

Draft Guidance on Epinephrine

November 2025

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Active Ingredient:	Epinephrine
Dosage Form:	Solution
Routes:	Intramuscular, subcutaneous
Strengths:	0.3 mg/0.3 mL (0.3 mg/0.3 mL), 0.15 mg/0.3 mL (0.15 mg/0.3 mL)
Recommended Studies:	Request for waiver of in vivo bioequivalence study requirements; and one in vitro bioequivalence studies with supportive comparative characterization studies on the test and reference prefilled syringe device containing epinephrine

Request for waiver of in vivo bioequivalence study requirements:

To qualify for a waiver of in vivo bioequivalence study requirement 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

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.

provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product³.

One in vitro bioequivalence study with supportive comparative characterization studies on the test and reference prefilled syringe device containing epinephrine:

FDA recommends that prospective applicants conduct the following studies using three or more batches of the test product and three or more batches of the RLD, 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 and RLD should be studied under the same instrumental conditions. Method validation should be performed using the RLD, and the lot number(s) for the RLD 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.

One in vitro bioequivalence study:

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 RLD 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

Supportive comparative characterization studies:

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

³ 21 CFR 314.94(a)(9)(iii).

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

2. 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 RLD. 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 RLD. All choices should be adequately justified in the abbreviated new drug application (ANDA) submission.

Additional information:

Device:

The RLD is presented in a prefilled syringe with a staked needle, attached needle guard system and additional components. The syringe with the needle, needle guard system and the additional components constitute 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:

- Device-controlled, single-dose, fixed-dose, prefilled syringe format
- Needle gauge and length
- Needle guard system
- Tactile, audible, and visual feedback

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>