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Draft Guidance on Cytarabine; Daunorubicin

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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 cytarabine; daunorubicin.

Active Ingredient:	Cytarabine; Daunorubicin
Dosage Form; Route:	Powder; intravenous
Recommended Studies:	One in vivo bioequivalence study with pharmacokinetic endpoints, and one in vitro bioequivalence study with supportive characterization studies

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).

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.

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 studies.
3. Equivalent liposome characteristics including liposome composition, state of encapsulated drug, internal environment of liposome, lamellarity, electrical surface potential or charge, and in vitro leakage rates comparable to the Reference Standard (RS) product.

One in vivo bioequivalence study with pharmacokinetic endpoints:

1. Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
Design: Fasting³, parallel
Strength: 100 mg cytarabine; 44 mg daunorubicin
Dose: Daunorubicin 44 mg/m² and cytarabine 100 mg/m²
Subjects: Adult patients with newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) who are already scheduled to start liposomal combination of cytarabine and daunorubicin therapy per RLD labeling.
Additional comments:
 1. Conduct the pivotal bioequivalence study using the test product produced by the proposed commercial scale manufacturing process.
 2. Daunorubicin and cytarabine are cytotoxic drugs. Therefore, a Bio-IND is required for bioequivalence studies of a liposomal combination of daunorubicin and cytarabine injection to ensure the safety of human test subjects.
 3. Calculate the dose based on individual patient's body surface area (BSA).
 4. A full course of liposomal daunorubicin and cytarabine injection consists of 1-2 cycles of induction and up to 2 cycles of consolidation at the dose and schedule recommended on the RLD label.
 5. Perform PK study during the first cycle of induction.
 6. For the first cycle of induction, the recommended dose is daunorubicin 44 mg/m² and cytarabine 100 mg/m² administered via intravenous infusion over 90 minutes on days 1, 3, and 5.
 7. Collect PK samples on days 1 and 5 of the first cycle of induction.
 8. Do not alter the standard of care treatment regimen.
 9. Obtain a baseline electrocardiogram and document baseline cardiac function by multi-gated radionuclide angiography (MUGA) scan or echocardiography.
 10. Document renal and hepatic functions at baseline.
 11. Any patient with weight changes during the study requiring a $\pm 5\%$ dose adjustment must be discontinued from the study and excluded from the analysis.

Exclusion criteria:

1. Patients with prior anthracycline exposure that would result in a total lifetime exposure of 550 mg/m² or more after two cycles of induction and two cycles of consolidation.

³ If the health conditions of patients prevent fasting, the sponsor 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.

2. Patients with clinically significant or unstable cardiac disease.
3. Severe renal impairment (CL_{CR} 15 mL/min to 29 mL/min) or end-stage renal disease.
4. Patients with significantly impaired hepatic function defined as bilirubin level greater than 3 mg/dL.
5. Patients with Wilson's disease or other copper related metabolic disorder.
6. Patients who have a history of hypersensitivity reactions to daunorubicin, cytarabine or any components of the RLD should not be included in the study.
7. Female patients who are pregnant or lactating.
8. Patients who are < 18 years or > 75 years of age.

Analytes to measure: Free daunorubicin, free cytarabine, liposome encapsulated daunorubicin, liposome encapsulated cytarabine in plasma.

Bioequivalence based on (90% CI): AUC and C_{max} for liposome encapsulated daunorubicin and liposome encapsulated cytarabine of samples collected on day 5 of the first cycle of induction. Submit AUC and C_{max} of free daunorubicin and free cytarabine of samples collected on day 5 of the first cycle of induction as supportive data.

One in vitro bioequivalence study with supportive characterization studies:

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

Parameters to measure: D10, D50, D90; or z -average diameter and polydispersity index (PDI).

Bioequivalence based on (95% upper confidence bound): Population Bioequivalence (PBE) approach on D50 and SPAN [i.e. (D90-D10)/D50], or alternatively on the harmonic intensity-weighted average particle diameter (z -average) and PDI 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* (NDA 020929)^a for additional information regarding PBE.

Additional information:

Same drug product composition:

Per 21 CFR § 314.94 (a)(9)(iii), as a parenteral drug product, a generic daunorubicin and cytarabine liposome injection must be Q1 and Q2 the same as the RLD, except 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 affect 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.

Information concerning the chemistry, manufacturing and control of the lipid components should be provided as per the recommendations the most recent version of the FDA guidance for industry on *Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation*.^b ANDA applicants should have specifications on lipid excipients that are comparable to the lipid excipients used to produce the RLD. Provide additional comparative characterization (beyond meeting specifications) of lipid excipients, including the distribution of the molecular species.

Equivalent liposome characteristics:

Additional in vitro characterizations are recommended to demonstrate the sameness between the Test and Reference products in terms of liposome composition, contents of free and encapsulated drug, state of encapsulated drug, internal liposome environment, liposome morphology and number of lamellae, lipid bilayer phase transitions, 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: 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 the Test and Reference products. Specifications will be determined upon review of the ANDA.

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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>.