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Draft Guidance on Imetelstat Sodium

May 2026

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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:	Imetelstat sodium
Dosage Form:	Powder
Route:	Intravenous
Strengths:	EQ 47 mg Base/vial | EQ 188 mg Base/vial
Reference Listed Drug:	NDA 217779
Recommended Studies:	Comparative characterization studies to support active ingredient sameness and request for waiver of in vivo bioequivalence study requirements

Recommendations to support active ingredient sameness:
For characterization to support sameness between the test active ingredient and the active ingredient in the reference listed drug (RLD), FDA recommends that potential applicants develop and use appropriately validated orthogonal analytical methods to perform comparative testing of the test active ingredient and the active ingredient in the RLD. The comparative characterizations may be performed with active ingredient or drug product depending on the analytical methods used and the purpose of the tests. A minimum of three batches of the test active ingredient and the active ingredient from three batches of the RLD should be characterized to assess active ingredient sameness and robustness of the manufacturing process. The active ingredient sameness can be established by evaluating the equivalence of the following:

1. Nucleotide sequence, chemical structure and composition

The nucleotide sequence of the active ingredient can be controlled through each elongation cycle in the active ingredient synthesis. Due to the stereochemistry at the phosphorus chiral center of each thio-phosphoramidate linkage and the chiral center in the palmitoylated aminoglycerol linker, imetelstat contains numerous diastereomers. Reagents and reaction conditions that can impact the diastereomeric composition outcomes should be appropriately selected and adequately controlled.[1]

The test active ingredient sequence, chemical structure, diastereomeric composition, and counter ion type and quantity should be investigated and compared to those of the active ingredient in the RLD. A broad range of orthogonal analytical methods with sufficient sensitivity, discriminating and resolving power, could be used, including but not limited to the following:

a. Mass spectrometry (MS), including tandem mass spectrometry (MS/MS)
b. Nuclear magnetic resonance (NMR) spectroscopy
c. Liquid chromatography (LC)[2]
d. Duplex melting temperature (Tm) to a complementary strand
e. Flame atomic absorption spectroscopy (FAAS) or inductively coupled plasma optical emission spectroscopy/mass spectrometry (ICP-OES/MS)[3]

Approaches for demonstrating the sensitivity, discriminating and resolving power of an analytical method for diastereomeric composition analysis should be appropriately justified. For example, the sensitivity, discriminating and resolving power of an analytical method for diastereomeric composition analysis may be demonstrated through method suitability test or negative control studies on samples with Rp/Sp ratios changed in various combinations of small number of thio-phosphoramidate linkages.

2. Physicochemical properties

Comparative physicochemical characterizations of the test product and RLD should be performed to assess aggregation or higher order structures of the active ingredient in the drug product, using methods that could include, but are not limited to the following:

a. Circular dichroism (CD) spectroscopy
b. Fourier transform infrared spectroscopy (FTIR)
c. NMR including diffusion ordered spectroscopy (DOSY)
d. Dynamic light scattering (DLS)
e. Differential scanning calorimetry (DSC)
f. Size exclusion chromatography (SEC)
g. Sedimentation velocity analytical ultracentrifugation (SV-AUC)

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[1] The Rp/Sp ratio at each thio-phosphoramidate linkage following respective elongation cycle may also be measured using appropriate methods to establish a baseline to facilitate development of diastereomeric composition sameness and control strategies.

[2] Due to the very high number of potential diastereomers, multiple LC methods with orthogonal and complementary separation principles may be considered to facilitate the comparison of multiple diastereomeric composition profiles at maximized resolution.

[3] The counter ion (e.g., sodium ion) content in the test active ingredient may be evaluated and compared to the theoretical value based on the RLD labeling information.

If the sameness between the test product and RLD can be adequately demonstrated using alternative methods, applicants may submit comparative data for the test product and RLD along with appropriate justification as part of their product characterization within their ANDA. Where applicable, comprehensive method validation data should be submitted to demonstrate the adequacy (e.g., sensitivity, accuracy, precision, resolution, and discriminative power) of the selected methods in demonstrating the sameness between the test and RLD products.

Meeting recommendations: Applicants are advised to contact the FDA for questions related to generic development of imetelstat sodium including questions on immunogenicity and inflammation risk assessment, and comparability of impurities in the test product.

Waiver request of in vivo bioequivalence study: 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 imetelstat sodium intravenous powder should be qualitatively (Q1)[4] and quantitatively (Q2)[5] the same as the 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 proposed drug product.[6]

Document History: Recommended May 2026

[4] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD.
[5] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test products are within ±5% of those used in the RLD.
[6] 21 CFR 314.94(a)(9)(iii).