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Draft Guidance on Avacincaptad Pegol Sodium

February 2026

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

Active Ingredient:	Avacincaptad pegol sodium
Dosage Form:	Solution
Route:	Intravitreal
Strength:	EQ 2 mg Base/0.1 mL (EQ 2 mg Base/0.1 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 to discuss proposed strategies and any questions related to the generic development of avacincaptad pegol sodium, including those concerning immunogenicity and inflammation risk assessment, as well as the comparability of impurities in the test product.

Recommendations to support active ingredient sameness:

The active ingredient avacincaptad pegol sodium is a 39-mer oligonucleotide covalently linked to an approximately 43-kDa branched polyethylene glycol (PEG) moiety through a hexylamino linker. Applicants should fully characterize the non-PEGylated full-length oligonucleotide, the PEG moiety and the active ingredient. For characterization to support sameness between the test active ingredient and the active ingredient from the reference listed drug (RLD), FDA recommends that applicants develop and use appropriately validated orthogonal analytical methods to perform comparative testing of the test active ingredient and the active ingredient in the RLD product. The comparative characterizations may be performed with active ingredient or drug product depending on the analytical methods used and the purpose of the tests. A minimum

of three batches of the test active ingredient and the active ingredient from three batches of 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. Nucleotide sequence, chemical structure and composition of the non-PEGylated full-length oligonucleotide[1]

Oligonucleotide sequence can be controlled through each elongation cycle in the oligonucleotide synthesis. The sequence, chemical structure and the linker position of the test non-PEGylated full-length oligonucleotide should be characterized and compared to the labeling using a broad range of orthogonal analytical methods with sufficient sensitivity 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. Duplex melting temperature (Tm) to a complementary strand

2. PEG moiety molecular weight distribution

The branched PEG moiety in both test and RLD active ingredient should be characterized and compared to demonstrate that the molecular weight and distribution including polydispersity index (PDI) of the branched PEG moieties are equivalent.

3. Chemical structure and composition of the active ingredient

Comparative physicochemical characterizations of the test active ingredient and the active ingredient in the RLD should be performed using methods that could include, but are not limited to the following:

a. Molecular weight determination by MS
b. Molecular weight distribution by size exclusion chromatography (SEC)[2]
c. Liquid chromatography (LC)
d. NMR spectroscopy
e. Fourier transform infrared (FTIR) spectroscopy
f. Ultraviolet (UV) spectroscopy
g. Flame atomic absorption spectroscopy (FAAS) or inductively coupled plasma optical emission spectroscopy (ICP-OES)

[1] These studies only apply to test non-PEGylated oligonucleotide.
[2] SEC with multi-angle light scattering (SEC-MALS) or other suitable detection techniques may be used. Refer to Wang J, Tang S, Zhang K. Quantitation of polyethylene glycol by size exclusion chromatography with charged aerosol, differential refractive index, and multi-angle light scattering detectors. *Journal of Pharmaceutical and Biomedical Analysis*. 2024;238:115854. https://doi.org/10.1016/j.jpba.2023.115854

4. High order structure and biological activity

Oligonucleotide aptamer folds into three-dimensional structure to bind to its target. Comparative characterization of the high order structure of active ingredient in test drug product and RLD product should be performed. The high order structure and biological activity should be characterized and compared between drug products using methods that could include, but are not limited to the following:

a. Circular dichroism (CD) spectroscopy
b. FTIR spectroscopy
c. NMR spectroscopy
d. Dynamic light scattering (DLS)
e. SEC
f. Cell-based bioassay on inhibiting complement protein C5

Request for 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)(1), a generic avacincaptad pegol sodium intravitreal solution should be qualitatively (Q1)[3] and quantitatively (Q2)[4] the same as the RLD.

An applicant may seek approval of a drug product that differs from the RLD in preservative, buffer, or antioxidant provided that 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.[5]

Additional information:

Device:
The RLD is presented in a kit containing a single-dose vial of drug, a Luer lock syringe, and a filter needle. The co-packaged syringe and needle are considered the device constituent parts.

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 device including:

- Injection syringe design
- Graduation markings
- Filter needle: filter pore size, gauge, and length

[3] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD.
[4] 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.
[5] 21CFR 314.94(a)(9)(iii).

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 guidance for industry *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, refer to the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.