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Draft Guidance on Naloxone Hydrochloride

May 2023

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

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Active Ingredient:	Naloxone hydrochloride
Dosage Form; Routes:	Solution; Intramuscular, Subcutaneous
Strength:	10 mg/0.4 mL
Recommended Studies:	Request for waiver of in vivo bioequivalence study requirements; and in vitro bioequivalence studies with supportive comparative studies on the test and reference auto-injectors containing naloxone hydrochloride

Waiver of in vivo bioequivalence study requirements:

In vivo bioequivalence study may be waived on the basis that bioequivalence is self-evident under 21 CFR 320.22(b), for a generic naloxone hydrochloride injection product that is qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).

An applicant may seek approval of a test product 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 test product.[3]

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference listed drug.
[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 listed drug.
[3] 21 CFR 314.94(a)(9)(iii)

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

FDA recommends that the following in vitro studies be conducted with the test and reference auto-injectors containing naloxone 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) analysis of delivered volume.
   Please refer to the most recent version of the FDA product-specific guidance on *Budesonide inhalation suspension*[a] for additional information regarding PBE.

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.

Additional information:

Device:
The RLD is presented as a pre-filled auto-injector that 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 (T) device including:

- Single-use, single-dose design, fixed dose
- Pressure activated
- Needle gauge and extension length
- Automatic needle safety system

User interface assessment:
An abbreviated new drug application (ANDA) 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 web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.