

Draft Guidance on Epinephrine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

Active Ingredient: Epinephrine

Dosage Form; Route: Injectable; intramuscular, subcutaneous

Strengths: 0.3 mg/delivery
0.15 mg/delivery

Overview:

The reference (R) product is a drug-device combination product¹ in which the drug constituent part consists of a parenteral solution and the device constituent part consists of an auto-injector. FDA recommends the following criteria be met for the proposed test (T) product with respect to formulation and in vitro studies, in which case an in vivo bioequivalence (BE) study will likely not be necessary.

Formulation:

FDA recommends that the T formulation be qualitatively (Q1)² and quantitatively (Q2)³ the same as the R formulation.

In Vitro Studies:

FDA recommends that the following in vitro studies be conducted with the T and R auto-injectors containing epinephrine.

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)⁴ analysis of delivered volume.

¹ See 21 CFR 3.2(e)(1).

² Q₁ (qualitative sameness) means that the T formulation uses the same inactive ingredient(s) as the R formulation.

³ Q₂ (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T formulation are within ± 5% of those used in the R formulation.

⁴ Refer to the product-specific recommendation for Budesonide Inhalation Suspension for relevant principles regarding population bioequivalence (PBE) analysis procedures.

2. 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.
Equivalence based on: PBE analysis of ejection time.
3. Type of study: Trigger force
Design: The trigger force test should be performed to determine the force required to activate the device.
Equivalence based on: PBE analysis of trigger force.
4. 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.
5. 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 T product to trigger and penetrate when utilized at different angles of incidence and against different cloth materials, and compare these attributes to the R product. 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 of the R product, which includes the following language: “Your auto-injector is designed to work through clothing” and “Place the orange tip against the middle of the outer thigh (upper leg) at a right angle (perpendicular) to the thigh.” All choices should be adequately justified in the ANDA submission.
Equivalence based on: Qualitative comparison between T and R devices with respect to (i) ability to trigger the injection at the angle of incidence, (ii) ability of the needle to penetrate the material, and (iii) integrity of the needle post-injection

In certain circumstances, FDA may request information and/or comparative data including, but not limited to, the following: residual volume, injection force, break force, needle cover lockout force and ability to lockout needle cover, break loose force, and extrusion force.

Additional comments:

FDA recommends that applicants conduct the above in vitro studies for both strengths of the T and R products. For each strength, use at least three batches each of the T and R products, with no fewer than 10 units from each batch. A single batch of solution can be split-filled into three equal size sub-lots of product. The three batches of the T product should be prepared from three different batches of the same critical device components. The T product should consist of the final device constituent part and final drug constituent formulation intended to be marketed. The manufacturing process for the T batches should be reflective of the manufacturing process to be utilized for the commercial batch. T and R products should be studied under the same instrumental conditions. Method validation should be performed using the R product, and the lot

number(s) for the R products 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 above.

Device:

FDA recommends sponsors consider the following characteristics of the R product in designing the T product:

- Single-use, single-dose, fixed-dose, pre-filled auto-injector device.
- External operating principles and external critical design attributes of the R product.
- Size and shape of the R product.

FDA recommends that sponsors consider the following characteristics of the T product in designing the T trainer:

- External operating principles and external critical design attributes of the T product.
- Size and shape of the T product.

Prior to product development or submission of an ANDA, FDA strongly encourages applicants to submit to OGD via controlled correspondence and/or pre-ANDA meeting request, the following:

- Working model(s) of the proposed T product and T trainer.
- Sample(s) of the R product and R trainer.
- In certain circumstances, FDA may request additional information and/or data, as appropriate.

In addition, in vitro studies should be conducted to support the functionality, accuracy, and robustness⁵ of the proposed T product.

⁵ Refer to the guidance for industry and FDA staff “Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products” (June 2013) for relevant principles regarding studies to support auto-injector devices.