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Draft Guidance on Enfuvirtide

November 2024

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Active Ingredient:	Enfuvirtide
Dosage Form:	Injectable
Route:	Subcutaneous
Strength:	90 mg/vial
Recommended Studies:	Request for waiver of in vivo bioequivalence study requirements and comparative characterization studies to support active ingredient sameness

Waiver of in vivo bioequivalence study requirements:

To qualify for a waiver from submitting an in vivo bioequivalence study on the basis that bioequivalence is self-evident under 21 CFR 320.22(b)(1), a generic enfuvirtide subcutaneous injectable product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).

An applicant may seek approval of a drug product intended for parenteral use that differs from the RLD in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the test product.[3]

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ± 5% of those used in the RLD.
[3] 21 CFR 314.94(a)(9)(iii).

In addition to ensuring active ingredient sameness (i.e., same primary sequence and physiochemical properties) for the drug substance, it is recommended to conduct the following comparative analyses of the proposed generic enfuvirtide 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 product aged prior to expiry, after aging under conditions consistent with the label storage conditions.[4]

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.[5]
4. Active ingredient-related impurity profile comparison: new impurities found in the proposed generic drug product but not in the reference standard (RS) and impurities found at a significantly higher level in the proposed generic drug product than in the RS, should be identified and characterized. If upon Agency assessment, an impurity is identified that has the potential to increase the immunogenicity risk, further immunogenicity assessments or studies may be recommended.

Additional information:

Device:
The RLD is presented as a kit that consists of: vials of enfuvirtide, vials of sterile water, 3 mL reconstitution syringes with attached needle and needle guard, and 1 mL administration syringes with attached needle and needle guard. The syringes with needles and needle guards are the device constituent parts.

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:

- Single-use reconstitution syringes
- Single-use administration syringes
- Needle gauge and length
- Needle guard system

[4] Samples should be aged under conditions consistent with the worst-case label storage conditions.
[5] Applicant may provide justification for not conducting biological assays as part of the comparative analyses if there is evidence that any secondary and higher order structure of the peptide active ingredient that may be present does not contribute to the functional activity.

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*.[a]

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