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Draft Guidance on Inclisiran Sodium

May 2023

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Active Ingredient:	Inclisiran sodium
Dosage Form; Route:	Solution; Subcutaneous
Strength:	EQ 284 mg Base/1.5 mL (EQ 189 mg Base/mL)
Recommended Studies:	Comparative characterization studies to support active pharmaceutical ingredient (API) sameness and request for waiver of in vivo bioequivalence study requirements

This guidance provides recommendations for developing generic inclisiran sodium subcutaneous solution containing inclisiran sodium as the 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 inclisiran sodium including comparability of product- and process-related impurities in the test product and strategies to address immunogenicity and inflammation risk assessment.

Recommendations to Support API Sameness:

For characterization to support sameness between the test API and the API 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 API and the API from the RLD product. A minimum of three batches of the test API and three Fin the manufacturing process. The API sameness can be established by evaluating the equivalence in the following:

1. Primary sequence, chemical structure, and composition

The inclisiran sodium drug substance duplex is formed by Watson-Crick base pairing of the antisense and the sense single strand intermediates. The primary sequence of the sense and antisense stands in the test inclisiran API can be controlled through each elongation cycle in the API synthesis. Sequence, chemical structure and diastereomeric composition related to the phosphorothioate linkages as well as the P=S to P=O ratios of both single 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 API sequence, chemical structure and composition including strand composition, duplex vs residual single strands, diastereomeric composition, and P=S to P=O ratios should be compared to those 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. Flame atomic absorption spectroscopy (FAAS)
e. Duplex melting temperature (Tm)

2. Physicochemical properties

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

If the sameness between the test and reference products can be adequately demonstrated using validated alternative analytical methods, applicants may submit comparative data for test and reference products along with appropriate justification as part of their product characterization within their abbreviated new drug application (ch 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 from submitting an in vivo bioequivalence study on the basis that bioequivalence is self-evident under 21 CFR 320.22(b), a generic inclisiran sodium subcutaneous solution 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 differ 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 in a pre-filled syringe which is the device constituent.
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 (T) device including:

- Single-dose, fixed-dose, prefilled syringe format
- 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 web page 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 product.
[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 product.
[4] 21CFR 314.94(a)(9)(iii)