Contains Nonbinding Recommendations

Draft Guidance on Fish Oil Triglycerides

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Emulsion; intravenous

Strength: 5 g/50 mL (0.1 g/mL); 10 g/100 mL (0.1 g/mL)

Recommended Study: Two options: in vitro or in vivo

I. In vitro option:[1]

To qualify for the in vitro option for this drug product all the following criteria should be met:

i. The Test and Reference Listed Drug (RLD) formulations are qualitatively (Q1)[2] and quantitatively (Q2)[3] the same (Q1/Q2).

ii. Acceptable comparative physicochemical characterization of the test and Reference Standard (RS) products. The comparative study should be performed on at least three exhibit batches of both the test and RS products.

Parameters to measure: Globule size distribution. The applicant should compare the size parameter upon serial dilution (if applicable) of the test and the RS products and provide histograms of globule size distribution data of each diluted sample. In addition, the applicant should also perform other physicochemical characterizations including, but not limited to, zeta potential, pH, osmolality and viscosity profile, on the test and the RS products.

Bioequivalence based on (95% upper confidence bound): Population bioequivalence (PBE) based on D_{50} and SPAN (alternatively harmonic intensity weighted average particle diameter and polydispersity index derived from cumulate analysis of the intensity size distribution) for the globule size distribution only (the other parameters do not require PBE analysis). Please refer to the product-specific *Guidance on Budesonide* inhalation suspension for additional information

[1] Per 21 CFR 314.94(a)(9)(iii), parenteral injection drug product must contain the same inactive ingredients and in the same concentration as the reference listed drug (RLD). The generic version may differ from the RLD in preservative, buffer, or antioxidant which are exception excipients.
[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 the concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the RLD product.

regarding PBE. The applicant should provide no less than 10 datasets from a minimum of three batches of the test product and three batches of the RS product to be used in the PBE analysis.

II. In vivo option:

Type of study: Bioequivalence study with pharmacokinetic endpoint
Design: Single-dose, randomized, two-way crossover
Strength: 10 g/100 mL (0.1 g/mL)
Subject: Males and nonpregnant, nonlactating females, general population

Additional Comments: (1) The subjects should be encouraged to remain sedentary to minimize the activity. (2) PK parameters should be computed from the individual baseline-adjusted measurements.

Analytes to measure (in appropriate biological fluid): Triglycerides in serum

Bioequivalence based on (90% CI): Triglycerides in serum

Waiver request of in vivo testing: 5 g/50 mL based on (i) acceptable bioequivalence studies on the 10 g/100 mL strength, (ii) proportional similarity of the formulations across the two strengths

Dissolution test method and sampling times: Not applicable