



**U.S. FOOD & DRUG
ADMINISTRATION**

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Washington, D.C. 20005

Re: Docket No. FDA-2013-P-0608

JUL 06 2021

Dear Petitioner:

This letter responds to the citizen petition submitted by Janssen Research & Development, LLC (the petitioner) to the Food and Drug Administration (FDA or Agency) on behalf of Janssen Pharmaceuticals, Inc., which was received on May 9, 2013 (Petition). Janssen Pharmaceuticals, Inc. is the holder of approved new drug application (NDA) 022264 for Invega Sustenna (paliperidone palmitate) extended-release injectable suspension. The Petition requests that FDA apply certain bioequivalence parameters to the review and approval of any abbreviated new drug applications (ANDAs) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)) and any NDAs submitted under section 505(b)(2) of the FD&C Act that reference NDA 022264. More specifically, the Petition asks that, for ANDAs referencing NDA 022264 and where a bioequivalence assessment was conducted in connection with a 505(b)(2) application referencing NDA 022264, FDA refrain from approving such an application unless the applicant has demonstrated bioequivalence by evaluating, in addition to the traditional bioequivalence parameters (i.e., area under the concentration versus time curve (AUC_{0-t} , $AUC_{0-\infty}$, and the maximum or peak drug concentration (C_{max})), partial AUC from zero to 72 hours ($pAUC_{0-72h}$) and from zero to 28 days ($pAUC_{0-28d}$).

In addition, the petitioner submitted three separate supplements to the Petition, dated April 10, 2014; February 29, 2016; and September 6, 2016 (collectively, Supplements). Each supplement contained the petitioner's comments to the docket for the *FDA Draft Guidance on Paliperidone Palmitate* (Draft Paliperidone Guidance).¹ Collectively, the Petition and Supplements request that:

¹ See Docket No. FDA-2007-D-0369. The *FDA Draft Guidance on Paliperidone Palmitate* is available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Paliperidone%20palmitate%20inj%20ER%20suspension%20RLD%2022264%20RV07-16.pdf. When final, this guidance will represent FDA's current thinking on this topic. We U.S. Food & Drug Administration
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- FDA require evaluation of $pAUC_{0-72h}$, $pAUC_{0-28d}$, AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} in a single-dose bioequivalence study
- If FDA declines to adopt the Petition's recommendation to require such a single-dose bioequivalence study, the Agency modify the approach laid out in the Draft Paliperidone Guidance by:
 - Limiting the study design to a two-sequence, two-way crossover switching study² and requiring evaluation of transient trough level (C_{min}), C_{max} , and AUC during a dosing interval at steady-state (AUC_t) in all dosing intervals upon switching
 - Indicating the minimum number of cycles in period 1 and period 2 (the petitioner notes that patients stabilized on Invega Sustenna 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)
 - Revising the pharmacokinetic (PK) parameters to be assessed in the study such that: (1) the 90-percent confidence interval (CI) for the ratio of geometric means of trough level at steady state ($C_{min,SS}$) should be within 80–125 percent; and (2) the minimum and maximum drug concentrations at steady state ($C_{min,SS}$ and $C_{max,SS}$) are defined based on transient minimum and maximum exposure values estimated in each dosing interval upon switching
 - 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

We have carefully considered the issues raised in the Petition and Supplements. For the reasons stated below, the requests advanced in the Petition and Supplements are denied.³

update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

² The Petition uses the term *cross-over switching study* instead of the term *crossover study*, which is used in the Draft Paliperidone Guidance. We interpret both of these terms to describe a study where each subject receives each of the drugs (i.e., Invega Sustenna and the proposed generic drug) in randomized order in two successive periods. In this response, we refer to this study design as a *crossover study* to be consistent with the Draft Paliperidone Guidance.

³ Today FDA is approving ANDA 211149 for paliperidone palmitate extended-release injectable suspension.

I. BACKGROUND

A. Invega Sustenna

FDA approved Invega Sustenna on July 31, 2009. Invega Sustenna is an atypical antipsychotic drug product indicated for the treatment of schizophrenia and the treatment of schizoaffective disorder as a monotherapy and as an adjunct to mood stabilizers or antidepressants. Invega Sustenna is an extended-release injectable suspension for intramuscular use.

B. Legal and Regulatory Background

1. ANDAs and the Bioequivalence Requirement

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created, among other things, section 505(j) of the FD&C Act, which established the ANDA approval pathway for generic drugs.⁴ To obtain approval, an ANDA applicant is not required to provide independent clinical studies to demonstrate the safety and effectiveness of the proposed generic drug product. Instead, the application relies on FDA's previous finding that the reference listed drug (RLD) is safe and effective.⁵ The ANDA applicant must identify the listed drug on which it seeks to rely, and, with limited exceptions, a drug product described in an ANDA must contain the same active ingredients, conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD.⁶

An ANDA applicant must also demonstrate that its proposed generic drug is bioequivalent to the RLD.⁷ Section 505(j)(8)(B)(i) of the FD&C Act states that a generic drug is 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 absorption of the listed drug when administered at the same molar dose

⁴ For the purposes of this response, the term *generic drug* refers to a new drug product for which approval is sought in an ANDA submitted under section 505(j) of the FD&C Act.

⁵ An RLD is “the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA” (§ 314.3(b)(21 CFR 314.3(b))). RLDs are identified in FDA’s *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book), available at <https://www.accessdata.fda.gov/scripts/cder/ob/>.

⁶ Section 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act; see also § 314.94(a) (21 CFR 314.94(a)).

⁷ See, e.g., section 505(j)(2)(A)(iv) of the FD&C Act (requiring “information to show that the new drug is bioequivalent to the listed drug”); § 314.3 (defining an RLD); § 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the RLD); 21 CFR 314.127(a)(6)(i) (providing that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the RLD referred to in the ANDA).

of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses⁸

In § 314.3(b), FDA defines *bioequivalence* (in pertinent part) as:

the absence of a significant difference in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.⁹

A showing that the active ingredient or therapeutic ingredient in the proposed generic drug reaches the site of drug action at a rate and to an extent not significantly different from that of the RLD, along with other information required for approval, permits FDA to conclude that the proposed generic drug can be expected to perform the same way in the body as the RLD. Bioequivalence testing determines whether differences in formulation (e.g., differences in inactive ingredients) between a proposed generic drug and the RLD have an impact on the rate and extent to which the active ingredient becomes available at the site of action. The scientific premise underlying the Hatch-Waxman Amendments is that bioequivalent drug products with the same active ingredients, route of administration, dosage form, and strength are therapeutically equivalent and may be substituted for each other.¹⁰

2. *Bioequivalence Testing*

Under FDA regulations, an applicant must use “the most accurate, sensitive, and reproducible approach available among those set forth” in § 320.24(b) (21 CFR 320.24(b)) to demonstrate bioequivalence.¹¹ These methodologies include PK studies, pharmacodynamic studies, comparative clinical trials, in vitro studies, and any other approach deemed adequate by FDA. The selection of the method used depends on the purpose of the study, the analytical methods available, and the nature of the drug product under consideration.¹² The courts have expressly upheld FDA’s regulatory implementation of the FD&C Act’s bioequivalence requirements.¹³

For systemically acting drug products, the rate and extent of systemic absorption is usually the most accurate, sensitive, and reproducible indicator of the rate and extent to which the active

⁸ See also §§ 314.3(b) and 320.23(b) (21 CFR 320.23(b)).

⁹ See also §§ 320.1 (21 CFR 320.1) and 320.23(b)(1).

¹⁰ See, e.g., section 505(j)(4)(F), (j)(8) of the FD&C Act. *Therapeutic equivalents* are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling (§ 314.3(b)).

¹¹ § 320.24.

¹² Id.

¹³ See, e.g., *Schering Corp. v. FDA*, 51 F.3d 390, 397–400 (3d Cir. 1995), *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 863–67 (D.D.C. 1994).

ingredient becomes available at the site of drug action.¹⁴ The determination of bioequivalence of drug products whose primary mechanism of action depends on systemic absorption generally rests on a comparison of “the concentration of the active ingredient or active moiety, and, when appropriate, its active metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid . . . as a function of time.”¹⁵

For most systemically acting drugs, FDA recommends conducting a two-period, two-sequence, two-treatment, single-dose crossover study in healthy subjects. In this design, each study subject receives each treatment (i.e., the test drug and the reference drug) in random order.¹⁶ Single doses of the test and reference drugs are administered, and each drug’s concentration in the blood or other biological fluid is measured over time. To evaluate the rate and extent of drug absorption, the measured concentrations for each subject can be plotted graphically against the time of measurement. The graph depicts the sampling time on the horizontal (x) axis and the corresponding drug concentration on the vertical (y) axis. The relevant PK parameters calculated from these data include AUC calculated to the last measurable concentration time (AUC_{0-t}) and extrapolated to infinity ($AUC_{0-\infty}$). These parameters represent the extent of absorption (i.e., how much of the drug in the given dose was absorbed by the body). To assess the rate of absorption, we recommend measuring the peak drug concentration (C_{max}). Generally, to establish bioequivalence, the calculated 90-percent confidence interval (CI) for the ratio of the geometric mean for AUC and C_{max} values of the generic test product and the RLD should fall entirely within an 80-percent to 125-percent acceptance interval (0.8–1.25).¹⁷ The time-to-peak drug plasma concentration (T_{max}) can also provide important information regarding the rate of absorption.

Under certain circumstances, if the shape of the PK profile is considered to be clinically relevant, it also may be appropriate to assess partial AUC metrics as part of a demonstration of bioequivalence. In the Agency’s draft guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*, FDA explains that “[t]he time to truncate the partial area should be related to a clinically relevant pharmacodynamic . . . measure.”¹⁸

¹⁴ § 320.24(b)(1)(i).

¹⁵ Id.

¹⁶ See FDA’s draft guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (December 2013) at 3. When final, this guidance will represent FDA’s current thinking on this topic.

¹⁷ See FDA’s guidance for industry *Statistical Approaches to Establishing Bioequivalence* (January 2001).

¹⁸ See FDA’s draft guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* at 5.

C. FDA's Bioequivalence Recommendations for Invega Sustenna (Paliperidone Palmitate)

FDA's draft guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* describes our general recommendations for demonstrating bioequivalence for products submitted under an ANDA. FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed as recommendations, unless specific regulatory or statutory requirements are cited.

In addition to our general recommendations, we often provide product-specific recommendations for demonstrating bioequivalence. Our process for making product-specific bioequivalence guidance available to the public is explained in the guidance for industry *Bioequivalence Recommendations for Specific Products* (June 2010). FDA announced the availability of the first iteration of the Draft Paliperidone Guidance in August 2011. FDA subsequently issued revised versions of the Draft Paliperidone Guidance in December 2013 and December 2015. On July 1, 2016, FDA announced the availability of the most recent version of the Draft Paliperidone Guidance. The Draft Paliperidone Guidance recommends either a parallel or crossover, steady-state,¹⁹ *in vivo* bioequivalence study with PK endpoints in patients. The Draft Paliperidone Guidance recommends that more than three doses may be necessary to reach steady state and that PK data should be submitted to demonstrate that steady state has been reached for each individual. The Draft Paliperidone Guidance recommends submitting the following PK data to evaluate bioequivalence:

- Individual and mean blood drug concentration levels in a dosing interval after steady state is reached
- Individual and mean trough levels ($C_{\min \text{ ss}}$)
- Individual and mean peak levels ($C_{\max \text{ ss}}$)
- Calculation of individual and mean steady-state AUC_{τ} (AUC_{τ} is AUC during a dosing interval at steady-state)
- Individual and mean percent fluctuation [$= 100 * (C_{\max \text{ ss}} - C_{\min \text{ ss}}) / C_{\text{average ss}}$]
- Individual and mean time to peak concentration²⁰

¹⁹ Steady state is a time when after multiple administrations of a dose of the drug, the amount absorbed is equal to the amount eliminated per unit time. *Pharmacokinetics. Basic Concepts in Pharmacology: What You Need to Know for Each Drug Class*, 5e Ed. Janet L. Stringer. New York, NY: McGraw-Hill, available at <http://accessmedicine.mhmedical.com/content.aspx?bookid=2147§ionid=161351042>.

²⁰ Draft Paliperidone Guidance at 1–2.

Bioequivalence should be demonstrated based on a 90-percent CI (i.e., the ratio of the geometric means of the PK parameters (AUC and C_{max}) should be within 80–125 percent). Comparability of the fluctuation of the test product with the fluctuation of the reference product should also be used to evaluate bioequivalence. Additionally, an analysis of trough concentration data should be performed to demonstrate that steady state was achieved before PK sampling.

A waiver of in vivo bioequivalence testing may be granted for the strengths of 39 milligrams (mg)/0.25 milliliter (mL), 78 mg/0.5 mL, 117 mg/0.75 mL, and 234 mg/1.5 mL based on:

- An acceptable in vivo bioequivalence study of the 156 mg/mL strength
- Acceptable in vitro dissolution testing of all strengths
- Proportional similarity of the formulations across all strengths

The Draft Paliperidone Guidance recommends that comparative dissolution testing be performed on 12 dosage units for each of the strengths of the test and reference products using the dissolution methods that can be found on the FDA Recommended Dissolution Methods website.²¹ The specifications for the dissolution testing will be determined as part of the review of the ANDA.

II. DISCUSSION

The petitioner requests that FDA require specific bioequivalence parameters to govern the review and approval of any ANDA submitted under section 505(j) or follow-on product submitted pursuant to section 505(b)(2) of the FD&C Act that references Invega Sustenna (paliperidone palmitate). Below, we address the issues raised in the Petition.²²

A. FDA Does Not Agree That $pAUC_{0-72h}$, $pAUC_{0-28d}$, AUC_{0-t} , and $AUC_{0-\infty}$ From a Single-Dose In Vivo Bioequivalence Study Are Necessary for Detecting Clinically Meaningful Differences Between a Proposed Generic Product and the Reference Product

The petitioner asserts that a crossover or parallel study at steady state, as described in the Draft Paliperidone Guidance, is insufficient for detecting inadequate release of paliperidone during the first phase of release, and that FDA has not demonstrated that the study design described in the Draft Paliperidone Guidance is an adequate alternative to the study proposed by the petitioner. To support this, the petitioner relies on two simulations intended to show how switching between

²¹ The FDA Recommended Dissolution Methods website can be accessed at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>.

²² Drug products proposed in applications submitted under section 505(b)(2) of the FD&C Act can differ from the listed drug in a variety of ways, and we cannot speculate here as to what demonstrations would be needed for a 505(b)(2) application referencing Invega Sustenna as the listed drug. Therefore, this response focuses on the Petition's request with respect to ANDAs and does not address its individual assertions with respect to 505(b)(2) applications.

products with different release profiles but the same C_{max} and AUC could result in different C_{min} , C_{max} , and AUC_r in dosing intervals after switching. The petitioner claims that these simulations demonstrate that two seemingly identical products with the same C_{max} and AUC, but with delayed or altered release properties, can result in significant changes in the systemic drug concentrations.

We do not agree with the petitioner's analysis of the simulations because they appear to reflect an assumption that bioequivalence is evaluated by analyzing C_{max} and AUC following the administration of a single dose. However, the bioequivalence studies described in the Draft Paliperidone Guidance are steady-state bioequivalence studies. Also, the simulation results cited in the Petition suggest that products with the same single-dose C_{max} and AUC, but different release properties at steady state, would fail the steady-state bioequivalence testing as recommended in the Draft Paliperidone Guidance. For example, products with a longer lag time or smaller absorption rate constant (ka) may appear to have the same C_{max} and AUC following single-dose administration, but will differ in T_{max} or $C_{min,SS}$. As such, these products would not be considered bioequivalent under the approach described in the Draft Paliperidone Guidance.

Additionally, a single-dose bioequivalence PK study in either healthy subjects or patients with schizophrenia or schizoaffective disorder washed out from long-acting oral paliperidone may raise additional safety concerns when compared to the studies recommended in the Draft Paliperidone Guidance. Bioequivalence studies in healthy subjects are not recommended because of the potential for serious adverse events associated with the use of this drug. Nor are single-dose bioequivalence studies in patients with schizophrenia or schizoaffective disorder recommended, because such studies would require washout of stable patients' current medication and thereby put patients at unnecessary risk for relapse. Because the type of study recommended by the petitioner poses potential safety concerns for healthy subjects and patients already stabilized on paliperidone, and (as discussed below) would be unlikely to provide clinically significant information that would not be collected as part of the studies recommended in the Draft Paliperidone Guidance, we do not agree that this type of study should be used to evaluate bioequivalence.

FDA performed its own simulations in alignment with the study recommendations in the Draft Paliperidone Guidance, and based on those simulations we do not expect that switching patients from Invega Sustenna to a generic product with a delayed-release profile or altered-release profile would result in a clinically meaningful change in the efficacy or safety profile, as long as the two paliperidone products achieve bioequivalence at steady state. The worst-case scenario of these simulations (i.e., a proposed generic with a 5-week lag time or $ka = 10$ percent that of Invega Sustenna) showed that switching from a generic product to Invega Sustenna could result in a C_{min} increase of up to 66 percent and an increase in C_{max} of up to 50 percent before steady state is reached. Based on experience, such an increase of antipsychotic agents is usually not considered clinically relevant in terms of safety. Therefore, from a clinical perspective, we would not expect an increase in the frequency of adverse events if a patient were to switch from a generic product to Invega Sustenna, as long as that product is bioequivalent to Invega Sustenna at steady state.

The question of the consequences of changes in paliperidone C_{\max} and C_{\min} on efficacy is more complex. In general, the antipsychotic response appears to be related to drug exposure, and it is possible that lower plasma concentrations could lead to a more modest antipsychotic response. However, when patients with schizophrenia who have responded to treatment with an antipsychotic stop their medication (a fairly common scenario in the clinical setting), relapse does not occur immediately; it takes, in general, a few weeks. Similar results can be seen in maintenance trials with antipsychotics in which patients who have responded to an antipsychotic are randomized to continuing active treatment or placebo. Relapse in the placebo group tends to occur sooner than that in the active treatment group, but it still occurs after several weeks of treatment withdrawal. It is also of note that, in terms of drug exposure, treatment discontinuation represents a much worse situation than a possible decrease in C_{\max} and C_{\min} . Accordingly, we expect that switching from Invega Sustenna to a generic product that is bioequivalent at steady state would not have a clinically significant impact on efficacy in patients who have responded to antipsychotic treatment.

Regardless, as noted above, the studies described in the Draft Paliperidone Guidance should be able to detect differences in T_{\max} and $C_{\min,SS}$. Under the approach described, if T_{\max} or $C_{\min,SS}$ were significantly different when comparing the generic product to Invega Sustenna, the products would not be deemed bioequivalent. Furthermore, as discussed below, the release profiles of the two products should be shown to be similar using a validated in vitro dissolution method, and such in vitro dissolution testing would also be expected to detect differences in release profiles between test and reference products. In sum, any difference in release profiles undetectable by the in vivo bioequivalence studies and/or by in vitro dissolution testing are unlikely to result in clinically significant differences in safety or effectiveness.

B. FDA Does Not Agree With the Petitioner’s Proposed Changes to the Steady-State Bioequivalence Study Recommendations in the Draft Paliperidone Guidance

1. FDA Does Not Agree With the Petitioner That the Agency Should Limit the Study Design in the Draft Paliperidone Guidance to a Two-Sequence, Two-Way Crossover

The petitioner requested that FDA limit the study design recommended in the Draft Paliperidone Guidance to a two-sequence, two-way crossover study. The petitioner contends that a crossover study is preferable to a parallel study because “a parallel design does not allow the within-subject (intra-subject) determination of equivalence of the release profiles of test and reference paliperidone palmitate intramuscular drug products.”²³

We do not agree with the petitioner. The current Draft Paliperidone Guidance recommends either a parallel or crossover steady-state study design, which is consistent with FDA’s current thinking that both study designs would be acceptable methods of evaluating bioequivalence. Each of these study designs has its own benefits and limitations with respect to long-acting drug

²³ February 29, 2016 Supplement to Petition at 2.

products like paliperidone palmitate. Specifically, a crossover design requires a much smaller number of subjects for a similar statistical power as a parallel study, because patients in a crossover study act as their own controls. However, for drugs with long half-lives, like paliperidone, due to the washout needed between the first treatment (e.g., RLD) and the second treatment (e.g., generic), the crossover approach can lead to very long in vivo bioequivalence studies, which may lead to subject dropout, thus making it more difficult to conduct such studies.²⁴

In contrast, a parallel study requires a much larger number of subjects to achieve the same statistical power as a crossover study. However, because a parallel study does not require a second dosing period, a parallel study takes less time and typically results in less patient dropout.

With respect to the petitioner's contention that "a parallel design does not allow the within-subject (intra-subject) determination of equivalence of the release profiles of test and reference paliperidone palmitate intramuscular drug products," FDA routinely accepts a bioequivalence approach based on the average results across the study subjects and does not require demonstration of subject-specific bioequivalence.²⁵ As mentioned, the greater number of subjects required for a parallel study lends such studies statistical power comparable to that of a crossover study.

2. *FDA Does Not Agree That It Is Necessary To Indicate the Number of Cycles in Each Sequence of the Crossover Study*

The petitioner requested that FDA amend the Draft Paliperidone Guidance to specify a minimum number of doses (cycles) that are necessary to ensure patients are stabilized on the treatments or reach steady state with the treatments.²⁶ FDA revised the Draft Paliperidone Guidance in December 2015 to state that more than three doses (cycles) may be needed to reach steady state, and that applicants should submit PK data to demonstrate that steady state has been reached for each individual. This recommendation, which is also contained in the current Draft Paliperidone Guidance, serves the same purpose as the revision requested by the petitioner (i.e., it seeks to ensure subjects have achieved steady state before PK sampling), without recommending a specific number of doses (cycles) for achieving steady state.

3. *FDA Does Not Agree That It Is Necessary to Revise the Recommendations as to the PK Parameters To Be Assessed in the Bioequivalence Study*

The petitioner asserts that the Draft Paliperidone Guidance should provide specific criteria for $C_{min,SS}$, and specifically that the Draft Paliperidone Guidance should apply the same criteria to

²⁴ We note that for steady-state studies, complete washout is not required. The washout of the last dose of the first treatment period can overlap with the build-up of the second treatment. Accordingly, we believe that a crossover steady-state study, in contrast to a single-dose study, is acceptable from a patient safety perspective.

²⁵ See, for example, FDA's guidance for industry *Statistical Approaches to Establishing Bioequivalence* at 2.

²⁶ We note that the petitioner did not specifically assert or renew this particular request in its February 29, 2016, or September 6, 2016, supplement to the Petition.

$C_{min,ss}$ as it does to AUC and C_{max} (i.e., that the 90-percent CI for the ratio of the geometric means of $C_{min,ss}$ should be within 80–125 percent). The petitioner claims that this criterion is necessary because of the risk of clinical relapse if the level of paliperidone falls below the therapeutic level. The petitioner also requests that the Draft Paliperidone Guidance state that generic applicants should estimate $C_{min,ss}$ and $C_{max,ss}$ based on transient minimum and maximum exposure values estimated in each dosing interval.

The variability of C_{min} is anticipated to be greater compared to the variability of C_{max} and AUC. As a result, C_{min} is less sensitive in detecting differences compared to C_{max} and AUC. Assessing bioequivalence using the conventional 80- to 125-percent limit on C_{min} is generally not recommended. Therefore, without adequate justification, which was not provided by the petitioner, FDA does not agree that the Draft Paliperidone Guidance should be revised to recommend that bioequivalence be evaluated applying the conventional 80- to 125-percent limit to C_{min} .

Furthermore, it is not necessary to define $C_{min,ss}$ and $C_{max,ss}$ based on transient minimum and maximum exposure values estimated in each dosing interval upon switching. As shown in the petitioner's simulated results, differences in lag time, which can lead to differences in early plasma concentration profile, also lead to differences in T_{max} in a steady-state study. Because such differences would be evaluated for any clinical implications by FDA during our review of a generic drug application, revisions to the Draft Paliperidone Guidance to address the effect of transient minimum and maximum exposure value estimates are not necessary.²⁷

4. FDA Does Not Agree That It Is Necessary To Revise the Draft Paliperidone Guidance To Include the Same Dissolution Specifications as Those Defined for Invega Sustenna

The petitioner asserts that the crossover or parallel study at steady state as described in the Draft Paliperidone Guidance is not sensitive enough to be able to detect inadequate release from a generic product during the initial release phase of the product. Therefore, to account for this asserted lack of sensitivity, the petitioner requests that generic product applicants use the same dissolution specifications as those defined for Invega Sustenna. FDA does not agree that the Draft Paliperidone Guidance should be revised to recommend that generic applicants use the same dissolution specifications as those defined for Invega Sustenna for two reasons.

First, as noted above, FDA disagrees with the petitioner that the in vivo studies described in the Draft Paliperidone Guidance would not detect significant differences in release profiles between a generic product and the RLD. FDA believes that the recommended in vivo studies, together with in vitro dissolution testing and the expectation that a proposed generic product generally will be qualitatively and quantitatively the same as the RLD,²⁸ would detect a significant difference in release profiles, including during the early release phase.

²⁷ For these reasons, we also reject the petitioner's contention that the Draft Paliperidone Guidance should be revised to recommend evaluation of C_{min} , C_{max} , and AUC, in all dosing intervals upon switching.

²⁸ See § 314.94(a)(9)(iii).

Second, consistent with the Draft Paliperidone Guidance, FDA believes it is appropriate to recommend that ANDA applicants conduct comparative dissolution testing as part of the demonstration of bioequivalence, with dissolution specifications to be determined upon review of the ANDA. The Draft Paliperidone Guidance refers prospective ANDA applicants to the FDA Recommended Dissolution Methods website, which contains, among other things, the dissolution specifications for Invega Sustenna. The specific method available in the FDA dissolution database may be used as a starting point for method development and validation to support generic development. FDA does not believe it is appropriate to include a recommendation to use the dissolution specifications for Invega Sustenna in the Draft Paliperidone Guidance because those specifications are set to ensure quality of Invega Sustenna, which may not be readily adaptable to a proposed generic product. In general, similarity between the drug release profiles of the proposed test product and the reference product should be demonstrated by comparing the release profiles using an appropriate statistical approach (i.e., f2 analysis). A generic product applicant is responsible for developing and validating an appropriate dissolution method for its proposed generic product. The proposed in vitro dissolution method should be able to demonstrate similarity between drug release profiles of the proposed generic product and the reference product as well as provide sufficient quality control of the generic product. The adequacy of the proposed dissolution methodology and specifications is determined during the review of an ANDA. To avoid discouraging the exploration of other, potentially better methodologies, FDA does not believe it is appropriate to include in the Draft Paliperidone Guidance the same dissolution specifications as those defined for Invega Sustenna.

III. CONCLUSION

For the reasons explained above, the Petition is denied. FDA believes that the bioequivalence recommendations stated in the current Draft Paliperidone Guidance are sufficient to assess bioequivalence for products referencing Invega Sustenna.

Sincerely,

Patrizia A.
Cavazzoni -S

Digitally signed by Patrizia A. Cavazzoni -S
DN: c=US, o=U.S. Government, ou=HHS, ou=fda,
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