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Draft Guidance on Dasiglucagon Hydrochloride

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This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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This is a new draft product-specific guidance for industry on generic dasiglucagon hydrochloride.

Active Ingredient:	Dasiglucagon hydrochloride
Dosage Form; Route:	Solution; subcutaneous
Recommended Studies:	Request for waiver of in vivo bioequivalence study requirements; and in vitro bioequivalence studies with supportive comparative studies on the test and reference auto-injectors containing dasiglucagon hydrochloride

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 dasiglucagon injection product that is qualitatively (Q1)¹ and quantitatively (Q2)² the same as the Reference Listed Drug (RLD).

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 dasiglucagon 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 test and RLD products.
- Biological activities³.

In vitro bioequivalence studies with supportive comparative studies on the test and reference auto-injectors containing dasiglucagon hydrochloride:

FDA recommends that the following in vitro studies be conducted with the test and reference autoinjectors containing dasiglucagon hydrochloride.

Supportive 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.

¹ Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference list drug product.

² Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within $\pm 5\%$ of those used in the reference listed product.

³ 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.

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.
Additional comments: 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.

Additional information:

Devices:

The reference listed drug (RLD) product is presented in a prefilled syringe and an autoinjector. The prefilled syringe and autoinjector are the device constituents.

FDA recommends that prospective applicants examine the size and shape, external critical design attributes, and external operating principles of the RLD devices when designing the test devices. In addition, the test device designs should take into consideration the following characteristics of the RLD devices:

- Single-use, single-dose, prefilled format of the syringe device
- Single-use, single-dose, fixed-dose, prefilled format of the autoinjector device

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

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^a For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at <https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm>.

^b 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>.