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Draft Guidance on Risperidone

August 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

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Active Ingredient:	Risperidone
Dosage Form:	For suspension, extended release
Route:	Intramuscular
Strengths:	12.5 mg, 25 mg, 37.5 mg, 50 mg
Recommended Studies:	One in vitro bioequivalence study and one in vivo bioequivalence study with pharmacokinetic endpoints

One in vitro bioequivalence study:

1. Type of study: Comparative in vitro drug release test (IVRT)
   Design: In vitro bioequivalence study on at least three batches of both test and reference standard (RS) products
   Strength: 25 mg
   Additional comments:
   a. A properly developed and validated IVRT method that can detect potential formulation differences and capture the complete release profile of risperidone should be provided. Equivalence in risperidone release should be established using a proper statistical method from test and RS products. 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 FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.[a]
   b. Waiver request of IVRT for other strengths based on (i) acceptable in vitro bioequivalence study on the 25 mg strength, and (ii) evidence supporting identical formulation composition across all strengths.

One in vivo bioequivalence study:

2. Design: Parallel or cross-over, steady-state
   Strength: 25 mg
   Subjects: Male and non-pregnant female patients with schizophrenia or bipolar I disorder who are already receiving a stable regimen (25 mg) of risperidone for extended-release injectable suspension via 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 may be eligible to participate 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 appropriate statistical method to demonstrate that the steady state of test and reference product 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 reference product. 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: 12.5 mg, 37.5 mg and 50 mg based on (i) acceptable bioequivalence study on the 25 mg 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 and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Additional information:

Formulation:
The proposed test product[1] should be qualitatively (Q1)[2] and quantitatively (Q2)[3] the same as the reference listed drug (RLD) for all strengths (12.5 mg, 25 mg, 37.5 mg, and 50 mg). To support Q1 sameness, provide comparative characterization data on the poly(lactide-coglycolide) (PLGA) component extracted from the test and RLD. The characterization on the extracted PLGA mixture should include, but not limited to polymer composition (molar ratio between glycolide and lactide), molecular weight and weight distribution, polymer end cap analysis, inherent viscosity, glass transition temperature, and PLGA architecture (e.g., linear or branched PLGA). Sufficient validation data for the methods used for comparative characterization of PLGA should be provided in the ANDA submission.

Device:
The RLD is presented as a kit containing a vial of drug in powder form, a prefilled syringe with diluent, a needle with safety shield, and a sterile vial adaptor. The device constituent parts are the pre-filled syringe, the needle with needle guard, and the vial adaptor.
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:

- Vial adaptor
- Needle gauge and length
- Needle guard 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]

[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.

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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.