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Draft Guidance on Zilucoplan Sodium

May 2025

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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:	Zilucoplan sodium
Dosage Form:	Solution
Route:	Subcutaneous
Strengths:	EQ 16.6 mg Base/0.416 mL (EQ 16.6 mg Base/0.416 mL), EQ 23 mg Base/0.574 mL (EQ 23 mg Base/0.574 mL), EQ 32.4 mg Base/0.81 mL (EQ 32.4 mg Base/0.81 mL)
Recommended Studies:	Comparative characterization studies to support active ingredient sameness and request for 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 zilucoplan sodium subcutaneous solution 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.
[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).

Comparative characterization studies to support active ingredient sameness:

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 zilucoplan sodium and the designated reference standard (RS) 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 RS aged prior to expiry, after aging under conditions consistent with the label storage conditions.[4]

1. Oligomer/aggregation states: Oligomer/aggregation propensity and the nature of the aggregates formed for the proposed product should be similar to that of the RS.
2. Active ingredient-related impurity profile comparison: New impurities found in the proposed generic drug product but not in the RS and impurities found at a significantly higher level in the proposed generic drug product than in the RS, should be identified and characterized.

Additional information:

Device:
The RLD is presented in a prefilled syringe with a staked needle and an attached needle guard system. The syringe with the needle and needle guard system is the device constituent part.

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 devices including:

- Single-dose, fixed-dose, prefilled syringe format
- Needle gauge and length
- Needle guard system

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]

Document History: Recommended May 2025

Unique Agency Identifier: PSG_216834

[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.

[4] Samples should be aged under conditions consistent with the worst-case label storage conditions.