*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

**Draft Guidance on Fitusiran Sodium**

**May 2026**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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| **Active Ingredient:** | Fitusiran sodium |
| **Dosage Form:** | Solution |
| **Route:** | Subcutaneous |
| **Strengths:** | EQ 20 mg Base/0.2 mL (EQ 20 mg Base/0.2 mL) \| EQ 50 mg Base/0.5 mL (EQ 50 mg Base/0.5 mL) |
| **Reference Listed Drug:** | NDA 219019 |
| **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 sense and antisense strands in the test active ingredient can be controlled through each elongation cycle in the active ingredient synthesis. Reagents and reaction conditions that can impact the diastereomeric composition outcomes should be appropriately selected and adequately controlled.[1] The individual sense and antisense strand intermediates should be well characterized and controlled, where applicable.

The test active ingredient sequence, chemical structure, and composition including diastereomeric composition of each individual strand in the duplex and their hybridization profile (fingerprint profile at maximized resolution using suitable analytical methods) in the duplex, P=S to P=O ratios for each individual strand, 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. Flame atomic absorption spectroscopy (FAAS) or inductively coupled plasma-optical emission spectrometry/mass spectrometry (ICP-OES/MS)[3]
e. Duplex melting temperature (Tm)

2. Physicochemical properties

Comparative characterizations on physicochemical properties including higher order structure of the test and RLD products should be performed 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)

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.

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[1] The Rp/Sp configuration ratio at each phosphorothioate 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] If resolution of all diastereomers of a strand could not be achieved by an analytical method, multiple LC methods with orthogonal and/or complementary separation principles may be considered.

[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.

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 fitusiran 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 fitusiran sodium subcutaneous solution product 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 if 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 auto-injector. The auto-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, single-dose format
- Inspection window
- Needle gauge and length
- Automatic needle safety 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 guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

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**Document History**: Recommended May 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.

[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 product are within ±5% of those used in the RLD.
[6] 21 CFR 314.94(a)(9)(iii)