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Draft Guidance on Olezarsen Sodium

August 2026

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Active Ingredient:	Olezarsen sodium
Dosage Form:	Solution
Route:	Subcutaneous
Strength:	EQ 80 mg Base/0.8 mL (EQ 80 mg Base/0.8 mL)
Reference Listed Drug:	NDA 218614
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 prospective 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. Comparative characterizations may be performed with active ingredient and/or drug product depending on the analytical methods used, the purpose of the tests and other relevant factors such as drug product formulation. 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 phosphorothioate (PS) linkage, olezarsen contains numerous diastereomers. Reagents, reaction conditions, purification procedures and other factors that can impact the diastereomeric composition outcomes should be appropriately selected and adequately controlled. The Rp/Sp ratio at each PS linkage may be measured after each respective elongation cycle using appropriate analytical methods to establish a baseline to facilitate the evaluation of stereochemical consistency during manufacturing and development of control strategies.

The test active ingredient sequence, chemical structure,[1] 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 suitable analytical methods with sufficient sensitivity, discriminating and resolving power, could be used. Multiple suitable orthogonal methods should be used when a single analytical method fails to provide unambiguous results. Examples of suitable analytical methods include but are 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)
d. Electrophoresis
e. Methods for measuring duplex melting temperature (Tm) to a complementary strand
f. Flame atomic absorption spectroscopy (FAAS) or inductively coupled plasma optical emission spectroscopy/mass spectrometry (ICP-OES/MS)[2]

Approaches for demonstrating the sensitivity, discriminating and resolving power of orthogonal analytical methods 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. These studies may use multiple samples in which the Rp/Sp ratios of a small number of PS linkages are deliberately altered. Such samples may include those with Rp/Sp ratio changes at one, two or more PS linkages at a time. The positions of these PS linkages may vary across the oligonucleotide chain. For samples involving changes at two or more PS linkages, the affected linkages may be either adjacent to one another or distributed at discrete, non-consecutive positions.

[1] Including but not limited to structural and positional accuracy of any structural modifications such as PS modification and conjugation. Molecules with incorrect or incomplete structural modifications are considered impurities.
[2] 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.

Due to the large number of potential diastereomers, multiple suitable diastereomeric composition distribution profiling methods with orthogonal and/or complementary separation principles and maximized resolution may be considered to facilitate the quantitative comparison of multiple diastereomeric composition distribution profiles between the test active ingredient and the active ingredient in the RLD.[3] Such methods may include multiple LCs; combinations of LC(s) with electrophoresis method(s), and/or other suitable profiling method(s).

2. Physicochemical properties

Side-by-side comparative physicochemical characterizations of the test product and RLD should be performed, including an assessment of potential higher order structures and/or aggregates of the active ingredient in the drug product. Multiple suitable analytical methods should be used for such characterization studies, including but not limited to the following examples:

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

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 the product characterization within their abbreviated new drug application (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 product and RLD.

Meeting recommendations: Applicants are advised to contact the FDA for questions related to generic development of olezarsen 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 olezarsen sodium subcutaneous solution should be qualitatively (Q1)[4] and quantitatively (Q2)[5] the same as the RLD.

[3] This includes quantitative comparison of small segments of the distribution profiles and overall distribution profiles.
[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.

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]

Device: The RLD is presented in an autoinjector. The autoinjector 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, single-dose format
- Inspection window
- Needle gauge and length
- Automatic needle safety system

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 guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

Document History: Recommended August 2026

[a] We update guidances periodically. For the most recent version of a guidance, refer to the FDA guidance webpage at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[6] 21 CFR 314.94(a)(9)(iii).