must be met for $C_{min,SS}$;
- Specify how to estimate $C_{min,SS}$ and $C_{max,SS}$;
- Specify that T_{max} should be carefully evaluated for each of the dosing cycles in the *in vivo* study;
- Specify that intensive PK sampling be performed during the first, second and third cycles of Period 1 and Period 2;
- Require demonstration of bioequivalence at least at the lowest and the highest strengths;
- Evaluate bioequivalence both after deltoid and gluteal injections; and
- Require a single-dose PK study and evaluate the drug release during the early release phase and the lag phase.

Thank you for the opportunity to review and comment on the Revised Draft Guidance. Should you have any questions or comments, please contact me directly.

Sincerely,

JACQUELINE BROWN

Digitally signed by JACQUELINE BROWN
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LUYE PHARMA GROUP LTD.

绿叶制药集团有限公司

(Incorporated in the Bermuda with limited liability)

(Stock Code: 02186)

ANNOUNCEMENT

THE COMPANY HAS SUCCESSFULLY COMPLETED THREE CLINICAL STUDIES FOR LY03004 IN THE U.S.

The board of directors of Luye Pharma Group Ltd. (the "**Company**") is pleased to announce that the Company has completed the following three clinical studies involving a total of 172 patients in the United States (the "**U.S.**") for an investigational drug product of risperidone ("**LY03004**"), formulated as extended release microspheres for intramuscular injection for the treatment of schizophrenia and/or schizoaffective disorders:

- In the pivotal clinical study, 108 patients with schizophrenia and/or schizoaffective disorders were enrolled at ten study sites with significant experiences in the U.S., each of whom received five consecutive injections (once every two weeks) of either LY03004 or another marketed product (the "**Marketed Drug**") at 25.0 mg. The results indicated stable plasma drug level was reached about two weeks after the first injection of LY03004 compared to four weeks after the first injection of the Marketed Drug. Furthermore, this pivotal study demonstrated pharmacokinetic bioequivalence of LY03004 compared to the Marketed Drug at steady state, based on the U.S. Food and Drug Administration (the "**FDA**") standard method to assess bioequivalence, i.e., the 90% confidence interval for the ratio of total plasma drug level (AUC) and peak plasma drug level (Cmax) between LY03004 (the test drug) and the Marketed Drug (the reference drug) after the fifth injection is within 80% to 125%. Similar safety profiles were also observed between LY03004 and the Marketed Drug after received five consecutive injections.

- In the single dosage study, 32 patients with schizophrenia and/or schizoaffective disorders in the U.S. received an injection of either LY03004 or the Marketed Drug at 25.0 mg or 50.0 mg. The results showed that LY03004 commenced releasing drug on the first day after injection and reached peak plasma drug level in about 14 days, while the Marketed Drug only released a small amount of drug following a single injection with very limited drug release in the subsequent 21 days, reaching peak plasma drug level in about 32 days. This result indicated that unlike the

Marketed Drug, LY03004 does not need the administration of oral drugs three weeks after the first injection. However, LY03004 and the Marketed Drug showed similar safety profiles after a single administration at either 25.0 mg or 50.0 mg.

- In the single ascending dose study, 32 patients with schizophrenia and/or schizoaffective disorders in the U.S. received a single ascending injection of LY03004 at one of the four doses (12.5 mg, 25.0 mg, 37.5 mg and 50.0 mg). The results of this study demonstrated a good safety profile and dose proportionality of LY03004.

The Company believes that LY03004 as an injectable drug can improve medication compliance in patients with schizophrenia which is a common issue with oral antipsychotic drugs and would simplify treatment regimen since it needs to be injected only once every two weeks. Furthermore, LY03004 has several advantages over the Marketed Drug, for example, there is no need to administer oral formulation during the three weeks after the first injection of LY03004 compared to the Marketed Drug. The stable plasma drug level can also be reached much faster with LY03004 compared to the Marketed Drug.

Schizophrenia is a severe mental disorder, characterized by profound disruptions in thinking, affecting language, perception and the sense of self. According to World Health Organization (WHO), schizophrenia affects more than 21 million people worldwide, and one in two people living with schizophrenia does not receive care for the condition. According to the U.S. National Institutes of Health (NIH) report, an estimated of 2.4 million Americans have schizophrenia. The Company expects that LY03004 could be used to improve medication compliance in the patients with schizophrenia and/or schizoaffective disorders, which represents a significant medical need for those patients and their families as well as the society.

The Company believes that LY03004 has good marketing potential and will enrich the Company's product pipeline. The Company plans to discuss with the FDA about the possibility of a New Drug Application (NDA) submission based on the results of these three studies. In addition, the Company is also targeting to obtain regulatory approval for LY03004 in Europe and Japan. Besides LY03004, the Company is currently developing several new pharmaceutical products in the U.S.

By Order of the Board
LUYE PHARMA GROUP LTD.
Liu Dian Bo
Chairman

Hong Kong, 14 May 2015

As at the date of this announcement, the Executive Directors of the Company are Mr. LIU Dian Bo, Mr. YANG Rong Bing, Mr. YUAN Hui Xian and Ms. ZHU Yuan Yuan; the Non-executive Directors are Mr. PAN Jian, Mr. LIU Dong and Ms. WANG Xin; and the Independent Non-executive Directors are Mr. ZHANG Hua Qiao, Professor LO Yuk Lam, Mr. LEUNG Man Kit and Mr. CHOY Sze Chung Jojo.