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Draft – Not for Implementation

Draft Guidance on Glucagon

February 2023

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Glucagon

Dosage Form; Route: Powder; nasal

Strength: 3 mg

Recommended Studies: One in vitro bioequivalence study and one in vivo bioequivalence study with pharmacokinetic endpoints

FDA recommends the following in vitro and in vivo studies to establish bioequivalence of the test (T) and reference (R) nasal powders containing glucagon.

In vitro bioequivalence studies:

FDA recommends that applicants conduct the following in vitro bioequivalence study on samples from each of three or more batches of the T product and three or more batches of the R product, with no fewer than 10 units from each batch. FDA recommends that three primary stability batches be also used to demonstrate in vitro bioequivalence. The three batches of the T product should be manufactured from, at minimum, three different batches of the drug substance, three different batches of critical excipients, and three different batches of the device components (e.g., plunger and actuator) proposed for the final device configuration of the commercial product. The T product should consist of the final device constituent part and final drug constituent formulation intended to be marketed.

1. Type of study: Drug in Small Particles
   Design: Determination of drug in small particles is recommended to be performed using the USP <601> Apparatus 2, Apparatus 5 (flow rate of 30 L/min), or another appropriate method using a validated, highly sensitive assay. Drug in small particles should be

determined using fewest numbers of actuations (generally not exceeding 10 actuations), justified by the sensitivity of the assay, to be more reflective of individual doses.
Equivalence based on: PBE modified to be one-sided for mean comparison of drug mass in the small particles/ droplets less than 9.0 μm.
Additional comments: Drug deposition should be reported in mass units. Mass balance should be based on drug deposition on each of valve stem, actuator, adapters, induction port, any other accessories, the top stage, and all lower stages to the filter. Mass balance accountability should be reported based on the sum of all deposition sites. The total mass of drug collected on all stages and accessories is recommended to be between 85 and 115 percent of label claim on a per actuation basis.

In vivo bioequivalence study with pharmacokinetic endpoints:

1. Type of study: Fasting
Design: Single-dose, two-way crossover
Strength: 3 mg
Dose: 3 mg glucagon (one actuation)
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: (1) Subjects should adhere to the R product labeling for administration. (2) The analytical method should have sufficient sensitivity to adequately quantify the concentration of glucagon in plasma or serum.

Analyte to measure: Glucagon in plasma or serum

Since glucagon is an endogenous substance, the plasma or serum concentrations of glucagon should be corrected for baseline endogenous levels by subtracting the mean pre-dose baseline value (average of at least three pre-dose values, e.g., -1.0, -0.5, and 0 hours). Any negative values obtained from baseline correction at time 0 hour, should be designated as zero (0) and any subject with pre-dose concentration more than 5% of their C_{max} should be excluded from BE statistical analysis and the 90% confidence intervals based on the remaining subjects. Refer to the most recent version of the FDA guidance on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*[a] for additional information regarding endogenous compounds.

Equivalence based on: Baseline-corrected AUC and C_{max} for glucagon. The 90% confidence intervals for the geometric mean T/R ratios of AUC and C_{max} should fall within the limits of 80.00-125.00%.

Additional information:

Device:
The Reference Listed Drug (RLD) is presented as in a single-dose intranasal device which is the device constituent.

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 (T) device including:

- Single unit-dose design
- Metered spray
- No priming

User interface assessment:
An Abbreviated New Drug Application (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]

Immunogenicity risk assessment:

In addition to ensuring active pharmaceutical ingredient (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 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 tested prior to expiry, after aging under conditions consistent with the label storage conditions.

- 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.
- Secondary structure.
- 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.
- Comparative study demonstrating comparable innate immune response risk of the T and RLD products.
- Biological activities.[1]

Unique Agency Identifier: PSG_210134

[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[b] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatoryinformation/search-fda-guidance-documents.

[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.