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Draft Guidance on Aripiprazole

May 2026

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Active Ingredient:	Aripiprazole
Dosage Form:	For suspension, extended release
Route:	Intramuscular
Strengths:	300 mg | 400 mg | 300 mg/vial | 400 mg/vial
Reference Listed Drug:	NDA 202971
Recommended Studies:	Two options: (I) two in vitro bioequivalence studies with supportive characterization studies, or (II) one in vivo bioequivalence study with pharmacokinetic endpoints

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

Eligibility: 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] 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.

1. Class of study: Bioequivalence
Type of study: Drug particle size and size distribution of aripiprazole
Strength: Any one of the strengths including 300 mg, 400 mg, 300 mg/vial, 400 mg/vial
Study design recommendations:

- In vitro bioequivalence study should be performed on three batches of test product, and three batches of the reference standard (RS).
- 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 and RS products should be provided for PBE analysis. Refer to the section of "Recommendation Related to the PBE Statistical Analysis Procedure" in the product-specific guidance *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. Class of study: Bioequivalence
Type of study: Comparative in vitro drug release test (IVRT) of aripiprazole
Strength: Any one of the strengths including 300 mg, 400 mg, 300 mg/vial, 400 mg/vial
Study design recommendations:

- 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
- Provide a properly developed and validated IVRT method that captures the complete release profile of aripiprazole 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).
- 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) and/or manufacturing processes.
- 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.
- Equivalence in aripiprazole release should be established using a proper statistical method from test product and RS.

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 should include:

1. Polymorphic form of aripiprazole
2. Crystalline shape and morphology of aripiprazole
3. Water content of lyophilized powder
4. Appearance
5. pH
6. Osmolality
7. Specific gravity
8. Viscosity over a range of shear rates

Option II: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Class of study: Bioequivalence
   Type of study: Parallel or cross-over, steady-state
   Strength: 400 mg (prefilled dual-chamber syringe) or 400 mg/vial
   Dose: 400 mg
   Subjects: Male and non-pregnant female patients with schizophrenia or bipolar I disorder who are already receiving a stable regimen (400 mg or 400 mg/vial) of aripiprazole extended-release injectable suspension via the intramuscular route.
   Safety recommendations:
   - FDA does not recommend that studies be conducted using healthy subjects or patients on a different antipsychotic treatment.
   - Patients who are receiving oral aripiprazole may be eligible to participate in the study by switching to aripiprazole extended-release injectable suspension. The decision for switching a patient from oral aripiprazole 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.

   Study design recommendations:
   - 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: Aripiprazole in plasma

Bioequivalence based on (90% CI): Aripiprazole

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

- Individual and mean blood drug concentration levels 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 and C_{max}) should be within 80-125%. 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.

Additional information for both options:

Device: The RLD has two presentations: (1) a prefilled dual-chamber syringe co-packaged with three needles and (2) a kit containing a single-use vial of drug, a single-use vial of diluent (sterile water), two syringes, a vial adapter, and three syringe needles. The prefilled dual-chamber syringe and co-packaged needles, and co-packaged syringes, a vial adapter, and needles in the kit are the device constituent parts for these presentations, respectively.

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:

1. Pre-filled syringe presentation:
    - Single-dose, fixed-dose, prefilled, dual-chamber syringe format
    - Needle gauge and length
    - Needle guard system

2. Vial kit presentation:
    - Vial adapter
    - Syringe with attached needle for reconstitution
    - Syringe for injection
    - 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

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

Bioequivalence 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 and RLD.[4] Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Document History: Recommended December 2014; Revised May 2025, May 2026

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

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