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Draft Guidance on Pegcetacoplan

May 2024

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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:	Pegcetacoplan
Dosage Form:	Solution
Route:	Subcutaneous
Strength:	1080 mg/20 mL (54 mg/mL)
Recommended Studies:	Request for waiver of in vivo bioequivalence study requirements and comparative characterization studies to support active ingredient sameness

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 pegcetacoplan 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 reference list drug 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 reference listed product.
[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 pegcetacoplan and the designated reference standard (RS) 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 RS 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 RS.
3. Biological activities[5].
4. 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. 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.
5. Comparative study demonstrating comparable innate immune response risk of the test and RS products.

Additional information:

Device:
The RLD is presented in a single-dose vial for administration with a commercially available infusion pump with a reservoir of at least 20 mL or with the EMPAVELI on-body injector. The RLD is a drug-device combination product, and the EMPAVELI on-body injector 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 device including:

- Single-use, on-body injector format
- Dose delivery profile
- Needle gauge, length, and safety features

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*

[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.

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.