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Draft Guidance on Methylprednisolone Acetate

February 2022

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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.

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In December 2014, FDA issued a draft product-specific guidance for industry on generic methylprednisolone acetate. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient: Methylprednisolone acetate

Dosage Form; Route: Injectable; injection

Recommended Study: Two options: in vitro or in vivo studies

I. In vitro option:

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.

[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.

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 for all strengths of the two configurations (multi-dose vials: 20 mg/mL, 40 mg/mL and 80 mg/mL; single-dose vials: 40 mg/mL and 80 mg/mL) and should include:
    a. Polymorphic form of methylprednisolone acetate.
    b. Crystalline shape and morphology of methylprednisolone acetate.
    c. Appearance, pH, osmolality, specific gravity, and viscosity over a range of shear rates.
    d. Drug particle size and size distribution. 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.

3. Acceptable comparative in vitro drug release of methylprednisolone acetate from the test and RS products for all strengths of the two configurations (multi-dose vials: 20 mg/mL, 40 mg/mL and 80 mg/mL; single-dose vials: 40 mg/mL and 80 mg/mL).

II. In vivo option:

1. Type of study: Fasting
   Design: Single-dose, two-way crossover, in vivo; or single-dose, parallel, in vivo
   Strength: 80 mg/mL (multi-dose vials)
   Subjects: Males and non-pregnant females, general population
   Additional comments: None

2. Type of study: Fasting
   Design: Single-dose, two-way crossover, in vivo; or single-dose, parallel, in vivo
   Strength: 80 mg/mL (single-dose vials)
   Subjects: Males and non-pregnant females, general population
   Additional comments: None

Analyte to measure: Methylprednisolone in plasma

Bioequivalence based on (90% CI): Methylprednisolone

Waiver request of in vivo testing: 20 mg/mL, 40 mg/mL (multi-dose vials) and 40 mg/mL (single-dose vial) based on (i) acceptable bioequivalence studies on the respective 80 mg/mL

[3] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.

strength, (ii) acceptable dissolution testing across all strengths, and (iii) proportional similarity in the formulations across all strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: 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.

Revision History: Recommended October 2011; Revised December 2014, February 2022

Unique Agency Identifier: PSG_011757

[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