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Draft Guidance on Epinephrine

August 2023

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Active Ingredient:	Epinephrine
Dosage Form:	Solution
Routes:	Intramuscular, Subcutaneous
Strengths:	EQ 0.1 mg/delivery, EQ 0.15 mg/delivery, EQ 0.3 mg/delivery
Recommended Studies:	Request for wavier of in vivo bioequivalence study requirements and, for test and reference products with an auto-injector presentation, two in vitro bioequivalence studies with supportive comparative studies

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 epinephrine injectable product is qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD) formulation.

An applicant may seek approval of a drug product that differs from the RLD in preservative, buffer, or antioxidant if 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 T formulation uses the same inactive ingredient(s) as the R formulation
[2] 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.
[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 (T) and reference (R) product with an autoinjector presentation, the FDA recommends that prospective applicants conduct the following studies. For each strength, use three or more batches of the T product and three or more batches of R product, with no fewer than 10 units from each batch. 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 below.

Two in vitro bioequivalence studies:

1. Type of study: Delivered volume
   Design: The delivered volume test should be performed to compare the volume of fluid ejected out of the T and R devices
   Equivalence based on: Population Bioequivalence (PBE) analysis of delivered volume
   Additional comments: Refer to the most recent version of FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929) [a] for additional information regarding PBE.

2. Type of study: Extended needle length
   Design: The extended needle length test should be performed to compare the needle length that extends out of the T and R 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 compare the time to eject the volume of fluid out of T and R devices

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

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 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 end of product 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 abbreviated new drug application (ANDA) submission.

Additional information:

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

- Single-use, single-dose design, fixed dose
- Pressure activated
- Automatic needle safety system
- Visual cues and audible prompt

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

- Pressure activated
- Visual cues and audible prompt

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]

Document History: Recommended August 2023

Unique Agency Identifier: PSG_201739

[a] For the most recent version of the 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.