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*Draft – Not for Implementation*

# Draft Guidance on Aripiprazole Lauroxil

**November 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:** | Aripiprazole lauroxil |
| **Dosage Form:** | Suspension, extended release |
| **Route:** | Intramuscular |
| **Strength:** | 675 mg/2.4mL (281.25 mg/mL) |
| **Recommended Studies:** | Two in vitro bioequivalence studies and in vitro supportive characterization studies |

To be eligible for the bioequivalence studies recommended in this guidance, the test (T) 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 distribution
   Design: In vitro bioequivalence study on at least three batches of both test and reference standard (RS) products
   Strength: 675 mg/2.4 mL
   Additional comments: The applicant should provide no fewer than ten datasets from at least three different batches of both the test and RS products for population bioequivalence (PBE) analysis. Full particle size distribution profiles should also be submitted for all samples tested.

[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 T product uses the same inactive ingredient(s) as the RLD product.
[3] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T product are within ±5% of those used in the RLD product.

**Parameters to measure:** $D_{10}$, $D_{50}$, and $D_{90}$

**Bioequivalence based on (95% upper confidence bound):** PBE analysis of the $D_{10}$ and $D_{50}$. 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. Comparable $D_{90}$ should be provided as supporting evidence for bioequivalence.

2. Type of study: Comparative in vitro drug release test (IVRT)
   Design: In vitro bioequivalence study on at least three batches of both test and RS products
   Strength: 675 mg/2.4 mL
   Additional comments: A properly developed and validated IVRT method that can detect potential formulation differences and capture the complete release profile of aripiprazole lauroxil should be provided. Equivalence in aripiprazole lauroxil 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*.[b]

**Supportive characterization studies**
Comparative physicochemical characterization of the test and RS products. The comparative studies should be performed on a minimum of three exhibit batches of the T product and three batches of the RS product and should include:

- Polymorphic form of aripiprazole lauroxil
- Crystalline shape and morphology of aripiprazole lauroxil
- Appearance
- pH
- Osmolality
- Specific gravity
- Viscosity over a range of shear rates

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

[4] 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:**

Device:
The RLD is presented as a kit that consists of one prefilled syringe of aripiprazole suspension, and three needles with needle guards. The prefilled syringe and the needles with needle guard systems are the device constituent parts.
FDA recommends that prospective applicants examine 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

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*.[b]

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**Unique Agency Identifier:** PSG_209830

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