Contains Nonbinding Recommendations

Draft Guidance on Barium Sulfate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Barium sulfate

Dosage Form; Route: For suspension; oral

Strength: 98% (334 g / bottle)

Recommended Studies: In vitro study

Additional Comments:

- The proposed test drug product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).
- Test and reference drug products should have comparable physicochemical properties, including but not limited to, viscosity across a range of shear rates (e.g., low, medium, and high), and pH.
- The comparative analyses should be performed on at least three lots of the test drug product and three lots of the reference drug product.

In Vitro Study: Particle Size Distribution

Parameters to measure: Particle Size Distribution

Bioequivalence based on (95% upper confidence bound): The shape of the particle size distribution of this product 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 BE.

Instead, the equivalence between the test and RLD formulations in the shape of the particle size distribution (such as the presence of multiple peaks) should be demonstrated by a method proposed by the sponsor. A statistical metric is preferred to assess the difference (e.g., in terms of distance) between the shapes of distribution profiles. One suggested approach is the earth mover's distance (EMD) method[3], which computes the minimal cost needed to transform one distribution into the other using an optimization algorithm. An average profile of all RLD

[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] 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.

samples (i.e., RLD center) is calculated and served as the reference profile to compute the distance between a RLD or a test sample to the RLD center. After obtaining the profile distances between each RLD sample and the RLD average ('RLD' – 'RLD center' distance), and the profile distances between each test sample and the RLD average ('TEST' – 'RLD center' distance), a statistical metric should be employed to quantify the difference between the two categories of distances. One suggested method is PBE analysis.[4,5] Sponsors are also referred to the Guidance on Budesonide inhalation suspension for additional information regarding PBE. To properly account for variability of the reference product and to achieve adequate power, a sufficient number of samples and replicates should be used.

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

[4] FDA Guidance for Industry – Statistical Approaches to Establishing Bioequivalence. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070244.pdf.

[5] Please note that the proposed EMD/PBE method may not be the only approach for particle size distribution comparison. Sponsors may also propose their own statistical approach.