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Draft Guidance on Penicillin G Benzathine

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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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This is a new draft product-specific guidance for industry on generic penicillin G benzathine.

Active Ingredient: Penicillin G benzathine

Dosage Form; Route: Injectable; injection

Recommended Studies: Two options: in vitro or in vivo

I. In vitro option:

To qualify for the in vitro option for this drug product, 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 (Q1/Q2).

[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 characterizations of the test and Reference Standard (RS) products. Comparative analysis should be performed on at least three batches of both the test[3] and RS products and should include:
    - Crystalline shape and morphology of penicillin G benzathine
    - pH, osmolality, viscosity over a range of shear rates, specific gravity
    - Drug particle size and size distribution. The particle size distribution should be compared using the population bioequivalence (PBE) statistical analysis procedure (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 size distribution should also be submitted for all samples tested. Please refer to the Guidance on Budesonide inhalation suspension for additional information regarding PBE

3. Acceptable comparative release of penicillin G benzathine from the test and RS products.

II. In vivo option:

Type of study: Bioequivalence study with pharmacokinetic (PK) endpoints
Design: Single-dose, parallel, in-vivo
Strength: Single-dose of 1mL (600,000 units/mL)
Subjects: Males and non-pregnant, non-lactating females, general population

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Analyte to measure: Penicillin G in plasma

Bioequivalence based on (90% CI): Penicillin G

Waiver request of in vivo testing: Not applicable

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