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Draft Guidance on Paclitaxel

August 2021

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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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In September 2012, FDA issued a draft product-specific guidance for industry on generic paclitaxel. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient: Paclitaxel

Dosage Form; Route: For suspension; IV (infusion)

Recommended Studies: Two studies

1. Type of study: Bioequivalence study with pharmacokinetic (PK) endpoints
   Design: Single-dose, two-way crossover, in vivo
   Strength: 100 mg/vial (260 mg/m^2 dose administered in 30 minutes)
   Subjects: Breast cancer patients after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy
   Additional comments:

   a. Submission of a Bio Investigational New Drug Application (Bio-IND) is required prior to the conduct of a bioequivalence in vivo study for a cytotoxic drug product such as paclitaxel (see 21 CFR § 320.31).

b. The pivotal bioequivalence study should be conducted using test product manufactured on the proposed commercial scale.

c. If the patient's health status prevents fasting, the sponsor may provide a non-high-fat diet during the proposed study provided that both study periods are conducted under same conditions.

d. If the patient's health status necessitates a dose reduction or any change in the recommended 260 mg/m^2 dose administered in 30 minutes, they are to be withdrawn from the study.

e. Patients must have baseline neutrophil counts ≥ 1500 cells/mm^3; Patients who experience a severe hypersensitivity reaction to paclitaxel should not be rechallenged with the drug; Frequent peripheral blood counts are to be performed; Prior therapy should have included an anthracycline unless clinically contraindicated; Female patients should be nonpregnant and non-lactating; Women of childbearing potential should be advised to avoid becoming pregnant while receiving paclitaxel injectable suspension, and men should be advised not to father a child while receiving paclitaxel injectable suspension.

f. The use of antiemetic prophylaxis is acceptable provided that the patient receives the same prophylaxis in both periods of the study.

Analytes to measure: Unbound and total paclitaxel in plasma

Bioequivalence based on (90% CI): AUC and Cmax for unbound and total paclitaxel

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2. Type of study: In vitro particle size distribution
Design: In vitro bioequivalence study on at least three lots of both test and reference products
Strength: 100 mg/vial
Additional comments: None

Parameters to measure: D_{10}, D_{50}, and D_{90}

Bioequivalence based on (95% upper confidence bound): Population bioequivalence based on D_{50} and SPAN $[(D_{90}-D_{10})/D_{50}]$

As per 21 CFR § 314.94(a)(9)(iii), the proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the corresponding reference listed drug product (RLD).[1] In addition, firms are recommended to obtain assurance from OGD that the test product

[1] It is recommended that human serum albumin be sourced from a CBER licensed facility and comply with USP standards and other applicable requirements.

has the same in vitro characteristics as the reference product prior to conducting any bioequivalence study for submission. Additional in vitro characterization is recommended to demonstrate the sameness between the test and reference products in terms of particle morphology, particle size, surface potential, paclitaxel crystallinity, fraction of free (in solution) and particle-bound paclitaxel and albumin in reconstituted suspension, nature of bond between paclitaxel and albumin, and in vitro release kinetics. In addition, characterization of the oligomeric status of albumin in both the albumin excipient and the final drug product is recommended. The in vitro characterization tests are recommended to be conducted on three batches of the test product and reference product. The test product batches should not be smaller than the exhibit scale, and at least one test product batch should be produced by the commercial scale process.

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Applicants are encouraged to explore methods to characterize in vitro release.

Revision History: Recommended September 2012; Revised August 2021

Unique Agency Identifier: PSG_021660