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Draft Guidance on Barium Sulfate

February 2026

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Active Ingredient: Barium sulfate

Dosage Form For suspension

Route: Oral

Strengths: 2%, 24%, 40%, 60%

Recommended Study: One in vitro bioequivalence study (particle size distribution)

The test product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD)[3] in inactive ingredients, and demonstrate comparable physicochemical properties to the RLD, including particle size distribution, pH, viscosity across a range of shear rates (e.g., low, medium and high), and specific gravity. Comparative analyses should be conducted using at least three lots of the test product and three lots of the RLD. Acceptance criteria should be predefined and scientifically justified based on the characterization of the RLD.

Recommendations for demonstrating comparable physicochemical properties

1. Type of study: In vitro bioequivalence study

Parameters to measure: Particle size distribution

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD.
[2] Q2 (Quantitative sameness) means that the percentage (weight/weight) of each inactive ingredient used in the test product is within ±5% of those used in the RLD.
[3] If the RLD is not available, refer to the most recent version of the guidance for industry *Referencing Approved Drug Products in ANDA Submissions*.

Bioequivalence based on the 95% upper confidence bound: The shape of the particle size distribution of barium sulfate for oral suspension may not be monomodal; therefore, the conventional population bioequivalence (PBE) analysis on the D_{50} and SPAN $[(D_{90} – D_{10}) / D_{50}]$ parameters may not be sufficient to demonstrate bioequivalence.

Instead, the equivalence between the test product and RLD in the shape of the particle size distribution (such as the presence of multiple peaks) should be demonstrated by a method proposed by the applicant. A statistical metric is preferred to assess the difference (e.g., a distance measure) between the shapes of distribution profiles. One approach is the earth mover's distance (EMD) method[4], which computes the minimal cost needed to transform one distribution into the other using an optimization algorithm.

An average profile of all RLD samples (i.e., RLD center) should be calculated and used as the reference profile to compute the distance between each test or RLD sample and the RLD center. After obtaining the distances between each RLD sample and the RLD center ("RLD – RLD center" distances), and the distances between each test sample and the RLD center ("TEST-RLD center" distances), a statistical method should be employed to quantify the difference between these two categories of distances. PBE analysis, as described in the guidance for industry *Statistical Approaches to Establishing Bioequivalence*[a], may be used for this purpose. Refer to the most recent version of the product-specific guidance for *Budesonide Inhalation Suspension (*020929)[b] for additional information regarding PBE.

To properly account for variability of the RLD and to achieve adequate power, use a sufficient number of samples and replicates.

Note: The proposed EMD/PBE method is not the only approach for particle size distribution comparison. Applicants may propose a scientifically justified alternative statistical approach.

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

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[a] For the most recent version of a guidance, refer to the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[b] For the most recent version of a product-specific guidance, refer to the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.

[4] Yossi Rubner, Carlo Tomasi and Leonidas J. Guibas. The earth mover's distance as a metric for image retrieval. International Journal of Computer Vision, 40(2):99-121, 2000.