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Draft Guidance on Irinotecan Hydrochloride

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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 irinotecan hydrochloride.

Active Ingredient: Irinotecan hydrochloride

Dosage Form; Route: Injectable, liposomal; intravenous

Recommended Studies: Two studies: in vivo and in vitro

To be eligible for the bioequivalence studies recommended in this guidance, the test product should meet the following criteria:

1. Qualitatively (Q1)¹ and quantitatively (Q2)² the same as the Reference Listed Drug (RLD).
2. At least one batch of the Test product should be produced by the commercial scale process and be used in the in vivo bioequivalence study.

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 $\pm 5\%$ of those used in the reference product.

* If the health conditions of patients prevent fasting, the applicant can provide a non-high-fat diet during the proposed study. Alternatively, the treatment can be initiated 2 hours after a standard (non-high-fat) breakfast.

3. Equivalent liposome characteristics including state of encapsulated drug, internal environment of liposome, liposome size distribution, number of lamellar, grafted PEG at the liposome surface, electrical surface potential or charge, and in vitro leakage rates comparable to the reference standard (RS).

In vivo study:

1. Type of study: Fasting*
Design: Single-dose, two-way crossover in vivo
Strength: EQ 43 mg Base/10 mL
Dose: 70 mg/m² intravenous infusion over 90 minutes
Subjects: Patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy and who are already receiving or scheduled to start therapy with the reference product in combination with fluorouracil and leucovorin.
Additional comments:
 1. Irinotecan is a cytotoxic drug. Therefore, submission of a Bio Investigational New Drug (Bio-IND) is required prior to conducting a bioequivalence study of irinotecan liposome injection to ensure the safety of human test subjects (see 21CFR § 320.31).
 2. The two arms of the crossover study are to be conducted on two of the days when patients are scheduled to receive their usual therapy so that the treatment regimen is not altered or delayed.
 3. The established care treatment regimen should not be altered except to randomizing patients to the test or reference therapy on the specified dosing days.
 4. Given that the dosing frequency is every two weeks, two consecutive treatment cycles should be used for the two treatment periods.
 5. Any concomitant medications must be exactly the same in both periods of the study.

Inclusion Criteria (the applicant may add additional criteria):

1. Male or non-pregnant, non-lactating female patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy
2. Age \geq 18 years
3. Karnofsky Performance Status (KPS) \geq 70
4. Adequate hepatic function (serum total bilirubin within institutional normal range, albumin level 3.0 g/dL etc.)
5. Adequate renal function

Exclusion Criteria (the applicant may add additional criteria):

1. Patients with expected changes in concomitant medications that can potentially affect the pharmacokinetics of irinotecan.
2. Patients with any evidence of bone marrow depression (e.g., absolute neutrophil count $<$ 1500/mm³)
3. Clinically significant gastrointestinal disorders

4. New York Heart Association (NYHA) Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure
5. Active infection or uncontrolled fever
6. Known hypersensitivity to conventional formulation of irinotecan hydrochloride or the components of the RLD or reference standard

Analytes to measure: Liposome encapsulated irinotecan and free irinotecan.

Bioequivalence based on (90% CI): AUC and C_{\max} for liposome encapsulated irinotecan. AUC and C_{\max} of free irinotecan serve as supportive data.

In vitro study:

1. Type of study: Liposome size distribution
Design: In vitro bioequivalence study on at least three batches of both Test and RS products

Equivalence based on (95% upper confidence bound): The ANDA applicant should select an appropriate particle size analysis method to determine the particle size distributions of both the Test and RS products. The number of vials studied should not be fewer than 30 for each of the Test and Reference products (i.e., no fewer than 10 from each of the three batches). Population bioequivalence (PBE) based on D50 and SPAN [i.e. (D90-D10)/D50] or alternatively on the harmonic intensity-weighted average particle diameter (z-average) and polydispersity index derived from cumulant analysis of the size intensity distribution. Refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension*^a for additional information regarding PBE.

Additional comments:

Same drug product composition:

Per 21 CFR § 314.94 (a) (9) (iii), as a parenteral drug product, a generic irinotecan HCl liposome injection must be Q1/Q2 the same as the RLD, except for differences in buffers, preservatives and antioxidants provided that the applicant identifies and characterizes these differences and demonstrates that the differences do not impact the safety/efficacy profile of the drug product. Currently, FDA has no recommendations for the type of studies that would be needed to demonstrate that differences in buffers, preservatives and antioxidants do not impact the safety/efficacy profile of the drug product.

Lipid excipients are critical in the liposome formulation. ANDA applicants should obtain lipids from the same category of synthesis route (natural or synthetic) as found in the RLD or reference standard. Information concerning the chemistry, manufacturing and control of the lipid components should be provided as per the recommendations in the most recent version of the FDA guidance for industry: *Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation*.^b ANDA applicants should have specification on lipid excipients that are similar to those used to produce the RLD or

reference standard. Additional comparative characterization (beyond meeting specifications) of lipid excipients including the distribution of the molecular species should be provided.

ANDA applicants are expected to use the same loading agent as the RLD product. Multiple batches of the RLD product may be analyzed, and the results should be used to justify the amount of drug loading/entrapment agent added in the manufacturing process and levels of its associated components in the finished product.

ANDA applicants should use an active loading process and identify critical material attributes and critical process parameters, and guide process optimization. It is recommended to identify the critical process parameters and critical material attributes by evaluating the sensitivity of liposome characteristics to changes in process parameters and attributes. The optimal values of critical process parameters should be selected based on comparison of resulting liposome characteristics to those of the RS product.

Equivalent liposome characteristics:

Additional in vitro characterizations are recommended to demonstrate the sameness between the Test and Reference products in terms of liposome composition, state of encapsulated drug, internal liposome environment, liposome morphology and number of lamellae, lipid bilayer phase transitions, grafted PEG at the liposome surface, electrical surface potential or zeta-potential, and in vitro leakage rates. The comparative physicochemical characterization studies should be conducted on at least three batches of the Test and the RS products, at least one Test batch should be produced by the commercial scale process and used in the in vivo bioequivalence study.

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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^a For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at <https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm>.

^b For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.