

Draft Guidance on Azacitidine

May 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 November 2019, FDA issued a draft product-specific guidance for industry on generic azacitidine. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient: Azacitidine

Dosage Form; Route: Powder; intravenous, subcutaneous

Strength: 100 mg/vial

Additional comments: The proposed drug product should be qualitatively (Q1)¹ and quantitatively (Q2)² the same as the Reference Listed Drug (RLD). Bioequivalence may be established based on comparative in vitro testing of three batches, if available, of both the test product and designated Reference Standard (RS) product.

¹ Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD 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 RLD product.

The criteria of in vitro evidence that the test product, when reconstituted as a suspension for subcutaneous administration, demonstrates bioequivalence to the RLD product are:

1. **Physicochemical Characteristics.** Evidence that test and RS products have comparable physicochemical properties, such as viscosity, osmolality, and pH.
2. **Particle Morphology.** It is recommended that a suitable method for qualitative determination be used to allow observation of particles in the size range in which azacitidine particles are expected to fall. Representative micrographs should be submitted. These data are supportive, and formal statistical testing is not applicable.
3. **In Vitro Drug Release.** Acceptable comparative in vitro drug release of azacitidine from the test and RS formulations. It is recommended that the developed in vitro drug release method to support bioequivalence be based on USP Apparatus 4 (flow-through cell) and be appropriately designed to measure the rapid solubility of the product.
4. **Particle Size Distribution.** Particle size distribution should be compared using the population bioequivalence (PBE) statistical procedure (95% upper confidence bound) based on D_{50} and SPAN [i.e., $(D_{90}-D_{10})/D_{50}$]. Refer to the product-specific *Guidance on Budesonide* inhalation suspension for additional information regarding PBE.

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

Revision History: Recommended August 2008; Revised July 2009, September 2012, April 2017, November 2019, May 2021

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