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Draft Guidance on Risperidone

May 2025

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Risperidone

Dosage Form: For suspension, extended release

Route: Intramuscular

Strengths: 75 mg, 100 mg

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Steady state
   Design: Parallel or crossover
   Strength: 100 mg
   Subjects: Male and non-pregnant female patients with schizophrenia who are already receiving a stable regimen (100 mg) of risperidone for extended-release injectable suspension via the intramuscular route.
   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 risperidone (4 mg/day) may be eligible to participate in the study by switching to risperidone for extended-release injectable suspension. The decision for switching a patient from oral risperidone 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. Trough concentration data should be analyzed using an appropriate statistical method to demonstrate that the steady state of test product and reference listed drug (RLD) has been reached for each individual.

Analyte to measure: Risperidone in plasma

Bioequivalence based on (90% CI): Risperidone

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

- Individual and mean blood drug concentration levels in a dosing interval after steady state is reached
- Individual and mean trough levels (C_{min} ss)
- Individual and mean peak levels (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 and C_{max}) should be within 80 – 125%. Fluctuation for the test product should be evaluated for comparability with the fluctuation of the RLD. The trough concentration data should also be analyzed to verify that steady state was achieved prior to pharmacokinetic sampling.

Waiver request of in vivo testing: 75 mg strength based on (i) acceptable bioequivalence study on the 100 mg strength, and (ii) evidence supporting identical formulation composition between both 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 for each of all strengths of the test product and RLD.[1] Specifications will be determined upon review of the abbreviated new drug application (ANDA).

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

Additional information:

Formulation:
The proposed test product[2] should be qualitatively (Q1)[3] and quantitatively (Q2)[4] the same as the RLD for both strengths (75 mg and 100 mg). To support Q1 sameness of poly(lactide-co-glycolide) (PLGA), provide comparative characterization data including polymer composition (molar ratio between glycolide and lactide), molecular weight and weight distribution, and PLGA architecture (e.g., linear or branched) of the PLGA polymer extracted from the test product and RLD. In addition, to support quality assessment of the test product, provide characterization of the extracted PLGA including, but not limited to polymer end cap analysis, inherent viscosity, and glass transition temperature. Sufficient validation data for the methods used for comparative characterization of PLGA should be provided in the ANDA submission.

Device:
The RLD is presented co-packaged in a kit with one syringe containing the drug product, one syringe containing diluent, and two needles with needle safety systems. The device constituent parts include two pre-filled syringes and needles with safety systems.

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, pre-filled drug product syringe and pre-filled diluent syringe format
- Connection between drug product and diluent pre-filled syringes
- Needle gauge and length (appropriate for site of injection)
- Needle safety system

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 FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

[2] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.
[3] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD
[4] 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.

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.