Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Medroxyprogesterone Acetate

August 2022

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

In December 2016, FDA issued a draft product-specific guidance for industry on generic medroxyprogesterone acetate. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient:	Medroxyprogesterone acetate
Dosage Form; Route:	Injectable; injection
Recommended Studies:	Two options: (1) two in vitro bioequivalence studies with supportive characterization studies or (2) one in vivo bioequivalence study with pharmacokinetic endpoints

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

To qualify for the in vitro option for this drug product, all the following criteria should be met:

1. The test and reference listed drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same.

2. Acceptable comparative physicochemical characterization of the test and the reference standard (RS) products. The comparative study should be performed on a minimum of three exhibit batches of the test product[3] and three batches of the RS product and should include:
    a. Polymorphic form of medroxyprogesterone acetate
    b. Crystalline shape and morphology of medroxyprogesterone acetate
    c. Appearance, pH, osmolality, specific gravity, sedimentation rate and volume, and viscosity over a range of shear rates

In vitro bioequivalence study 1:
Drug particle size and size distribution of medroxyprogesterone acetate

Additional comments: The particle size distribution should be compared using population bioequivalence (PBE) (95% upper confidence bound) based on D50 and SPAN [i.e. (D90-D10)/D50)]. The applicant should provide no fewer than ten data sets from three different batches of both the test and RS products for PBE analysis. Full profiles of the particle distribution should also be submitted for all samples tested. Refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension*[a] for additional information regarding PBE.

In vitro bioequivalence study 2:
Comparative in vitro drug release of medroxyprogesterone acetate from the test and RS products.

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

1. Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, parallel, in vivo
   Strength: 150 mg/mL
   Subjects: Healthy non-pregnant females
   Additional comments:
    - Females should not be pregnant and if applicable, should practice abstention or contraception during the study.
    - Both sites of injection (gluteal and deltoid) should be included in the study design.

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

- Subjects should be randomized into the following four (4) groups: Test treatment at gluteal site, Test treatment at deltoid site, Reference treatment at gluteal site, and Reference treatment at deltoid site.
- n addition, if more than one dosing date is planned, approximately equal number of subjects representing each of the 4 groups should be included in each of the dosing dates.
- Demonstration of bioequivalence at each of the injection sites is not recommended, only demonstration of bioequivalence between the test and reference formulations, with the effect of the two injection sites taken into account and analyzed; i.e., the factor, injection site, should be included in the statistical analysis model.

Analyte to measure: Medroxyprogesterone acetate in plasma

Bioequivalence based on (90% CI): Medroxyprogesterone acetate

Waiver request of in vivo testing: Not applicable

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.

Additional information:

Device:
The reference listed drug (RLD) product is presented in a vial or in a prefilled syringe with a co-packaged needle. For the prefilled syringe presentation, the prefilled syringe and needle are device constituents used to administer the drug.

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

- Needle gauge and length

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]

Revision History: Recommended June 2013; Revised December 2016, August 2022

Unique Agency Identifier: PSG_020246

[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.

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