Janssen Research & Development, LLC.
Global Regulatory Affairs
Neuroscience

Janssen

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

6 September 2016

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: Third Supplement to Citizen Petition, Docket No. FDA-2013-P-0608/CP with cross-submission to FDA "Draft Bioequivalence Guidance on Paliperidone Palmitate", Docket No. FDA-2007-D-0369 (1 July 2016)

Dear Sir or Madam:

The purpose of this letter is to inform you that the attached Third Supplement to Citizen Petition, Docket No. FDA-2013-P-0608/CP is hereby also being submitted to the FDA "Draft Bioequivalence Guidance on Paliperidone Palmitate", Docket No. FDA-2007-D-0369 (1 July 2016).

Sincerely,

Beth Geter-Douglass, Ph.D.
Associate Director, Regulatory Affairs

Cc: Ann Sohn, Pharm.D., LT USPHS, Regulatory Project Manager, DPP

Docket No. FDA-2013-P-0608/CP

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

1125 Trenton-Harbourton Road
Titusville, NJ 08560

6 September 2016

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

RLD Application Number: NDA 22-264

Re: Third Supplement to Citizen Petition, Docket No. FDA-2013-P-0608/CP

Dear Sir or Madam:

As you are aware, Janssen Research & Development, LLC (the "Company"), a company of Johnson & Johnson, has made numerous attempts to engage the U.S. Food and Drug Administration ("FDA") on the complex issues associated with demonstrating bioequivalence of paliperidone palmitate extended-release injectable suspension, including through the submission of a Citizen Petition (Docket No. FDA-2013-P-0608/CP) and comments to various iterations of FDA's "Draft Guidance for Industry: Bioequivalence Recommendations for Paliperidone Palmitate (the "Draft Bioequivalence Guidance")."[1] To date, FDA has neither responded to the

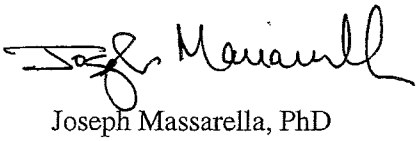
[1] FDA issued a draft bioequivalence guidance on paliperidone palmitate extended-release injectable suspension in August 2011 and the Company, formerly Johnson & Johnson Pharmaceutical Research & Development, LLC submitted comments to the docket in February 2012. Thereafter, in May 2013, the Company submitted a Citizen Petition requesting that FDA require that any Abbreviated New Drug Application referencing INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension meet certain conditions, including conditions related to demonstrating bioequivalence. In December 2013, without responding to the Citizen Petition, FDA issued a revised version of a draft bioequivalence guidance concerning paliperidone palmitate. The 2013 Draft Bioequivalence Guidance addressed some, but not all, of the concerns the Company had raised in the Citizen Petition and in the February 2012 comments. Thus, in response to the 2013 Draft Bioequivalence Guidance, the Company submitted additional comments to the docket in February 2014 and subsequently cross-filed those comments in a supplement to the Citizen Petition in April 2014. In December 2015, FDA issued a further revised draft version of the guidance that again failed to address all of the concerns previously described by the Company. The Company accordingly submitted comments to the docket in February 2016 and cross-filed those comments in a second supplement to the Citizen Petition in February 2016. Our comments to the various versions of FDA's Draft Bioequivalence Guidance are filed to Docket No. FDA-2007-D-0369 (formerly Docket No. 2007-D-0168); our Citizen Petition and subsequent supplements are filed to Docket No. FDA-2013-P-0608/CP.

Company's various submissions nor adopted the recommendations conveyed therein. Most recently, we submitted comments to the version of the Draft Bioequivalence Guidance that FDA issued in July 2016 (Docket No. FDA-2007-D-0369, formerly Docket No. FDA-2007-D-0168). We hereby request that those comments, which are attached hereto, be considered a supplement to the Citizen Petition.

The undersigned makes the following verification for this submission, as required by 21 U.S.C. § 355(q)(1)(l):

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 July 1, 2016. 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: not applicable. I verify under penalty of perjury that the foregoing is true and correct of the date of the submission of this petition.

Sincerely,



Joseph Massarella, PhD
Quantitative Sciences, Clinical Pharmacology & Pharmacometrics Group Leader
Established Products and Medical Affairs

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

Docket No. FDA-2007-D-0369

Janssen Research & Development, LLC.
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1125 Trenton-Harbourton Road
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6 September 2016

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

RLD Application Number: NDA 22-264

Re: Docket No. FDA-2007-D-0369 (Formerly Docket No. 2007-D-0168): Draft Guidance for Industry on Bioequivalence Recommendations for Paliperidone Palmitate Extended-Release Injectable Suspension, Revised July 2016

Dear Sir or Madam:

On behalf of Janssen Research & Development, LLC (the "Company"), a company of Johnson & Johnson, we are providing the following comments in response to the Food and Drug Administration ("FDA") guidance entitled, "Draft Guidance for Industry: Bioequivalence Recommendations for Paliperidone Palmitate," as revised in July 2016 (the "Draft Bioequivalence Guidance").

As you are aware, the Company has made numerous attempts to engage FDA on the complex issues associated with demonstrating bioequivalence of paliperidone palmitate extended-release injectable suspension.[1] The complexities result from the biphasic release

[1] FDA issued a draft bioequivalence guidance on paliperidone palmitate extended-release injectable suspension in August 2011 and the Company, formerly Johnson & Johnson Pharmaceutical Research & Development, LLC submitted comments to the docket in February 2012. Thereafter, in May 2013, the Company submitted a Citizen Petition requesting that FDA require that any Abbreviated New Drug Application referencing INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension meet certain conditions, including conditions related to demonstrating bioequivalence. In December 2013, without responding to the Citizen Petition, FDA issued a revised version of a draft bioequivalence guidance concerning paliperidone palmitate. The 2013 Draft Bioequivalence Guidance addressed some, but not all, of the concerns the Company had raised in the Citizen Petition and in the February 2012 comments. Thus, in response to the 2013 Draft Bioequivalence Guidance, the Company submitted additional comments to the docket in February 2014 and subsequently cross-filed those comments in a supplement to the Citizen Petition in April 2014. In December 2015, FDA issued a further revised draft version of the guidance that again failed to address all of the concerns previously described by the Company.

profile of INVEGA SUSTENNA® (paliperidone palmitate): an initial zero-order release phase during the first two weeks, and subsequently a first-order release phase. As described in the Company's Citizen Petition, as well as in comments to three prior iterations of FDA's Draft Bioequivalence Guidance, potentially significant safety and efficacy issues may emerge with *de novo* treatment with a generic product or in a product-switching scenario if FDA accepts bioequivalence determinations for proposed generic versions of paliperidone palmitate extended-release injectable suspensions based solely on C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. Because those traditional metrics may not detect clinically meaningful differences arising from variations in the pharmacokinetic ("PK") profiles of INVEGA SUSTENNA® and proposed generic versions, the Company has repeatedly requested that the agency require evaluation of AUC_{0-72h} and $_pAUC_{0-28d}$—in addition to C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$—in a single-dose bioequivalence study.

To date, FDA has neither responded to the Company's various submissions nor adopted the recommendations conveyed therein. Indeed, after evaluation of the recently released 2016 Draft Bioequivalence Guidance, the Company continues to believe that approval of a proposed generic version of INVEGA SUSTENNA® based upon the bioequivalence parameters currently contemplated by FDA may pose potentially significant risks for patients who rely on the product to treat their schizophrenia or schizoaffective disorder. The Company has previously described in considerable detail its concerns with FDA's approach and will not repeat them here. Rather, we incorporate by reference all of our prior submissions and request that the agency reconsider the modifications we most recently proposed to the Draft Bioequivalence Guidance issued in December 2015, as set forth in our comments to the docket and in our second supplement to the Citizen Petition.[2] Specifically, we renew our requests that

- FDA require evaluation of AUC_{0-72h}, $_pAUC_{0-28d}$, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ in a single-dose bioequivalence study; and
- if FDA declines to adopt this recommendation, it modify the approach laid out in the Draft Bioequivalence Guidance by
    - limiting the study design to a 2-sequence, 2-way cross-over switching study;
    - revising the PK parameters to be assessed in the study; and
    - referring to the same dissolution specifications as those defined for the original drug product, including at the early time points to ensure adequate control for the early release phase.

The Company accordingly submitted comments to the docket in February 2016 and cross-filed those comments in a second supplement to the Citizen Petition in February 2016. Our comments to the various versions of FDA's Draft Bioequivalence Guidance are filed to Docket No. FDA-2007-D-0369 (formerly Docket No. 2007-D-0168); our Citizen Petition and subsequent supplements are filed to Docket No. FDA-2013-P-0608/CP.

[2] *See* Note 1, *infra*.

Thank you for the opportunity to review and comment on the 2016 Draft Bioequivalence Guidance. The Company also plans to submit a third supplement to the Citizen Petition to raise these concerns. Should you have any questions or comments, please contact me directly at 609-730-4409.

Sincerely,

Beth Geter-Douglass, Ph.D.
Associate Director, Global Regulatory Affairs
Janssen Research and Development, L.L.C.