Contains Nonbinding Recommendations

Draft Guidance on Omega-3-Acid Ethyl Esters

Active Ingredient: Omega-3-acid ethyl esters

Dosage Form; Route: Capsule; oral

Strength: 1g contains at least 900mg of the ethyl esters of omega-3 fatty acids

Recommended Studies: Two options: in vitro or in vivo

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1) In vitro option:

Bioequivalence may be established based solely on an in vitro disintegration method that assures timely disintegration of the capsules, provided that the recommendations on the active pharmaceutical ingredient (API) and the inactive ingredients are met, and the capsule fills of the Test and reference listed drug (RLD) products are considered very similar.

Disintegration method

Disintegration method measures whether the Test capsules disintegrate at a similar time as the RLD. The applicant may refer to USP <701> when designing the disintegration test. Water is recommended as testing liquid medium. Comparative disintegration testing of 12 units per batch for all three batches, and all strengths, of the Test and Reference products, should be tested and found to be comparable. Both Test and Reference products should disintegrate within 30 minutes.

2) In vivo option:

Bioequivalence may be established by conducting in vivo studies with pharmacokinetic endpoints, providing equivalence of API is established by meeting the qualitative and/or quantitative criteria. Two in vivo bioequivalence studies (one fed and one fasted) are recommended.

1. Type of study: Fasting
   Design: Single-dose, partial or fully replicated crossover
   Strength: 1 gram contains at least 900mg of the ethyl esters of Omega-3 fatty acids
   (Dose: 4 × 1 gram capsules)
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments:
   a) In using the reference-scaled average bioequivalence approach for omega-3-acid ethyl esters capsules, provide evidence, from the study, of high variability in the bioequivalence parameters of AUC and/or Cmax (i.e., within-subject variability

≥ 30%). For details on the method for statistical analysis using the reference-scaled average bioequivalence approach, refer to the progesterone oral capsule guidance.

b) The subjects' diet should be controlled from at least 48 hours before and until at least 36 hours after drug administration. EPA and DHA limited meals should be given throughout the diet control period.

c) Baseline measures should be calculated from an average of three or more samples collected between 24 and 0 hours (inclusive) prior to dosing.

Analytes to measure:

1) EPA total lipids in plasma
2) Baseline-adjusted EPA total lipids in plasma
3) DHA total lipids in plasma
4) Baseline-adjusted DHA total lipids in plasma
5) EPA free fatty acids in plasma
6) Baseline-adjusted EPA free fatty acids in plasma
7) DHA free fatty acids in plasma
8) Baseline-adjusted DHA free fatty acids in plasma

Bioequivalence based on (90% CI):

1) Baseline-adjusted EPA total lipids in plasma
2) Baseline-adjusted DHA total lipids in plasma

Submit the data of baseline-adjusted EPA and DHA free fatty acids and the statistical analysis using the reference-scaled average bioequivalence approach as supportive evidence.

2. Type of study: Fed
Design: Single-dose, partial or fully replicated crossover in vivo
Strength: 1 gram contains at least 900mg of the ethyl esters of Omega-3 fatty acids (Dose: 4 × 1 gram capsules)
Subjects: Healthy males and females (nonpregnant), general population
Additional comments: A high-fat, high-calorie, EPA- and DHA-limited test meal should be given for the fed bioequivalence study. Also see comments in the fast bioequivalence study above.

Analytes to measure:

1) EPA ethyl esters in plasma
2) DHA ethyl esters in plasma
3) EPA total lipids in plasma
4) Baseline-adjusted EPA total lipids in plasma
5) DHA total lipids in plasma
6) Baseline-adjusted DHA total lipids in plasma
7) EPA free fatty acids in plasma
8) Baseline-adjusted EPA free fatty acids in plasma
9) DHA free fatty acids in plasma
10) Baseline-adjusted DHA free fatty acids in plasma

Bioequivalence based on (90% CI):

1) EPA ethyl esters in plasma
2) DHA ethyl esters in plasma

Submit the data of baseline-adjusted EPA and DHA total lipids and baseline-adjusted EPA and DHA free fatty acids, and the statistical analysis using the reference-scaled bioequivalence approach as supportive evidence.

Recommendations for Demonstrating API Equivalence

Omega-3-acid ethyl esters is a natural source drug obtained from the body oil of several fish sources. The omega-3-acid ethyl esters USP monograph defines the API as composed of seven individual omega-3-acid ethyl ester components. The omega-3-acid ethyl esters capsules USP monograph[1] establishes ranges for the two most abundant components (EPAee and DHAee) of the API and ranges for the sum of the two components. The reference product contains lesser quantities of the other five omega-3 acid ethyl esters, although quantitative ranges are not specified in the USP monographs. The Agency has determined the quantitative ranges of the other five omega-3-acid ethyl ester components based on assay of multiple batches of the RLD using the USP monograph analytical method.

The recommendation for each component of the API varies with its content. API in each batch of a test product must meet the quantitative ranges for all the seven components. The following are the specifications for each individual component of API. The unit of mg/g in the current recommendation means mg per gram of encapsulated oil.

1. Most abundant components: EPAee and DHAee

    - Eicosapentaenoic acid ethyl ester (EPAee; C20:5 n-3) 430 - 495 mg/g
    - Docosahexaenoic acid ethyl ester (DHAee; C22:6 n-3) 347 - 403 mg/g
    - Sum of EPAee and DHAee 800 - 880 mg/g
    - Total omega-3 acid ethyl esters NLT 90% (w/w)

2. Additional components present at greater than or equal to 10 mg/g encapsulated oil: SDAee, HPAee, DPAee

    - Moroctic acid ethyl ester (SDAee; C18:4 n-3) 4.0-37.0 mg/g
      Heneicosapentaenoic acid ethyl ester (HPAee; C21:5 n-3) 7.9-31.4 mg/g
      Docosapentaenoic acid ethyl ester (DPAee; C22:5 n-3) 16.3-50.0 mg/g

3. The component should be present: ETAee

    - Eicosatetraenoic acid ethyl ester (ETAee; C20:4 n-3) Present

4. The component present at below 1 mg/g encapsulated oil: ALAee

[1] Omega-3-Acid Ethyl Esters Capsules monograph, USP-35, official from August 1, 2012

- The content of Alpha-linolenic acid ethyl ester (ALAee; C18:3 n-3) is below 1 mg/g in the reference product and it will not be considered in the pharmaceutical equivalence assessment.

Recommendations for Demonstrating Inactive Ingredients Equivalence

1. Alpha-tocopherol

   The formulation of the RLD encapsulated oil contains a labeled concentration of antioxidant:[2]

   - Alpha-tocopherol 4 mg/g encapsulated oil
   - Alpha-tocopherol should be present in the same concentration as in the RLD. The alpha-tocopherol may be either the natural d-alpha-tocopherol, or the synthetic dl-alpha-tocopherol.

2. Soybean oil

   The test product may either contain or not contain soybean oil, depending on the commercial source of alpha-tocopherol. We recommend that a test product not add soybean oil unless it is present in the commercial form of alpha-tocopherol used by the ANDA applicant.

[2] LOVAZA Capsules labeling, revised 22 December 2010