Contains Nonbinding Recommendations

Draft Guidance on Omega-3-acid Ethyl Esters Type A

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Omega-3-acid Ethyl Esters Type A

Dosage Form; Route: Capsule; oral

Recommended Studies: One in vitro or two in vivo studies

In Vitro Option

Bioequivalence (BE) may be established based solely on an in vitro method [Quantitative Capsule Rupture Test (QCRT), described below] that assures equivalent release of the active pharmaceutical ingredient (API) from the capsules, provided that the recommendations on the API and the antioxidant in the Appendix are met and the capsule fills of the test and reference drug products are considered very similar. Firms should compare three lots of the test omega-3-acid ethyl esters type A capsules (with one lot manufactured with the commercial scale process) with three lots of the reference listed drug (RLD) using an optimized QCRT method.

Quantitative Capsule Rupture Test

A QCRT method should measure the release of eicosapentaenoic acid ethyl ester (EPAee) and docosahexaenoic acid ethyl ester (DHAee) in an aqueous testing medium. In order to obtain an accurate release profile, the test samples should be taken at early times (e.g. 5, 10, 15, 20, 25 minutes) and as frequently as possible, until at least 80% of the drug is released from the capsules. The method should demonstrate sufficient discrimination for detection of potential differences between formulations, with acceptable variability.

Based on the information available to the Agency, as well as the recommendation given in the U.S. Pharmacopeia (USP) Pharm Forum[1], USP Apparatus 4 (flow-through cell) has been shown to be the most appropriate apparatus for drugs with poor solubility, compared with the conventional USP Apparatus I (basket) and Apparatus II (paddle). In addition, the use of surfactant is also critical in the *in vitro* drug release method development for an omega-3-acid ethyl esters type A capsule drug product.

The firm should develop the *in vitro* drug release method for the drug product using USP Apparatus 4. A second method using USP Apparatus 2 may be developed in conjunction with the method using USP Apparatus 4 for comparison, if desired. The data from USP Apparatus 4, and

[1] Marques, MRC, Cole E et al., Stimuli to the Revision Process: Liquid-filled Gelatin Capsules. *USP Pharm Forum.* 2009; 35(4, July-Aug) 1029-41.

from USP Apparatus 2 (if conducted), should be included in the abbreviated new drug application (ANDA) submission for determination of the most suitable method.

The firm should provide all QCRT method development data showing that the QCRT method(s) studied have been systematically optimized for (but not limited to) the following parameters:

1. QCRT medium and volume
2. Surfactant and concentration
3. Filter type and size for sample collection and preparation, where applicable
4. Enzyme and concentration, where applicable
5. Rotation speed (USP Apparatus 2)
6. Flow rate (USP Apparatus 4)

Other parameters for USP Apparatus 4:

1. System mode (closed versus open)
2. Type of cell (size in mm)
3. Glass beads (size in mm)
4. Glass bead loading (weight in gm)
5. Sample load (volume in mL)
6. Split ratio (%)
7. Size of sample tube (volume in mL)

For each parameter, at least five values, in addition to zero value, around the selected final value should be tested in the optimization. The optimization data should demonstrate that the selected value is optimal and appropriate. For example, in order to select the final drug release medium of 0.5% Sodium Lauryl Sulfate (SLS), data from testing using the media of 0%, 0.25%, 0.35%, 0.65% and 0.75% SLS should also be submitted for comparison. In addition, other scientific justifications and evidence may be submitted to support the choices of the final parameter values. Optimizing testing should employ six dosage units for each determination. For final testing using the optimized method, twelve dosage units each of the test and reference products should be employed.

NOTE: It is critical that for USP Apparatus 4, when used for lipid-filled soft gelatin capsule (SGC) dosage forms, a modified flow-through cell designed for SGC[2] be used in the testing. For USP Apparatus 2, when used for this dosage form, the sampling probes should remain immersed in the QCRT medium throughout the duration of testing in order to obtain reproducible results. The use of a sinker with USP Apparatus 2 may be considered in preventing the capsules from floating to the top.

In Vivo Option

BE may be established by conducting in vivo studies with pharmacokinetic endpoints, providing equivalence of API is established by meeting the criteria specified in Appendix I. Two in vivo BE studies are recommended.

1. Type of study: Fasting

[2] USP *Revision Bulletin* Official August 1, 2011 <2040> Disintegration and Dissolution of Dietary Supplements.

Design: Single-dose, partially or fully replicated crossover in vivo
Strength: 1.2 gram containing at least 900 mg of the ethyl esters of omega-3 fatty acids (Dose: 4 X 1.2 gram capsules)
Subjects: Healthy males and females (nonpregnant), general population.
Additional Comments:

a) Females should practice abstinence or contraception during the study.
b) In using the reference-scaled average BE approach for omega-3-acid ethyl esters type A capsules, provide evidence of high variability in the BE parameters of AUC and/or Cmax (i.e., within-subject variability is ≥30%). For details on the method for statistical analysis using the reference-scaled average bioequivalence approach, refer to the draft Progesterone Oral Capsule Guidance at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf.
c) It is recommended that the subject's diet be controlled from at least 48 hours before until at least 36 hours after drug administration. Meals should be EPA- and DHA-limited throughout the diet control period.
d) Baseline measurements should be calculated from an average of 3 or more samples collected between 24 and 0 hours (inclusive) prior to dosing.

Analytes to measure (in appropriate biological fluid):

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

BE based on (90% CI): Baseline-adjusted total EPA lipids and total DHA lipids

Submit the data for baseline-adjusted EPA and DHA free fatty acids and the statistical analysis using the reference-scaled averaged BE approach as supportive evidence.

2. Type of study: Fed
Design: Single-dose, partially or fully replicated crossover in vivo
Strength: 1.2 gram containing at least 900 mg of the ethyl esters of omega-3 fatty acids (Dose: 4 X 1.2 gram capsules)
Subjects: Healthy males and females (nonpregnant), general population.
Additional Comments:

a) See additional comments above.

Analytes to measure (in appropriate biological fluid):

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

BE based on (90% CI): EPA ethyl esters and DHA ethyl esters

Submit the data for baseline-adjusted EPA and DHA total and free fatty acids and the statistical analysis using the reference-scaled averaged BE approach as supportive evidence.

APPENDIX I

API Equivalence

Omega-3-acid ethyl esters type A capsules are a naturally sourced drug product obtained from the body oil of several fish sources. The API consists of a mixture of omega-3-acid ethyl esters, with the predominate components being EPAee and DHAee. The Omega-3-Acid Ethyl Esters Capsules USP monograph[3] establishes quantitative ranges for EPAee, DHAee, their sum, and the total omega-3-acid ethyl esters content. The reference product also contains other omega-3-acid ethyl esters and non-omega-3-acid ethyl esters, although quantitative ranges for these components are not provided in the USP monograph. To demonstrate API equivalency with the RLD, a test drug product should meet the following:

1. Equivalent EPAee, DHAee, and Omega-3-Acid Ethyl Esters Content:

Component	Specification
Eicosapentaenoic acid ethyl ester (EPAee; C20:5 n-3)	365 – 435 mg / g*
Docosahexaenoic acid ethyl ester (DHAee; C22:6 n-3)	290 – 360 mg / g*
Sum of EPAee and DHAee	700 – 749 mg / g*
Total Omega-3-acid ethyl esters	NLT 78% (w/w)
* mg / g is mg per gram of encapsulated oil	

2. Minor Omega-3-Acid Ethyl Esters Content:

Component
Alpha-linolenic acid ethyl ester (ALAee; C18:3 n-3)
Moroctic acid ethyl ester (SDAee; C18-4 n-3)
Eicosatetraenoic acid ethyl ester (ETAee; C20:4 n-3)
Heneicosapentaenoic acid ethyl ester (HPAee; C21:5 n-3)
Docosapentaenoic acid ethyl ester (DPAee; C22:5 n-3)

Firms should identify and quantify the individual minor omega-3-acid ethyl esters in at least three lots of the RLD, and demonstrate that the test omega-3-acid ethyl esters type A capsules contain these omega-3-acid ethyl esters in equivalent amounts. Firms may submit a qualitative assessment (i.e., identifying as present in the API) for low content omega-3-acid ethyl esters that may be difficult to quantify. However, firms should submit justification for each omega-3-acid ethyl ester that will be qualitatively assessed.

3. Non-Omega-3-Acid Ethyl Esters Content:

[3] USP – Interim Revision Announcement for Omega-3-Acid Ethyl Esters Capsules. Official January 1, 2016. Last accessed January 22, 2016 via http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/iras/omega_3_ethyl_esters_capsules.pdf.

Naturally sourced fish oil drug products can contain additional ethyl esters of unsaturated fatty acids (e.g., omega-6, omega-9) as minor components of the API. Firms should identify and quantify the individual non-omega-3-acid ethyl esters in at least 3 lots of the RLD, and demonstrate that the test omega-3-acid ethyl esters type A capsules contain these non-omega-3-acid ethyl esters in equivalent amounts. Firms may submit a qualitative assessment (i.e., identifying as present in the API) for low content non-omega-3-acid ethyl esters that may be difficult to quantify. However, firms should submit justification for each non-omega-3-acid ethyl ester that will be qualitatively assessed.

APPENDIX II

Inactive Ingredient Equivalence

RLD labeling states that the drug product contains 4.6 mg of α-tocopherol as an antioxidant. Firms should demonstrate that the test omega-3-acid ethyl esters type A capsules contain equivalent amounts of α-tocopherol.