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Draft Guidance on Epinephrine

December 2025

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Active Ingredient:	Epinephrine
Dosage Form:	Injectable
Routes:	Intramuscular, subcutaneous
Strengths:	0.15 mg/delivery, 0.3 mg/delivery
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 epinephrine

Request for waiver of in vivo bioequivalence study requirements:

To qualify for a waiver from the requirement for submission of evidence of in vivo bioequivalence on the basis that bioequivalence is self-evident under 21 CFR 320.22(b)(1), a generic epinephrine injection product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).

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

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

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

For test product and reference standard (RS) with an autoinjector presentation, the FDA recommends that prospective applicants conduct the following studies for both strengths of the test product and RS. For each strength, use three or more batches of the test product and three or more batches of RS, with no fewer than 10 units from each batch. The three batches of the test product should be prepared from three different batches of the same critical device components. The test product should consist of the final device constituent part and final drug constituent formulation intended to be marketed. The manufacturing process for the test batches should be reflective of the manufacturing process to be utilized for the commercial batch. Test product and RS should be studied under the same instrumental conditions. Method validation should be performed using the RS, and the lot number(s) for the RS used for the validation should be provided. Applicants should provide all relevant standard procedures and validation data for each of the in vitro bioequivalence studies listed below.

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 test and reference devices.
   Equivalence based on: Population bioequivalence (PBE) analysis of delivered volume
   Additional comments: Refer to the section of "Recommendation Related to the PBE Statistical Analysis Procedure" in the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929) [a] for additional information regarding PBE computation.[4]

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 test and reference devices after ejection of the volume of fluid.
   Equivalence based on: PBE analysis of extended needle length.

Supportive comparative 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 test and reference devices.

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

[4] The recommendation on collecting data on different life stages is NOT applicable.

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 through materials of different penetration challenge at different angles of incidence. The purpose of this test is to determine the ability of the proposed test product to trigger and penetrate when utilized at different angles of incidence and against different cloth materials, and compare these attributes to the RS. The test should include at least three materials of different penetration challenges (material attributes include, e.g., material type, density, and thickness) and at least three angles of incidence. The choice of materials and angles should consider the labeling and Instruction for Use of the RS. All choices should be adequately justified in the abbreviated new drug application (ANDA) submission.

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:

- Single-use, single-dose format
- Inspection window
- Needle gauge and length
- Automatic needle safety system
- Needle-free, drug-free trainer device for repeated practice use

User interface assessment:
An 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.* [b]

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[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm
[b] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents