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Draft Guidance on Tofersen

August 2024

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Active Ingredient:	Tofersen
Dosage Form:	Solution
Route:	Intrathecal
Strength:	100 mg/15 mL (6.7 mg/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 tofersen 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 diastereomeric composition

The primary sequence of the oligonucleotide can be controlled through each elongation cycle in the active ingredient synthesis. Due to the stereochemistry at the phosphorus chiral center of the phosphorothioate linkage, tofersen contains many different diastereomers. To ensure the diastereomeric sameness of test active ingredient and the active ingredient 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 linkage following each elongation cycle should be measured using appropriate methods. The test active ingredient sequence, chemical structure, PS to PO ratio, and diastereomeric composition should be compared to that 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. Duplex melting temperature (Tm) 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 characterizations of the test and RLD should be performed to include aggregation or high 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. Differential scanning calorimetry (DSC)
c. Size exclusion chromatography (SEC)
d. Sedimentation velocity analytical ultracentrifugation (SV-AUC)

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)[1] and quantitatively (Q2)[2] the same as the RLD.

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD.
[2] 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 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]

Document History: Recommended August 2024

Unique Agency Identifier: PSG_215887

[3] 21CFR 314.94(a)(9)(iii)