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Draft Guidance on Midazolam Hydrochloride

August 2023

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Active Ingredient:	Midazolam hydrochloride
Dosage Form:	Solution
Route:	Intramuscular
Strength:	EQ 10 mg Base/0.7 mL
Recommended Studies:	Request for waiver of in vivo bioequivalence study requirements; and in vitro bioequivalence studies with supportive characterization studies on the test and reference auto-injectors containing midazolam hydrochloride

The reference listed drug (RLD) is a drug-device combination product[1] in which the drug constituent part consists of a parenteral solution and the device constituent part consists of a prefilled cartridge that co-packaged with an auto-injector. This guidance provides recommendations for developing generic midazolam hydrochloride intramuscular solution (auto-injector) containing midazolam hydrochloride as the active pharmaceutical ingredient (API). It includes recommendations for requesting waiver of in vivo bioequivalence study requirements, and in vitro bioequivalence studies with supportive characterization studies on the test and reference auto-injectors containing midazolam hydrochloride.

[1] See 21 CFR 3.2(e)(1).

Waiver of in vivo bioequivalence study requirements:

To qualify for a waiver of in vivo bioequivalence studies on the basis that bioequivalence is self-evident under 21 CFR 320.22(b), a generic midazolam hydrochloride EQ 10 mg Base/0.7 mL product must be qualitatively (Q1)[2] and quantitatively (Q2)[3] the same as the RLD.

An applicant may seek approval of a drug product intended for parenteral use that differs from the RLD in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.[4]

In vitro bioequivalence studies with supportive characterization studies on the test and reference auto-injectors containing midazolam hydrochloride:

FDA recommends that the following in vitro studies be conducted with the test and reference auto-injectors containing midazolam hydrochloride.

Supportive characterization studies:

1. Type of study: Ejection time
   Design: The ejection time test should be performed to determine the time to eject the volume of fluid out of the device.

2. Type of study: Trigger force
   Design: The trigger force test should be performed to determine the force required to activate the device.

In vitro bioequivalence studies:

1. Type of study: Delivered volume
   Design: The delivered volume test should be performed to determine the volume of fluid ejected out of the device.
   Equivalence based on: Population bioequivalence (PBE)[5] analysis of delivered volume.

2. Type of study: Extended needle length
   Design: The extended needle length test should be performed to determine the needle length that extends out of the device after ejection of the volume of fluid.
   Equivalence based on: PBE analysis of extended needle length.

[2] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product.
[3] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test products are within ±5% of those used in the RLD product.
[4] 21 CFR 314.94(a)(9)(iii).
[5] Refer to the product-specific guidance for Budesonide Inhalation Suspension for relevant principles regarding population bioequivalence (PBE) analysis procedures.

3. Type of study: Needle integrity post-injection
Design: The needle integrity post-injection test should be performed to determine the integrity of the needle after injection.
Equivalence based on: (i) ability to trigger the injection at the injection speed and at the angle of incidence, (ii) ability of the needle to penetrate the material, and (iii) integrity of the needle post-injection.

Additional information:

Device:
The RLD is presented in an auto-injector. The auto-injector is the device constituent part.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the test device including:

- A single-use, single-dose format of the auto-injector device
- Needle gauge and length

User interface assessment:
An abbreviated new drug application for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.