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Draft Guidance on Nedosiran Sodium

August 2024

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Active Ingredient:	Nedosiran sodium
Dosage Form:	Solution
Route:	Injection
Strengths:	EQ 80 mg Base/0.5 mL, EQ 128 mg Base/0.8 mL, EQ 160 mg Base/mL
Recommended Studies:	Comparative characterization studies to support active ingredient sameness and request for waiver of in vivo bioequivalence study requirements

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

Recommendations to support active ingredient sameness:

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

1. Primary sequence, chemical structure, and composition

The nedosiran sodium drug substance duplex is formed by Watson-Crick base pairing of the sense and the antisense strands. The primary sequence of the sense and antisense strands in the test nedosiran active ingredient can be controlled through each elongation cycle in the active ingredient synthesis. Sequence, chemical structure and diastereomeric composition related to the phosphorothioate linkages as well as the PS to PO ratios of both sense and antisense strands should be investigated and confirmed with a broad range of orthogonal analytical methods. 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 and composition including strand composition, duplex vs residual single strands, diastereomeric composition, and PS to PO ratios should be compared to those of the active ingredient from the RLD using a broad range of orthogonal analytical methods with sufficient sensitivity, discriminating and resolving power, that could 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. Flame atomic absorption spectroscopy (FAAS) or inductively coupled plasma-optical emission spectrometry (ICP-OES)
e. Duplex melting temperature (Tm)

2. Physicochemical properties

Comparative physicochemical characterizations of the test and RLD 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. Differential scanning calorimetry (DSC)
d. Size exclusion chromatography (SEC)
e. Sedimentation velocity analytical ultracentrifugation (SV-AUC)

If the sameness between the test and RLD can be adequately demonstrated using validated alternative analytical methods, applicants may submit comparative data for test and RLD along with appropriate justification as part of their product characterization within their abbreviated new drug application (ANDA). In such case, comprehensive method validation data should be submitted to demonstrate the adequacy (e.g., sensitivity, resolution, and discriminative power) of the selected methods in demonstrating the sameness between the test and reference product.

[1] If resolution of all diastereomers of both strands could not be achieved by the analytical methods, the Rp/Sp configuration ratio at each phosphorothioate nucleotide linkage following respective elongation cycle should be measured using appropriate methods.

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), the test product should be qualitatively (Q1)[2] and quantitatively (Q2)[3] the same as the RLD.

An applicant may seek approval of a drug product 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.[4]

Additional information:

Device:
The RLD is presented as a vial and a single-use pre-filled syringe. The pre-filled syringe presentation is a drug-device combination product, and the pre-filled syringe with staked needle 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, fixed-dose, prefilled syringe format with staked needle
- Needle gauge and length

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 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]

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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.

[2] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD.
[3] 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.
[4] 21CFR 314.94(a)(9)(iii)