

Draft Guidance on Paclitaxel

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Paclitaxel

Form/Route: Suspension/Injectable

Recommended Studies: 2 studies

1. Type of study: Bioequivalence study with pharmacokinetic (PK) endpoints
Design: Single-dose, two-way crossover, fasting, in vivo
Strength: 100 mg/vial (260 mg/m² 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a dose reduction or any change in the recommended 260 mg/m² dose administered in 30 minutes, they are to be withdrawn from the study.
 - e. Patients must have baseline neutrophil counts ≥ 1500 cells/mm³; Patients who experience a severe hypersensitivity reaction to ABRAXANE 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 C_{max} for unbound and total paclitaxel

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: D₁₀, D₅₀, and D₉₀

Bioequivalence based on (95% CI): Population bioequivalence based on D₅₀ and span (D₉₀-D₁₀)/D₅₀ or polydispersity index

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. In addition, firms are recommended to obtain assurance from OGD that the test product has the same in-vitro characteristics as those of reference listed drug product prior to conducting any bioequivalence study for submission. Additional in vitro characterizations are 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 and bound paclitaxel or albumin in reconstituted suspension, nature of bond between paclitaxel and albumin, and in vitro release kinetics. In addition, albumin, the only excipient in the final product, is critical to the formulation. The characterization of the oligomeric status of albumin in both the albumin excipient and the final drug product is also recommended. The in vitro characterization tests are recommended to be conducted on three batches of the ANDA and RLD products (at least one ANDA batch should be produced by the commercial scale process).

Waiver request of in vivo testing: Not applicable

In Vitro Release Testing Method: The applicants are encouraged to explore methods to characterize in vitro release.