Contains Nonbinding Recommendations

Draft Guidance on Icosapent Ethyl

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Capsule; oral

Recommended Studies: One in vitro study or two in vivo studies

In Vitro Option

Providing (1) the recommendations on the active pharmaceutical ingredient (API) and the antioxidant in the Appendix are both met, and (2) the capsule fills of the Test and Reference drug products are considered very similar, 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 API from the capsules. Firms should compare three batches of the test icosapent ethyl capsules (with one batch manufactured with the commercial scale process) with three batches of the RLD using an optimized QCRT method.

Quantitative Capsule Rupture Test

A QCRT method should measure the release of icosapent ethyl (eicosapentaenoic acid ethyl ester) 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 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 to the conventional USP Apparatus 1 (basket) and Apparatus 2 (paddle). In addition, the use of surfactant is also critical in the in vitro drug release method development for an icosapent ethyl drug product.

The firm should develop the in vitro drug release method for the drug product using USP Apparatus 4 (flow-through cell). A second method using USP Apparatus 2 may be developed in conjunction with the method using Apparatus 4 for comparison, if desired. The data from USP Apparatus 4 and Apparatus 2 (if conducted) should be included in the abbreviated new drug application (ANDA) submission for determination of the most suitable method.

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

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 (paddle))
6. Flow rate (USP Apparatus 4 (flow-through cell))

Other parameters for US Apparatus 4:

7. System mode (closed versus open)
8. Type of cell (size in mm)
9. Glass beads (size in mm)
10. Glass bead loading (weight in gm)
11. Sample load (volume in mL)
12. Split ratio (%)
13. Size of sample tube (volume in mL)

For each parameter, at least 5 values, in addition to the 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 justification and evidence may be submitted to support the choices of the final parameter values. Optimizing testing should employ 6 dosage units for each determination. For final testing using the optimized method, 12 dosage units each of the test and reference product 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

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

1. Type of study: Fasting
   Design: Single-dose, partial or fully replicated crossover *in vivo*

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

Strength: 1 gram of icosapent ethyl
(Dose: 4 x 1 gram capsules)
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments:

a) In using the reference-scaled average bioequivalence approach for icosapent ethyl capsules, please provide evidence of high variability in the bioequivalence parameters of AUC and/or Cmax (i.e. within-subject variability in ≥ 30%). For details on the method for statistical analysis using the reference-scaled average bioequivalence approach, please refer to the draft Progesterone Oral Capsule Guidance at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf.

b) It is recommended that the applicant control the subjects' diet from at least 48 hr prior to till at least 36 hr after drug administration. The meals during the diet control period should be EPA limited.

c) It is recommended that baseline measurements be calculated from an average of three or more (>3) samples collected between 24 and 0 hours (inclusive) prior to dosing.

Analytes to measure (in appropriate biological fluid):

1) Total EPA lipids in plasma
2) Baseline-adjusted total EPA lipids in plasma
3) Free (unesterified) EPA lipids in plasma
4) Baseline-adjusted free (unesterified) EPA lipids in plasma

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

Please submit data of baseline-adjusted free (unesterified) EPA lipids 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 of icosapent ethyl
(Dose: 4 x 1 gram capsules)
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: The recommended test meal should consist of a high-fat, high-calorie, EPA limited meal. Please see comments for the fasted study for additional details.

Analytes to measure (in appropriate biological fluid):

1) Total EPA lipids in plasma
2) Baseline-adjusted total EPA lipids in plasma
3) Free (unesterified) EPA lipids in plasma
4) Baseline-adjusted free (unesterified) EPA lipids in plasma

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

Please submit data of baseline-adjusted free (unesterified) EPA lipids and the statistical analysis using the reference-scaled average bioequivalence approach as supportive evidence.

APPENDIX

API Equivalence

Icosapent ethyl is the US Accepted Name for eicosapentaenoic acid ethyl ester (EPA-E), and is a long chain, poly-unsaturated omega-3 fatty acid ester derived from fish oil. The amount of icosapent ethyl listed in the drug is 1 gram. The agency recommends that to ensure equivalence to the RLD, generic products should contain the same amount of icosapent ethyl in their formulation. This can be achieved by the amount of icosapent ethyl in the generic formulation falling within the quantitative range for icosapent ethyl determined from several batches of the RLD, using an appropriately validated method.

Inactive Ingredient

As stated in the drug label, [3] the formulation of the RLD encapsulated oil contains the following antioxidant:

- Tocopherol

The amount of tocopherol in the generic formulation should be the same as the RLD. As with icosapent ethyl, equivalent amounts of tocopherol can be achieved by the amount of tocopherol in the generic formulation falling within the quantitative range for tocopherol determined in several batches of the RLD, using an appropriately validated method.

[3] Vascepa (icosapent ethyl) Capsule Labeling. Version posted July 26, 2012.