This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

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).

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\(^1\) 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.

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*Recommended Mar 2021*
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 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

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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The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.