Contains Nonbinding Recommendations

Draft Guidance on Ethiodized Oil

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Ethiodized oil

Dosage Form; Route: Injectable; intralymphatic, intrauterine, selective hepatic intra-arterial

Strength: 480 mg iodine organically combined with ethyl esters of fatty acids of poppy seed oil per mL

Overview:

Ethiodized oil injection is a parenteral product (non-aqueous solution) intended solely for administration by injection. In addition to the requirement of active ingredient sameness, as per 21 CFR §314.94(a)(9)(iii), a proposed generic drug product (Test) shall contain the same inactive ingredients and in the same concentration as the reference listed drug (RLD). Under this circumstance, in vivo bioequivalence (BE) of the generic parenteral injection may be self-evident according to 21 CFR §320.22(b)(1).

This draft guidance provides recommendations for the development of the generic ethiodized oil through demonstrating active ingredient sameness.

Recommendations for demonstrating active ingredient sameness:

The RLD is derived from a naturally obtained starting material, poppy seed oil. The generic applicant is advised to use the same starting material for a proposed generic ethiodized oil. The information on manufacturing process and in-process controls should be provided to the Agency. Sameness of active ingredient can be established based on comparative composition and physicochemical characterizations of the RLD and Test products. At least three batches of Test and the RLD products should be tested side-by-side. A generic applicant may analyze additional batches to assess the variations of the drug product. The following are the recommended studies:

1. Composition of active ingredient: According to the labeling information of the RLD[1], each mL of the ethiodized oil contains 480 mg iodine organically combined with ethyl esters of fatty acids of poppy seed oil. The generic applicant should identify and quantify individual ethyl ester components in the RLD and Test products using high resolution analytical procedures. The applicant should demonstrate that the Test product contains corresponding ethyl esters in equivalent amounts to those in the RLD product. Any ethyl

[1] http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/009190s024lbl.pdf

ester components that are present in the Test product batches, but not present at the RLD batches, should be justified or qualified.

2. Iodine content: The Test product should contain a quantitatively comparable amount of organically combined iodine as the RLD.
3. Physicochemical properties: The applicant should perform physicochemical properties measurements including, but not limited to, density and viscosity, to characterize the Test and Reference products.
4. Spectroscopic characterizations: The Agency encourages the applicant to perform spectroscopic studies including, but not limited to, Fourier transform infrared spectroscopy (FT-IR), proton and carbon nuclear magnetic resonance spectroscopy (NMR), and ultraviolet-visible spectroscopy (UV/Vis) to further characterize and compare the Test and RLD products.