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Draft Guidance on Paliperidone Palmitate

February 2026

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Active Ingredient:	Paliperidone palmitate
Dosage Form:	Suspension, extended release
Route:	Intramuscular
Strengths:	39 mg/0.25 mL (39 mg/0.25 mL), 78 mg/0.5 mL (78 mg/0.5 mL), 117 mg/0.75 mL (117 mg/0.75 mL), 156 mg/mL (156 mg/mL), 234 mg/1.5 mL (156 mg/mL), 351 mg/2.25 mL (156 mg/mL)
Recommended Studies:	Two options: (1) two in vitro bioequivalence studies with comparative characterization studies, or (2) one in vivo bioequivalence study with pharmacokinetic endpoints

I. Option 1: Two in vitro bioequivalence studies with comparative characterization studies

To be eligible for the bioequivalence studies recommended in this guidance, the test product[1] should be qualitatively (Q1)[2] and quantitatively (Q2)[3] the same as the reference listed drug (RLD).

1. Type of study: Drug particle size and size distribution of paliperidone palmitate
   Design: In vitro bioequivalence study should be performed on three batches of test product, and three batches of the reference standard (RS).

[1] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.
[2] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD.
[3] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the RLD.

Strength: Any one of the strengths including 39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, 156 mg/mL, 234 mg/1.5 mL, 351 mg/2.25 mL
Additional comments: The sample preparation method and selected particle sizing methodology should be validated to demonstrate repeatability, reproducibility, and robustness. Full particle size distribution profiles should also be submitted for all samples tested.

Parameters to measure: D_{50} and SPAN[$(D_{90}-D_{10})/D_{50}$]

Bioequivalence based on (95% upper confidence bound): Population bioequivalence (PBE) analysis of the D_{50} and SPAN. No fewer than 10 datasets from at least three different batches of both the test product and RS should be provided for PBE analysis. Refer to the section of "Recommendation Related to the PBE Statistical Analysis Procedure" in the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929)[a] for additional information regarding PBE computation. The recommendation on collecting data on different life stage is not applicable.

2. Type of study: Comparative in vitro drug release test (IVRT) of paliperidone palmitate
Design: In vitro bioequivalence study should be performed on three batches of test product, and three batches of the RS, using at least 12 units from each batch.
Strength: Any one of the strengths including 39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, 156 mg/mL, 234 mg/1.5 mL, 351 mg/2.25 mL
Additional comments:
    a. Provide a properly developed and validated IVRT method that captures the complete release profile of paliperidone palmitate from the suspensions. The IVRT method should reflect the extended-release feature of the drug product (e.g., release occurring over days rather than several hours).
    b. Provide a full method development and validation report to demonstrate that the selected IVRT parameters have been sufficiently optimized with reproducibility and discriminatory ability. To demonstrate discriminatory ability of the IVRT method, provide in vitro release data comparing drug product manufactured under target conditions and drug products intentionally manufactured with meaningful variations in formulation (e.g., particle size distribution, surface chemistry of drug particles[4]) and/or manufacturing processes.
    c. An aliquot of a unit may be acceptable provided that data and justification are submitted to demonstrate the aliquot is a representative sub-sample of the unit formulations.
    d. Equivalence in paliperidone palmitate release should be established using a proper statistical method from test product and RS. One suggested approach is a model independent similarity (f2) factor. For more information on calculation of f2 factor, refer to the most recent version of the guidance for industry *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.[b]

[4] Quanying Bao, Yuan Zou, Yan Wang, Stephanie Choi, and Diane J. Burgess (2021). Impact of formulation parameters on in vitro release from long-acting injectable suspensions. The AAPS Journal, 23, Article 42.

Comparative characterization studies:

The comparative physicochemical characterization of the test product and the RS should be performed on a minimum of three batches of the test product and three batches of the RS, and it should include the following:

a. Polymorphic form of paliperidone palmitate
b. Crystalline shape and morphology of paliperidone palmitate
c. Appearance
d. pH
e. Osmolality
f. Specific gravity
g. Viscosity over a range of shear rates

II. Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
Design: Parallel or crossover steady state
Strength: Any one of the strengths including 39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, 156 mg/mL, 234 mg/1.5 mL
Dose: 39 mg, 78 mg, 117 mg, 156 mg, or 234 mg
Subjects: Male and non-pregnant female patients with schizophrenia or schizoaffective disorder who are already receiving a stable regimen of paliperidone palmitate extended-release suspension via the intramuscular route. Patients who are already receiving any dosage regimen of paliperidone palmitate injection every month would be eligible to participate in the study by continuing their established maintenance dose.
Additional comments:
    a. FDA does not recommend that studies be conducted using healthy subjects or patients on a different antipsychotic treatment.
    b. Patients who are receiving oral paliperidone, oral risperidone, risperidone intramuscular injectable may be eligible to participate in the study by switching to paliperidone palmitate extended-release suspension. The decision for switching a patient from other antipsychotics (oral paliperidone, oral risperidone, risperidone intramuscular injectable) should be made by a healthcare professional based upon their knowledge and experience with the patient, and assessment of the benefits and risks. The transitioning should not be considered solely for the purpose of satisfying enrollment criteria for the bioequivalence study.
    c. The applicant may select any one of the strengths (39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, 156 mg/mL, 234 mg/1.5 mL) to conduct a bioequivalence study with pharmacokinetic endpoints based on number of eligible patients, provided that all strengths of test product only differ in fill volume.
    d. The applicant may conduct the study using one site of injection (either gluteal or deltoid). If both sites of injection (gluteal and deltoid) are included in the study, proportions of the patients should be similar between test and reference groups.
    e. Trough concentration data should be analyzed using appropriate statistical method to demonstrate that the steady state of test product and RS has been reached for each individual.

Analyte to measure: Paliperidone in plasma

Bioequivalence based on (90% CI): Paliperidone

In the evaluation of bioequivalence of the multiple dose study, the following pharmacokinetic data should be submitted for paliperidone:

- Individual and mean plasma drug concentration in a dosing interval after steady state is reached
- Individual and mean trough concentrations ($C_{min\ ss}$)
- Individual and mean peak concentrations ($C_{max\ ss}$)
- 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 [$=100 * (C_{max\ ss} - C_{min\ ss})/C_{average\ ss}$]
- Individual and mean time to peak concentration

The 90% confidence interval for the ratio of the geometric means of the pharmacokinetic parameters (AUC_{ss} and $C_{max\ ss}$) should be within 80.00% - 125.00%. Fluctuation for the test product should be evaluated for comparability with the fluctuation of the RS. The trough concentration data should be analyzed to verify that steady state was achieved.

Waiver request of in vivo testing of additional strengths: Any strengths that are not tested in the in vivo bioequivalence study based on (i) an acceptable in vivo bioequivalence study on the selected strength and (ii) evidence supporting identical formulation composition across all strengths

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test product and RLD.[5] Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Additional information:

Device:
The RLD is presented as a kit that consists of a prefilled syringe and two safety needles. The prefilled syringe and needles with needle guard are the device constituent part.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the test device including:

- Single-dose, fixed-dose, prefilled syringe format
- Needle gauge and length
- Needle guard system

[5] If the RLD is not available, refer to the most recent version of the guidance for industry *Referencing Approved Drug Products in ANDA Submissions*.

User interface assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[b]

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Unique Agency Identifier: PSG_216352

[a] For the most recent version of a product-specific guidance, refer to the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.
[b] For the most recent version of a guidance, refer to the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.