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Draft – Not for Implementation

Draft Guidance on Paclitaxel

May 2025

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Paclitaxel
Dosage Form:	Powder
Route:	Intravenous
Strength:	100 mg/vial
Recommended Studies:	One in vivo bioequivalence study with pharmacokinetic endpoints and one in vitro bioequivalence study with supportive characterization studies

One in vivo bioequivalence study with pharmacokinetic endpoints:

1. Type of study: Bioequivalence study with pharmacokinetic 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).[1]

[1] 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 (RLD). It is recommended that human serum albumin be sourced from a CBER licensed facility and comply with USP standards and other applicable requirements. Prospective applicants are recommended to obtain assurance from OGD that the test product has the same in vitro characteristics as the RS prior to conducting any in vivo bioequivalence study(ies).

b. The pivotal bioequivalence study should be conducted using test (T) 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a dose reduction or any change in the recommended 260 mg/m^2 dose administered in 30 minutes, they are to be withdrawn from the study.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 non-pregnant and non-lactating; women of childbearing potential should be advised to avoid becoming pregnant while receiving paclitaxel intravenous powder, and men should be advised not to father a child while receiving paclitaxel intravenous powder.
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): Area under the curve (AUC) and maximum concentration (C_{max}) for unbound and total paclitaxel

One in vitro bioequivalence study:

1. Type of study: In vitro particle size and size distribution
   Design: In vitro bioequivalence study on at least three lots of both T product and RS
   Strength: 100 mg/vial

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}]

One in vitro bioequivalence study with supportive characterization studies:

The comparative physicochemical characterization of the T product and the RS should be performed on at least three batches each of the T product[2] and RS, and it should include:

- Particle morphology
- Particle 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
- Oligomeric status of albumin in both the albumin excipient and the finished drug product
- In vitro release kinetics

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.

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