Contains Nonbinding Recommendations

Draft Guidance on Epinephrine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Strength: 0.3 mg / 0.3 mL

Overview:

The reference (R) product is a drug-device combination product[1] in which the drug constituent part consists of a parenteral solution and the device constituent part consists of a pre-filled syringe for manual injection. FDA recommends that 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 pre-filled syringe devices 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. The test should include at least three different injection speeds. The choice of injection speeds should consider the labeling of the R product, which includes the following language: “Push the plunger all the way down until it clicks and hold for 2 seconds”. All choices should be adequately justified in the ANDA submission.
   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.

2. Type of study: Trigger force
   Design: The trigger force test should be performed to determine the force required to activate the device. The test should include at least three different injection speeds. The choice of injection speeds should consider the labeling of the R product, which includes the following language: "Push the plunger all the way down until it clicks and hold for 2 seconds". All choices should be adequately justified in the ANDA submission.
   Equivalence based on: PBE analysis of trigger force.

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 injection speeds and 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 injection speeds, 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), at least three injection speeds and at least three angles of incidence. The choice of materials, injection speeds and angles should consider the labeling of the R product, which includes the following language: "Inject intramuscularly or subcutaneously into the anterolateral aspect of the thigh with the needle facing downwards" and "It can be injected through clothing if necessary" and "Push the plunger all the way down until it clicks and hold for 2 seconds." 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 injection speed and 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 loose force, extrusion force, and needle guard function.

Additional comments:
FDA recommends that applicants conduct the above in vitro studies using at least three batches each of the T and R products, with no fewer than 10 units from each batch. FDA recommends that three primary stability batches be also used to demonstrate in vitro BE, if appropriate. 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, if feasible. 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 in the ANDA submission. Applicants should provide all relevant standard procedures and validation data for each of the in vitro BE studies listed above.

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

Device:

Applicants should refer to the FDA Guidance for Industry entitled, *"Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA"* (January 2017), which provides the Agency's current thinking on the identification and assessment of any differences in the design of the user interface for a proposed generic drug-device combination product when compared to its RLD.

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

- Single-use, single-dose, fixed-dose, pre-filled syringe device for manual injection
- External operating principles and external critical design attributes
- Size and shape

In addition, in vitro studies should be conducted to support the functionality, accuracy, and robustness[5,6] 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 injector devices.

[6] Refer to the Guidance for Industry and FDA staff *"Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4"* (April 2013) for relevant principles regarding studies to support pre-filled syringe devices.