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Draft Guidance on Glucagon

August 2023

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Active Ingredient:	Glucagon
Dosage Form:	Solution
Route:	Subcutaneous
Strengths:	0.5 mg/0.1 mL, 1 mg/0.2 mL
Recommended Studies:	Comparative characterization studies to support active pharmaceutical ingredient (API) sameness and request for waiver of in vivo bioequivalence study requirements. For test and reference products with an auto-injector presentation two in vitro bioequivalence studies on delivered volume and extended needle length; and supportive characterization studies on trigger force and ejection time.

Recommendations to support API Sameness and Impurity Assessment:

In addition to ensuring API sameness (i.e., same primary sequence and physicochemical properties) for the drug substance, it is recommended to conduct the following comparative analyses of the proposed generic glucagon and the reference listed drug (RLD) product on no less than three batches of the proposed drug product tested on or near release and at the end of the proposed shelf life and no less than three batches of the RLD aged prior to expiry, after aging under conditions consistent with the label storage conditions:

1. Secondary structure
2. Oligomer/aggregation states: oligomer/aggregation propensity and the nature of the aggregates formed for the proposed product should be similar to that of the RLD

3. Biological activities[1]
4. API-related impurity profile comparison: new impurities found in the proposed generic drug product but not in the RLD and impurities found at a significantly higher level in the proposed generic drug product than in the RLD, should be identified. If upon Agency assessment, an impurity is identified that has the potential to increase the immunogenicity risk, further immunogenicity assessments or studies may be required
5. Comparative study demonstrating comparable innate immune response risk of the proposed product and RLD

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 glucagon injection product that is qualitatively (Q1)[2] and quantitatively (Q2)[3] the same as the RLD.

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.[4]

Two in vitro bioequivalence studies with supportive comparative studies on the test and reference auto-injectors containing glucagon:

FDA recommends that the following in vitro studies be conducted with the test and reference auto-injectors containing glucagon.

Two 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 device.
   Equivalence based on: Population bioequivalence (PBE) analysis of delivered volume.
   Please refer to the most recent version of the 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 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.

[1] Applicant may provide justification for not conducting biological assays as part of the comparative analyses if there is evidence that the structure of the API peptide would not interfere with the functional activity.
[2] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference list drug product.
[3] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ± 5% of those used in the reference listed product.
[4] 21CFR 314.94(a)(9)(iii)

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 device.

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

Additional information:

Device:
The RLD has three different presentations: (1) an auto-injector, (2) a pre-filled syringe, or (3) a kit that consists of a vial of drug co-packaged with a syringe with staked needle. The auto-injector, pre-filled syringe, and co-packaged syringe with needle are the device constituent parts for these presentations respectively.

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:

1. Auto-injector presentation:
   a. Single-dose, fixed-dose, auto-injector format capable of delivering the same dose as the RLD product
   b. Medication viewing window
   c. Needle gauge and length
2. Pre-filled syringe presentation:
   a. Single-dose, fixed-dose, prefilled syringe format with staked needle
   b. Needle gauge and length
3. Kit:
   a. Syringe with staked needle
   b. Needle gauge and length

User interface assessment:
An abbreviated new drug application 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.