

**Draft Guidance on Betamethasone Acetate; Betamethasone Sodium Phosphate**  
**October 2025**

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| <b>Active Ingredients:</b>  | Betamethasone acetate; Betamethasone sodium phosphate   |
| <b>Dosage Form:</b>         | Injectable  |
| <b>Route:</b>               | Injection   |
| <b>Strength:</b>            | 3 mg/mL; EQ 3 mg Base/mL  |
| <b>Recommended Studies:</b> | 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 be eligible for the bioequivalence studies recommended in this guidance, the test (T) product<sup>1</sup> should be qualitatively (Q1)<sup>2</sup> and quantitatively (Q2)<sup>3</sup> 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 product and reference standard (RS)  
Strength: 3 mg/mL; EQ 3 mg Base/mL

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<sup>1</sup> The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.

<sup>2</sup> Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD.

<sup>3</sup> 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.

Additional comments: Prospective applicants should provide data to support the selected experimental condition is suitable for characterizing the particle size including but not limited to impact of dilution and agitation prior to and/or during measurement (e.g., stirring rate, sonication).<sup>4</sup> No fewer than ten datasets from at least three different batches of both the test product and RS should be provided for population bioequivalence (PBE) analysis. Full particle size distribution profiles should also be submitted for all samples tested.

**Parameters to measure:** D<sub>10</sub>, D<sub>50</sub>, and D<sub>90</sub>

**Bioequivalence based on (95% upper confidence bound):** PBE analysis of the D<sub>10</sub> and D<sub>50</sub>. 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)<sup>a</sup> for additional information regarding PBE computation.<sup>5</sup> Comparable D<sub>90</sub> 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 product and RS  
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 product and RS. One suggested approach is a model independent similarity (f<sub>2</sub>) factor. For more information on calculation of f<sub>2</sub> factor, refer to the most recent version of the FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.<sup>b</sup>

### Supportive characterization studies:

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

- a. Polymorphic form of betamethasone acetate
- b. Crystalline shape and morphology of betamethasone acetate
- c. Appearance
- d. pH
- e. Osmolality
- f. Specific gravity
- g. Viscosity over a range of shear rates
- h. Sedimentation rate and volume

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<sup>4</sup> Smith WC, Bae J, Zhang Y, Qin B, Wang Y, Kozak D, Ashraf M, Xu X. Impact of particle flocculation on the dissolution and bioavailability of injectable suspensions. *International Journal of Pharmaceutics*. 2021 Jul 15;604:120767. <https://doi.org/10.1016/j.ijpharm.2021.120767>

<sup>5</sup> The recommendation on collecting data on different life stages is not applicable.

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

1. Type of study: Bioequivalence study with pharmacokinetic endpoints  
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 for each of all strengths of the test product and RLD. Specifications will be determined upon review of the abbreviated new drug application.

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**Document History:** Recommended April 2010; Revised November 2023, October 2025

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<sup>a</sup> 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>.

<sup>b</sup> For the most recent version of a guidance, check the FDA guidance website at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.