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Draft Guidance on Nusinersen Sodium

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This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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This is a new draft product-specific guidance for industry on generic nusinersen sodium.

Active Ingredient: Nusinersen sodium

Dosage Form; Route: Solution; intrathecal

Overview:

This guidance provides recommendations for developing generic nusinersen sodium intrathecal solutions containing nusinersen sodium as the active pharmaceutical ingredient (API). It includes recommendations for demonstrating API sameness and for requesting waiver of in vivo bioequivalence study requirements.

In addition, generic applicants are advised to contact the FDA for questions related to generic development of nusinersen including questions on immunogenicity and inflammation risk assessment, and comparability of impurities in the test product.

Recommendations for Demonstrating API Sameness:

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

1. Primary sequence, chemical structure and diastereomeric composition

The primary sequence of the oligonucleotide in the test API can be controlled through each elongation cycle in the API synthesis. Due to the stereochemistry at the phosphorus chiral center of the phosphorothioate linkage, nusinersen contains many different diastereomers. To ensure the diastereomeric sameness of the test API and the API from the RLD, reagents and reaction conditions that can impact the diastereomeric composition outcomes should be appropriately selected and adequately controlled. The R/S configuration ratio at each phosphorothioate nucleotide linkage following each elongation cycle should be measured using appropriate methods. The test API sequence, chemical structure and diastereomeric composition should be compared to that of the API 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. Duplex melting temperature (T_m) to a complementary strand

Approaches for demonstrating the sensitivity, discriminating and resolving power of an analytical method for diastereomeric composition analysis should be appropriately justified. Alternatively, the sensitivity, discriminating and resolving power of an analytical method for diastereomeric composition analysis may be demonstrated, for example, through negative control studies that introduce variations in the process and corresponding variations to the resulting diastereomeric composition, in conjunction with the corresponding analysis of the R/S configuration ratio at each phosphorothioate nucleotide linkage following each elongation cycle.

2. Physicochemical properties

Side-by-side comparative physicochemical characterization of the test and RLD products should be performed to include aggregation state or high order structure of the API in the drug product, using methods that could include but are not limited to the following:

- a. Circular dichroism (CD) spectroscopy
- b. Differential scanning calorimetry (DSC)
- c. Size exclusion chromatography (SEC)
- d. Sedimentation velocity analytical ultracentrifugation (SV-AUC)

Recommended Study: Request for waiver of in vivo bioequivalence study requirements

Waiver:

To qualify from submitting an in vivo bioequivalence (BE) study on the basis that BE is self-evident under 21 CFR 320.22(b), a generic nusinersen sodium intrathecal solution product should be qualitatively (Q1)¹ and quantitatively (Q2)² 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.³

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¹ Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product.

² Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test products are within $\pm 5\%$ of those used in the RLD product.

³ 21CFR 314.94(a)(9)(iii)