Draft – Not for Implementation

Draft Guidance on Patisiran Sodium

November 2022

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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.

Active Ingredient:	Patisiran sodium
Dosage Form; Route:	Solution; intravenous
Strength:	EQ 10 mg base/5 mL (EQ 2 mg base/mL)
Recommended Studies:	Comparative characterization studies to support active ingredient sameness, one in vivo bioequivalence study with pharmacokinetic endpoints, one in vitro bioequivalence study with particle size distribution endpoints, and supportive physicochemical characterization studies

This guidance provides recommendations for developing generic patisiran sodium intravenous solution containing patisiran sodium as the Active Pharmaceutical Ingredient (API). It includes recommendations for demonstrating API sameness and bioequivalence.

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

Recommendations to support API sameness:

For a comprehensive 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 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 composition

The patisiran 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 strands in the test patisiran API can be controlled through each elongation cycle in the API synthesis. Sequence, chemical structure and composition of the single strand intermediates should be investigated and confirmed with a broad range of orthogonal analytical methods.

The test API sequence, chemical structure and 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. 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. Differential scanning calorimetry (DSC)
   c. Size exclusion chromatography (SEC)
   d. 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 (ANDA). In such case, comprehensive method validation data should be submitted to demonstrate the adequacy of the selected methods in demonstrating the sameness between the test and reference product.

One in vivo bioequivalence study with pharmacokinetic endpoints:

1.   Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
        Design: Single dose, randomized, parallel, in vivo
        Strength: Eq 10 mg Base/5 mL (Eq 2 mg Base/mL)
        Dose: 0.3 mg/kg for subjects weighing ≤100 kg, or 30 mg for subjects weighing >100 kg
        Subjects: Healthy males and non-pregnant, non-lactating females
        Additional comments:
           a. The product should be administered according to the current RLD label. All subjects should consent to and receive relevant premedication prior to the administration of the test and reference products to reduce the risk of infusion-related reactions (IRRs). Closely monitor subjects during the infusion for signs

and symptoms of IRRs. If any events of IRRs occur, determine the management as clinically appropriate (e.g., stopping the infusion and use of additional medications for symptomatic treatment).
  b. Sufficient sampling points should be made to capture the biphasic PK profile.[1]

Analytes to measure: Lipid nanoparticle (LNP)-entrapped patisiran siRNA in plasma

Bioequivalence based on (90% CI): AUC and Cmax for LNP-entrapped patisiran siRNA

One in vitro bioequivalence study with particle size distribution endpoints:

1.   Type of study: Particle size distribution
       Design: In vitro testing on at least three batches of both test and reference products

Parameters to measure: Z-average size and polydispersity index (PDI) or D_{50} and SPAN as appropriate

Bioequivalence based on (95% upper confidence bound): Z-average and PDI or D_{50} and SPAN using the population bioequivalence (PBE) statistical approach. Applicants should provide no less than 10 datasets from 3 batches each of the test and Reference Standard (RS) products to be used in the PBE analysis. For additional information on PBE statistical analysis, refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929).[a]

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the ANDA.

Additional information:

1. The proposed parenteral drug 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]

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[1] X. Zhang et al., Pharmacokinetics of patisiran, the first approved RNA interference therapy in patients with hereditary transtryretin-mediated amyloidosis. The Journal of Clinical Pharmacology 2020, 60(5) 573-585
[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)

2. Lipid excipients are critical in the lipid nanoparticle drug products. Although not a liposomal drug product, for additional information on the chemistry, manufacturing and control of the lipid components, refer to the most recent version of the FDA guidance for industry on *Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation.*[b]

3. Comparative physicochemical characterization of test product and RS product with appropriately validated analytical methods. These in vitro characterization studies should be conducted on at least three batches of the test[5] and RS products. At least one test batch should be produced by the commercial scale process and used in the in vitro and in vivo bioequivalence studies. The attributes to be characterized should include, but are not limited to, the following:
   a. LNP drug product composition: lipid content, drug-to-lipid ratio, and siRNA location (e.g., free, surface-bound, and entrapped siRNA, if applicable)
   b. Physicochemical properties of the drug product: pH, osmolality, density, viscosity, PEG layer thickness, electrical surface charge, and LNP morphology
   c. In-vitro release of siRNA from patisiran drug product
   d. In-vitro bioassay for transthyretin (TTR) mRNA knockdown with IC50 value being determined

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Unique Agency Identifier: PSG_210922

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[5] The applicant should demonstrate that all test batches used for in vitro characterizations are manufactured using a process reflective of the proposed commercial scale manufacturing process.

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[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.
[b] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatoryinformation/search-fda-guidance-documents.