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Draft Guidance on Betamethasone Acetate; Betamethasone Sodium Phosphate

November 2023

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Active Ingredients:	Betamethasone acetate; Betamethasone sodium phosphate
Dosage Form:	Injectable
Route:	Injection
Strength:	3 mg/mL; EQ 3 mg Base/mL
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 demonstrate bioequivalence by this option, the test 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: 3 mg/mL; EQ 3 mg Base/mL

[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 product.
[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 product.

Additional comments: The applicant should provide no fewer than ten data sets from three different batches of both the test and RS products for population bioequivalence (PBE) analysis. Full PSD profiles should also be submitted for all samples tested.

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

Bioequivalence based on (95% upper confidence bound): PBE analysis of the D_{50} and SPAN [i.e., $(D_{90}-D_{10})/D_{50}$]. Refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929)[a] for additional information regarding PBE.

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: 3 mg/mL; EQ 3 mg Base/mL
   Additional comments: A properly developed and validated IVRT method that can detect potential formulation differences and capture the complete release profile of betamethasone acetate should be provided. Equivalence in betamethasone acetate 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 test product and three batches of the RS product and should include:

a. Polymorphic form of betamethasone acetate
b. Crystalline shape and morphology of betamethasone acetate
c. Appearance, pH, osmolality, specific gravity, sedimentation rate and volume, and viscosity over a range of shear rates

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

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in vivo
   Strength: 3 mg/mL; EQ 3 mg Base/mL
   Subjects: Healthy males and non-pregnant, non-lactating females

Analytes to measure: Betamethasone and betamethasone phosphate in plasma

Bioequivalence based on (90% CI): Betamethasone

Submit the following data for betamethasone phosphate as supportive evidence of comparable therapeutic outcome: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}.

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.

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[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.