*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

**Draft Guidance on Viltolarsen**

**February 2023**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

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.

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| **Active Ingredient:** | Viltolarsen |
| **Dosage Form; Route:** | Solution; intravenous |
| **Strength:** | 250 mg/5 mL (50 mg/mL) |
| **Recommended Studies:** | Comparative characterization studies to support active ingredient sameness and request for waiver of in vivo bioequivalence study requirements |

This guidance provides recommendations for developing generic viltolarsen intravenous solution containing viltolarsen 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 viltolarsen including questions on immunogenicity and inflammation risk assessment, and comparability of impurities in the test product.

**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 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 phosphorodiamidate linkage, viltolarsen contains many different diastereomers. To ensure the diastereomeric sameness of 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 phosphorodiamidate 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 not be 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 phosphorodiamidate nucleotide linkage following each elongation cycle.

2. Physicochemical properties

Side-by-side comparative physicochemical characterizations of the test and RLD products should be performed to include aggregation or high order structures of the API in the drug product, using method that could include but not be 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 from submitting an in vivo bioequivalence study on the basis that bioequivalence is self-evident under 21 CFR 320.22(b), a generic viltolarsen intravenous 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 ±5% of those used in the RLD product.
[3] 21CFR 314.94(a)(9)(iii)